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Essentials of MEDICAL PHARMACOLOGY

8th Edition

KD Tripathi



Essentials of Medical Pharmacology



Essentials of Medical Pharmacology

Eighth Edition

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JAYPEE BROTHERS MEDICAL PUBLISHERS
The Health Sciences Publisher
New Delhi | London | Panama

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Website: www.jaypeedigital.com

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Managing Editor: M. Tripathi

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Essentials of Medical Pharmacology

First Edition: 1985
Second Edition: 1988
Third Edition: 1994
Fourth Edition: 1999, Updated Reprint: 2001
Fifth Edition: 2003
Sixth Edition: 2008
Seventh Edition: 2013
Reprint: 2014
Eighth Edition: **2019**

ISBN: 978-93-5270-499-6

Printed at Replika Press Pvt. Ltd.

Preface

Medical pharmacology is a unique blend of basic pharmacology, clinical pharmacology and pharmacotherapeutics. The subject is highly dynamic with concepts and priority drugs changing rapidly. Innovations and developments are happening at an unprecedented pace. Several new molecular targets for drug action have been identified and novel drugs produced to attack them. On the other hand, a huge body of evidence has been generated to quantify impact of various drugs and regimens on well defined therapeutic end points, so that practice of medicine is transforming from 'impression based' to 'evidence based'. The present edition focuses on evidence based medicine by referring to numerous large randomized trials and other studies which have shaped current therapeutic practices. By evaluating such evidences, professional bodies, eminent health institutes, expert committees and WHO have formulated therapeutic guidelines for treating many conditions, as well as for use of specific drugs. The latest guidelines have been summarized and included in the present edition along with other developments and the core content.

Adopting the 'prototype drug' approach and a structured, systematic and user-friendly format, all chapters have been thoroughly revised and updated. In this edition, drug classifications have been presented as eye-catching charts which help create pictorial memory. A new chapter on 'Nitric Oxide and Vasoactive Peptide Signal Molecules' has been added along with some recently introduced drugs which act through receptors for these molecules or by altering their turnover.

Priority has been accorded to drugs that are marketed in India, and their leading brand names are mentioned along with dosage forms. All recently released drugs are included, while those not commercially available or infrequently used have been excluded or described in small type.

India specific information on drugs and diseases finds a place in relevant topics. Treatment of diseases like TB, leprosy, HIV-AIDS, malaria, Kala-azar which are covered under WHO and National Health Programmes are described as per the latest recommendations of these organizations. Several new figures, charts, tables and highlight boxes have been added and many older ones have been revised/improved. The recent material and data has been authenticated by quoting its source. A brief list of useful references for further reading is provided at the end of the book. The 'Problem Directed Study' at the end of most chapters provides an exercise in therapeutic decision making.

I thank my colleagues and students for providing valuable inputs and raising thoughtful queries. As ever, the driving force behind this book has been Shri Jitendar P Vij (Group Chairman) and Mr Ankit Vij (Managing Director) of M/s Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India. The staff of Jaypee Brothers, especially Ms Sunita Katla (Executive Assistant to Group Chairman and Publishing Manager), Ms Geeta Srivastava (Proof Reader), Mr Manoj Pahuja (Graphic Designer) and Mr Kapil Dev Sharma (DTP Operator) deserve special commendation for excellent production of this text. Cooperation and participation of my wife has been pivotal.

New Delhi
June 2018

KD Tripathi

Extract from Preface to the First Edition

Pharmacology is both a basic and an applied science. It forms the backbone of rational therapeutics. Whereas the medical student and the prescribing physician are primarily concerned with the applied aspects, correct and skilful application of drugs is impossible without a proper understanding of their basic pharmacology. Medical pharmacology, therefore, must include both fundamental background and clinical pharmacological information. Objective and quantitative data on the use of drugs in man, i.e., relationship between plasma concentration and intensity of therapeutic/toxic actions, plasma half lives, relative efficacy of different medications and incidence of adverse effects etc., are being obtained with the aim of optimising drug therapy. The concepts regarding mechanism of action of drugs are changing. In addition, new drugs are being introduced in different countries at an explosive pace. A plethora of information thus appears to be important. However, trying to impart all this to a medical student would be counter-productive.

One of the important aims of this book is to delineate the essential information about drugs. The opening sentence in each chapter defines the class of drugs considered. A 'prototype' approach has been followed by describing the representative drug of a class followed by features by which individual members differ from it. Leading trade names have been included. Clinically relevant drug interactions have been mentioned. Clear-cut guidelines on selection of drugs and their clinical status have been outlined on the basis of current information. Original, simple and self-explanatory illustrations, tables and flowcharts have been used with impunity. Selected chemical structures are depicted. Recent developments have been incorporated. However, discretion has been used in including only few of the multitude of new drugs not yet available in India. This is based on their likelihood of being marketed soon. The information and views have been arranged in an orderly sequence of distinct statements.

I hope this manageable volume book would serve to dispel awe towards pharmacology from the minds of medical students and provide a concise and uptodate information source for prescribers who wish to remain informed of the current concepts and developments concerning drugs.

My sincere thanks are due to my colleagues for their valuable comments and suggestions.

New Delhi
1st Jan., 1985

KD Tripathi

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List of Abbreviations

AA	Amino acid
Ab	Antibody
ABC	ATP-binding cassette (transporter)
ABLC	Amphotericin B lipid complex
AC	Adenylyl cyclase
ACE	Angiotensin II converting enzyme
ACh	Acetylcholine
AChE	Acetylcholinesterase
ACS	Acute coronary syndromes
ACT	Artemisinin-based combination therapy
ACTH	Adrenocorticotropic hormone
AD	Alzheimer's disease
ADCC	Antibody-dependent cellular cytotoxicity
ADE	Adverse drug event
ADH	Antidiuretic hormone
ADHD	Attention deficit hyperactivity disorder
ADP	Adenosine diphosphate
Adr	Adrenaline
ADR	Adverse drug reaction
ADS	Anti diphtheritic serum
AES	Atrial extrasystole
AF	Atrial fibrillation
AFl	Atrial flutter
AG	Antigen
AGS	Antigasgangrene serum
AHG	Antihaemophilic globulin
AI	Aromatase inhibitor
AIDS	Acquired immunodeficiency syndrome
AIP	Aldosterone induced protein
ALA	Alanine
ALS	Amyotrophic lateral sclerosis
Am	Amikacin
AMA	Antimicrobial agent
AMB	Amphotericin B
amp	Ampoule
AMP	Adenosine mono phosphate
AMPA	α-Aminohydroxy methylisoxazole propionic acid
ANC	Acid neutralizing capacity
Ang-I/II/III	Angiotensin I/II/III
ANP	Atrial natriuretic peptide
ANS	Autonomic nervous system
ANUG	Acute necrotizing ulcerative gingivitis
AP	Action potential
AP-1	Activator protein-1
APC	Antigen presenting cell
APD	Action potential duration
aPTT	Activated partial thromboplastin time
AQ	Amodiaquine
AR	Androgen receptor
ARB	Angiotensin receptor blocker
ARC	AIDS related complex
ARS	Anti rabies serum
ART	Antiretrovirus therapy
ARV	Antiretrovirus (drug)
AS	Artesunate
5-ASA	5-Amino salicyclic acid
ASCVD	Atherosclerotic cardiovascular disease
AT-III	Antithrombin III
ATG	Antithymocyte globulin
ATP	Adenosine triphosphate
ATPase	Adenosine triphosphatase
ATPIII	Adult treatment panel III
ATS	Antitetanic serum
AUC	Area under the plasma concentration-time curve
A-V	Atrioventricular
AVP	Arginine vasopressin
AZT	Zidovudine
BAL	British anti lewisite
BAN	British approved name
BB	Borderline leprosy
BBB	Blood-brain barrier
BCG	Bacillus Calmette Guérin
BCNU	Bischloroethyl nitrosourea (Carmustine)
BCRP	Breast cancer resistance protein
BD	Twice daily
β-ARK	β adrenergic receptor kinase
BHC	Benzene hexachloride
BHP	Benign hypertrophy of prostate
BI	Bacillary index
BL	Borderline lepromatous leprosy
BMD	Bone mineral density
BMR	Basal metabolic rate
BNP	Brain nartriuretic peptide
BOL	2-Bromolysergic acid diethylamide
BP	Blood pressure
BPN	Bisphosphonate
BSA	Body surface area
BT	Borderline tuberculoid leprosy
BuChE	Butyryl cholinesterase
BW	Body weight
BZD	Benzodiazepine
C-10	Decamethonium
CA	Catecholamine
CAB	Combined androgen blockade
CaBP	Calcium binding protein
CAD	Coronary artery disease

CAM	Calmodulin
cAMP	3', 5' Cyclic adenosine monophosphate
CAP	Community acquired pneumonia
cap	Capsule
CAse	Carbonic anhydrase
CAT	Computerized axial tomography
CBF	Cerebral blood flow
CBG	Cortisol binding globulin
CBS	Colloidal bismuth subcitrate
CCB	Calcium channel blocker
CCNU	Chloroethyl cyclohexyl nitrosourea (lomustine)
CCR5	Chemokine coreceptor 5
CD	Collecting duct/Cluster of differentiation
CDC	Complement dependent cytotoxicity
CFTR	Cystic fibrosis transport regulator
cGMP	3', 5' Cyclic guanosine monophosphate
CGRP	Calcitonin gene related peptide
CH	Cholesterol
ChE	Cholinesterase
CHE	Cholesterol ester
CHF	Congestive heart failure
Chy	Chylomicron
Chy. rem.	Chylomicron remnants
CI	Cardiac index
CINV	Chemotherapy induced nausea and vomiting
CKD	Chronic kidney disease
CL	Clearance
CLcr	Creatinine clearance
Cm	Capreomycin
CMI	Cell mediated immunity
CMV	Cytomegalovirus
CNS	Central nervous system
c.o.	Cardiac output
CoEn-A	Coenzyme-A
COMT	Catechol-O-methyl transferase
COX	Cyclooxygenase
c.p.s.	Cycles per second
CPS	Complex partial seizures
CPZ	Chlorpromazine
CQ	Chloroquine
CRABP	Cellular retinoic acid binding protein
CRBP	Cellular retinol binding protein
CrD	Crohn's disease
CREB	Cyclic AMP response element binding protein
CRF	Corticotropin releasing factor
CS	Cycloserine
CSF	Cerebrospinal fluid
CTL	Cytotoxic T-lymphocytes
CTZ	Chemoreceptor trigger zone
CV	Cardiovascular
CVP	Central venous pressure
CVS	Cardiovascular system
CWD	Cell wall deficient
CYP450	Cytochrome P450
DA	Dopamine
DA-B_{12}	Deoxyadenosyl cobalamin
DAD	Delayed after-depolarization
DAG	Diacyl glycerol
DAM	Diacetyl monoxime
DAMP	Diphenyl acetoxy-N-methyl piperidine methiodide
DAT	Dopamine transporter
dDAVP	Desmopressin
DDS	Diamino diphenyl sulfone (Dapsone)
DDT	Dichloro diphenyl trichloroethane
DEC	Diethyl carbamazine citrate
DHA	Dihydroartemisinin
DHE	Dihydroergotamine
DHFA	Dihydro folic acid
DHFRase	Dihydrofolate reductase
DHP	Dihydropyridine
DHT	Dihydrotestosterone
DI	Diabetes insipidus
DIT	Diiodotyrosine
dl	Decilitre
DLE	Disseminated lupus erythematosus
DMA	Dimethoxy amphetamine
DMARD	Disease modifying antirheumatic drug
DMCM	Dimethoxyethyl-carbomethoxy-β-carboline
DMPA	Depot medroxyprogesterone acetate
DMPP	Dimethyl phenyl piperazinium
DMT	Dimethyl tryptamine/Divalent metal transporter
DNA	Deoxyribose nucleic acid
DOC	Deoxycholate
DOCA	Desoxy corticosterone acetate
DOM	Dimethoxymethyl amphetamine
dopa	Dihydroxyphenyl alanine
DOPAC	3, 4, Dihydroxyphenyl acetic acid
DOSS	Dioctyl sulfosuccinate
DOTS	Directly observed treatment short course
DPD	Dihydropyrimidine dehydrogenase
DPP-4	Dipeptidyl peptidase-4
DPT	Diphtheria-pertussis-tetanus triple antigen
DRC	Dose-response curve
DRI	Direct renin inhibitor
DST	Drug sensitivity testing (for TB)
DT	Distal tubule
DT-DA	Diphtheria-tetanus double antigen
d-TC	d-Tubocurarine
DTIC	Dacarbazine
DTPA	Diethylene triamine pentaacetic acid
DVT	Deep vein thrombosis
DYN	Dynorphin
E	Ethambutol
EACA	Epsilon amino caproic acid
EAD	Early after-depolarization
ECE	Endothelin converting enzyme
e.c.f.	Extracellular fluid
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
ED	Erectile dysfunction

EDRF	Endothelium dependent relaxing factor
EDTA	Ethylene diamine tetraacetic acid
EEG	Electroencephalogram
EF	Ejection fraction
EGF	Epidermal growth factor
ELAM-1	Endothelial leukocyte adhesion molecule-1
β-END	β-Endorphin
eNOS	Endothelial nitric oxide synthase
ENS	Enteric nervous system
ENT	Extraneuronal amine transporter
EPAC	cAMP regulated guanine nucleotide exchange factors
EPEC	Enteropathogenic *E. coli*
EPO	Erythropoietin
EPP	End plate potential
EPSP	Excitatory postsynaptic potential
ER	Estrogen receptor
ERA	Endothelin receptor antagonist
ERP	Effective refractory period
ES	Extrasystole
ESR	Erythrocyte sedimentation rate
ET	Endothelin
ETEC	Enterotoxigenic *E. coli*
Eto	Ethionamide
FA	Folic acid
FAD	Flavin adenine dinucleotide
5-FC	5-Flucytosine
FDC	Fixed dose combination
FDT	Fixed duration therapy (of leprosy)
FEV_1	Forced expiratory volume in 1 second
FFA	Free fatty acid
FKBP	FK 506 (tacrolimus) binding protein
FLAP	Five-lipoxygenase activating protein
FMN	Favin mononucleotide
FP	Ferroportin
FQ	Fluoroquinolone
FRase	Folate reductase
FSH	Follicle stimulating hormone
5-FU	5-Fluorouracil
G	Genetic
GABA	Gamma amino butyric acid
GAT	GABA-transporter
GC	Guanylyl cyclase
GCP	Good clinical practice
G-CSF	Granulocyte colony stimulating factor
GDP	Guanosine diphosphate
GERD	Gastroesophageal reflux disease
g.f.	Glomerular filtration
g.f.r.	Glomerular filtration rate
GH	Growth hormone
GHRH	Growth hormone releasing hormone
GHRIH	Growth hormone release inhibitory hormone
GIP	Gastric inhibitory peptide/Glucose-dependent insulinotropic polypeptide
g.i.t.	Gastrointestinal tract
GITS	Gastrointestinal therapeutic system
GLP	Glucagon-like peptide
GLUT	Glucose transporter
GM-CSF	Granulocyte macrophage colony stimulating factor
GnRH	Gonadotropin releasing hormone
GPCR	G-protein coupled receptor
G-6-PD	Glucose-6-phosphate dehydrogenase
GPI	Globus pallidus interna
GST	Glutathione-S-transferase
GTCS	Generalised tonic-clonic seizures
GTN	Glyceryl trinitrate
GTP	Guanosine triphosphate
H	Isoniazid (Isonicotinic acid hydrazide)
HAP	Hospital acquired pneumonia
Hb	Haemoglobin
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDCV	Human diploid cell vaccine
HDL	High density lipoprotein
HETE	Hydroxyeicosa tetraenoic acid
5-HIAA	5-Hydroxyindole acetic acid
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HMG-CoA	Hydroxymethyl glutaryl coenzyme A
HMW	High molecular weight
HPA axis	Hypothalamo-pituitary-adrenal axis
HPETE	Hydroperoxy eicosatetraenoic acid
hr	Hour
HR	Heart rate
HRIG	Human rabies immuneglobulin
HRT	Hormone replacement therapy
5-HT	5-Hydroxytryptamine
5-HTP	5-Hydroxytryptophan
HVA	Homovanillic acid
I	Indeterminate leprosy
IAP	Islet amyloid polypeptide
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
ICAM-1	Intracellular adhesion molecule-1
ICSH	Interstitial cell stimulating hormone
i.d.	Intradermal (injection)
IDL	Intermediate density lipoprotein
IFN	Interferon
IG	Immuneglobulin
IGF	Insulin-like growth factor
IL	Interleukin
ILEU	Isoleucine
i.m.	Intramuscular
INH	Isonicotinic acid hydrazide
INR	International normalized ratio
i.o.t.	Intraocular tension
IP_3	Inositol trisphosphate
IP_4	Inositol tetrakisphosphate
IPSP	Inhibitory postsynaptic potential

IPV	Inactivated poliomyelitis vaccine
IRS	Insulin response substrate
ISA	Intrinsic sympathomimetic activity
ISH	Isolated systolic hypertension
IU	International unit
IUCD	Intrauterine contraceptive device
i.v.	Intravenous
JAK	Janus-kinase
Km	Kanamycin
KTZ	Ketoconazole
LA	Local anaesthetic
LCAT	Lecithin cholesterol acyl transferase
LC3-KAT	Long chain 3-ketoacyl-CoA-thiolase
LDL	Low density lipoprotein
LES	Lower esophageal sphincter
leu-ENK	Leucine enkephalin
LH	Luteinizing hormone
liq	Liquid
LL	Lepromatous leprosy
LMW	Low molecular weight
LOX	Lipoxygenase
LSD	Lysergic acid diethylamide
LT	Leukotriene
LVF	Left ventricular failure
MAbs	Monoclonal antibodies
MAC	Minimal alveolar concentration
MAC	*Mycobacterium avium* complex
MAO	Monoamine oxidase
MAP	Muscle action potential
MAPKinase	Mitogen activated protein kinase
max	Maximum
MBC	Minimum bactericidal concentration
MBL	Multibacillary leprosy
MCI	Mild cognitive impairment
MDI	Manic depressive illness
MDMA	Methylene dioxy methamphetamine
MDR	Multidrug resistant
MDT	Multidrug therapy (of leprosy)
met-ENK	Methionine enkephalin
mEq	milliequivalent
methyl B_{12}	Methyl cobalamin
Mf	Microfilariae
MF	Multifactorial
MHC	Major histocompatibility complex
MHT	Methylene dioxy methamphetamine
MI	Myocardial infarction
MIC	Minimal inhibitory concentration
MIF	Migration inhibitory factor
min	Minimum
MIT	Monoiodo tyrosine
MLCK	Myosin light chain kinase
MMF	Mycophenolate mofetil
6-MP	6-Mercaptopurine
MPPT	Methylprednisolone pulse therapy
MPTP	4-methyl-4-phenyltetrahydro pyridine
MQ	Mefloquine
MRP2	Multidrug resistance associated protein-2
MRSA	Methicillin resistant *Staphylococcus aureus*
MSH	Melanocyte stimulating hormone
mTOR	Mammalian target of rapamycin
Mtx	Methotrexate
mV	millivolt
MW	Molecular weight
NA	Noradrenaline
NABQI	N-acetyl-p-benzoquinoneimine
NADP	Nicotinamide adenine dinucleotide phosphate
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NAG	N-acetyl glucosamine
NAM	N-acetyl muramic acid
NANC	Nonadrenergic noncholinergic
NAPA	N-acetyl procainamide
NaSSA	Noradrenergic and specific serotonergic antidepressant
NAT	N-acetyl transferase
NCEP	National cholesterol education programme
NEE	Norethindrone enanthate
NEP	Neutral endopeptidase (Neprolysin)
NET	Norepinephrine transporter
NFAT	Nuclear factor of activated T-cell
NFκB	Nuclear factor κB
NICE	National Institute for Health and Care Excellence (UK)
NIS	Na^+ (sodium)-iodide symporter
NLEP	National leprosy eradication programme
NMDA	N-methyl-D-aspartate
nNOS	Neural nitric oxide synthase
NNRTI	Nonnucleoside reverse transcriptase inhibitor
NPY	Neuropeptide-Y
NR	Nicotinic receptor
N-REM	Non rapid eye movement (sleep)
NRTI	Nucleoside reverse transcriptase inhibitor
NSAID	Nonsteroidal antiinflammatory drug
NSTEMI	Non ST-segment elevation myocardial infarction
NTS	Nucleus tractus solitarius
NVBDCP	National vector borne diseases control programme
NYHA	New York Heart Association
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OC	Oral contraceptive
OCD	Obsessive-compulsive disorder
OCT	Organic cation transporter
OD	Once daily
OPG	Osteoprotegerin
OPV	Oral poliomyelitis vaccine
ORS	Oral rehydration salt (solution)
ORT	Oral rehydration therapy
PABA	Paraamino benzoic acid
PAE	Post antibiotic effect
PAF	Platelet activating factor

PAH	Pulmonary arterial hypertension
PAI-1	Plasminogen activator inhibitor-1
2-PAM	Pralidoxime
PAN	Primary afferent neurone
PAS	Paraamino salicylic acid
PBI	Protein bound iodine
PBL	Paucibacillary leprosy
PBPs	Penicillin binding proteins
PCA	Patient controlled anaesthesia
PCEV	Purified chick embryo cell vaccine (rabies)
PCI	Percutaneous coronary intervention
PCPA	Parachloro phenylalanine
PD	Parkinsons's disease
PDE	Phosphodiesterase
PE	Pulmonary embolism
PEMA	Phenylethyl malonamide
PEP	Postexposure prophylaxis
PF	Purkinje fibre
PFOR	Pyruvate: ferredoxin oxidoreductase
PG	Prostaglandin
PGI_2	Prostacyclin
Pgp	P-glycoprotein
PI	Protease inhibitor
PIG	Phosphatidyl inositol glycan
PIP_2	Phosphatidyl inositol-4,5-bisphosphate
PKA	Protein kinase: cAMP dependent
PKC	Protein kinase C
PL_A	Phospholipase A
PL_C	Phospholipase C
Pl. ph.	Platelet phospholipid
pMDI	pressurized multidose inhaler
PnG	Penicillin G
POMC	Pro-opio melanocortin
PONV	Postoperative nausea and vomiting
PP	Partial pressure
PPARγ	Paroxysome proliferator-activated receptor γ
PPH	Post partum haemorrhage
PPI	Proton pump inhibitor
ppm	Part per million
PPNG	Penicillinase producing *N. gonorrhoeae*
PRA	Plasma renin activity
PrEP	Pre-exposure prophylaxis (of HIV)
PRF	Prolactin releasing factor
PRIH	Prolactin release inhibitory hormone
PSVT	Paroxysmal supra-ventricular tachycardia
PT	Proximal tubule
PTCA	Percutaneous transluminal coronary angioplasty
PTH	Parathyroid hormone
PTMA	Phenyl trimethyl ammonium
PTP	Post-tetanic potentiation
PTSD	Post-traumatic stress disorder
PTZ	Pentylenetetrazol
PUV A	Psoralen-Ultraviolet A
PVRV	Purified verocell rabies vaccine
QID	Four times a day
R	Rifampin (Rifampicin)
RANK	Receptor for activation of nuclear factor κB
RANKL	RANK ligand
RAS	Renin-angiotensin system
RBC	Red blood cells
RBP	Retinol binding protein
RC	Respiratory centre
RCT	Randomized clinical trial
RE	Reticuloendothelial
REM	Rapid eye movement (sleep)
RGS	Regulator of G-protein synthesis
RIG	Rabies immuneglobulin
RIMA	Reversible inhibitor of MAO-A
rINN	Recommended international nonproprietary name
RMP	Resting membrane potential
RNA	Ribonucleic acid
RNTCP	Revised National Tuberculosis Control Programme
RP	Refractory period
RTF	Resistance transfer factor
RTKs	Receptor tyrosine kinases
RXR	Retinoid X receptor
RyR	Ryanodine receptor
S	Streptomycin
SA	Sinoauricular (node)
SABE	Subacute bacterial endocarditis
s.c.	Subcutaneous
SCC	Short course chemotherapy (of tuberculosis)
SCh	Succinylcholine
SCID	Severe combined immunodeficiency disease
SERCA	Sarcoplasmic-endoplasmic reticular calcium ATPase
SERDs	Selective estrogen receptor down regulators
SERM	Selective estrogen receptor modulator
SERT	Serotonin transporter
SGA	Second generation antihistaminic
SGLT	Sodium-glucose transporter
SHBG	Sex hormone binding globulin
SIADH	Syndrome of inappropriate ADH secretion
s.l.	Sublingual
SLC	Solute carrier
SLE	Systemic lupus erythematosus
SMON	Subacute myelo-optic neuropathy
SNP	Single nucleotide polymorphism
SN-PC	Substantia nigra-pars compacta
SN-PR	Substantia nigra-pars reticularis
SNRI	Serotonin and noradrenaline reuptake inhibitor
s.o.s.	as required
S/P	Sulfonamide + pyrimethamine
SP	Substance P
SPF	Sun protection factor
SPRM	Selective progesterone receptor modulator
SPS	Simple partial seizures

SR	Sustained release
SRS-A	Slow reacting substance of anaphylaxis
SSG	Sodium stibogluconate
SSI	Surgical site infection
SSRIs	Selective serotonin reuptake inhibitors
STAT	Signal transducer and activator of transcription
STEMI	ST-segment elevation myocardial infarction
StK	Streptokinase
SU	Sulfonylurea
SULT	Sulfotransferase
SUR	Sulfonyl urea receptor
susp	Suspension
SVR	Sustained viral response
SWD	Shift work disorder
SWS	Slow wave sleep
syr	Syrup
t½	Half life
T_3	Triiodothyronine
T_4	Thyroxine
tab	Tablet
TAB	Typhoid, paratyphoid A and B vaccine
TAL	Thick ascending limb (loop of Henle)
TB	Tubercle bacilli
TBG	Thyroxine binding globulin
TCII	Transcobalamin II
TCAs	Tricyclic antidepressants
$TCID_{50}$	Tissue culture infectious dose 50%
TDM	Therapeutic drug monitoring
TDS	Three times a day
Tf	Transferrin
TG	Triglyceride
6-TG	6-Thioguanine
TGF-β	Transforming growth factor β
THC	Tetrahydrocannabinol
THFA	Tetrahydro folic acid
Thio TEPA	Triethylene thiophosphoramide
THR	Threonine
TIAs	Transient ischaemic attacks
TNF-α	Tumour necrosis factor α
TOD	Target organ damage
TOF	Train-of-four
t-PA	Tissue plasminogen activator
TPMT	Thiopurine methyl transferase
t.p.r.	Total peripheral resistance
TR	Thyroid hormone receptor
TRE	Thyroid hormone response element
TRH	Thyrotropin releasing hormone
TSH	Thyroid stimulating hormone
TT	Tuberculoid leprosy
TTS	Transdermal therapeutic system
TX	Thromboxane
U	Unit
UA	Unstable angina
UDP	Uridine diphosphate
UFH	Unfractionated heparin
UGDP	University group diabetic programme
UGT	UDP-glucuronosyl transferase
USAN	United States adopted name
UT	Urea transporter
UTI	Urinary tract infection
v	Volt
V	Volume of distribution
VAL	Valine
VAP	Ventilator associated pneumonia
VDR	Vit D receptor
VES	Ventricular extrasystole
VF	Ventricular fibrillation
VIP	Vasoactive intestinal peptide
Vit	Vitamin
VKOR	Vitamin K epoxide reductase
VL	Visceral leishmaniasis
VLDL	Very low density lipoprotein
VMA	Vanillyl mandelic acid
VMAT	Vesicular monoamine transporter
VRE	Vancomycin resistant enterococci
VRSA	Vancomycin resistant *Staphylococcus aureus*
VRUT	Vasopressin regulated urea transporter
VT	Ventricular tachycardia
VTE	Venous thromboembolism
vWF	von Willebrand factor
WBC	White blood cells
WCVs	Water channel containing vesicles
WHO	World Health Organization
WPW	Wolff-Parkinson-White syndrome
XDR-TB	Extensively drug resistant-TB
Z	Pyrazinamide
ZE (syndrome)	Zollinger-Ellison (syndrome)

SECTION 1

GENERAL PHARMACOLOGICAL PRINCIPLES

Chapter 1 Introduction, Routes of Drug Administration

INTRODUCTION

Pharmacology

Pharmacology is the science of drugs (Greek: *Pharmacon*—drug; *logos*—discourse in). In a broad sense, it deals with interaction of exogenously administered chemical molecules with living systems, and any single chemical substance which can produce a biological response is a 'drug'. Pharmacology encompasses all aspects of knowledge about drugs, but most importantly those that are relevant to effective and safe use of drugs for medicinal purposes.

For thousands of years most drugs were crude natural products of unknown composition and limited efficacy. Only the overt effects of these substances on the body were rather imprecisely known, but how the same were produced was entirely unknown. Animal experiments, primarily aimed at understanding physiological processes, were started in the 18th century. These were pioneered by F. Magendie and Claude Bernard, who also adapted them to study effects of certain drugs. Pharmacology as an experimental science was ushered by Rudolf Buchheim who founded the first institute of pharmacology in 1847 in Germany. In the later part of the 19th century, Oswald Schmiedeberg, regarded as the 'father of pharmacology', together with his many disciples like J Langley, T Frazer, P Ehrlich, AJ Clark, JJ Abel propounded some of the fundamental concepts in pharmacology. Since then drugs have been purified, chemically characterized and a vast variety of highly potent and selective new drugs have been developed. The mechanism of action including molecular target of many drugs has been elucidated. This has been possible due to prolific growth of pharmacology which forms the backbone of rational therapeutics.

The two main divisions of pharmacology are pharmacodynamics and pharmacokinetics.

Pharmacodynamics (Greek: *dynamis*—power)—What the drug does to the body.

This includes physiological and biochemical effects of drugs and their mechanism of action at organ system/subcellular/macromolecular levels, e.g.—Adrenaline → interaction with adrenoceptors → G-protein mediated stimulation of cell membrane bound adenylyl cyclase → increased intracellular cyclic 3′,5′AMP → cardiac stimulation, hepatic glycogenolysis and hyperglycaemia, etc.

Pharmacokinetics (Greek: *Kinesis*—movement)—What the body does to the drug.

This refers to movement of the drug in and alteration of the drug by the body; includes absorption, distribution, binding/localization/storage, biotransformation and excretion of the drug, e.g. paracetamol is rapidly and almost completely absorbed orally attaining peak blood levels at 30–60 min; 25% bound to plasma proteins,

widely and almost uniformly distributed in the body (volume of distribution ~ 1L/kg); extensively metabolized in the liver, primarily by glucuronide and sulfate conjugation into inactive metabolites which are excreted in urine; has a plasma half life ($t_{½}$) of 2–3 hours and a clearance value of 5 ml/kg/min.

Drug (French: *Drogue*—a dry herb) It is the *single active chemical entity present in a medicine that is used for diagnosis, prevention, treatment/cure of a disease.*

This disease oriented definition of drug does not include contraceptives or use of drugs for improvement of health. The WHO (1966) has given a more comprehensive definition—"*Drug is any substance or product that is used or is intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient.*"

The term 'drugs' is being also used to mean addictive/abused/illicit substances. However, this restricted and derogatory sense usage is unfortunate degradation of a time honoured term, and 'drug' should refer to a substance that has some health promoting/therapeutic/diagnostic application. Nevertheless, to avoid any misinterpretation, the term 'medicine' is being employed to designate such a substance in place of the term 'drug'.

Some other important aspects of pharmacology are:

Pharmacotherapeutics It is the application of pharmacological information together with knowledge of the disease for its prevention, mitigation or cure. Selection of the most appropriate drug, dosage and duration of treatment taking into account the stage of disease and the specific features of a patient are a part of pharmacotherapeutics.

Clinical pharmacology It is the scientific study of drugs (both old and new) in man. It includes pharmacodynamic and pharmacokinetic investigation in healthy volunteers as well as in patients. Evaluation of efficacy and safety of drugs and comparative trials with other forms of treatment; surveillance of patterns of drug use, adverse effects, etc. are also part of clinical pharmacology.

The aim of clinical pharmacology is to generate data for optimum use of drugs and the practice of 'evidence based medicine'.

Chemotherapy It is the treatment of systemic infection/malignancy with specific drugs that have selective toxicity for the infecting organism/malignant cell with no/minimal effects on the host cells.

Drugs in general, can thus be divided into:

Pharmacodynamic agents These are designed to have pharmacodynamic effects in the recipient.

Chemotherapeutic agents These are designed to inhibit/kill invading parasites/malignant cell, but have no/minimal pharmacodynamic effects in the recipient.

Pharmacy It is the art and science of compounding and dispensing drugs or preparing suitable dosage forms for administration of drugs to man or animals. It includes collection, identification, purification, isolation, synthesis, standardization and quality control of medicinal substances. The large scale manufacture of drugs is called *Pharmaceutics*, which is primarily a technological science.

Toxicology It is the study of poisonous effect of drugs and other chemicals (household, environmental pollutant, industrial, agricultural, homicidal) with emphasis on detection, prevention and treatment of poisonings. It also includes the study of adverse effects of drugs, since the same substance can be a drug or a poison, depending on the dose.

NATURE OF DRUGS

All drugs are chemical entities with simple or complex molecules. While majority are organic compounds, some are purely inorganic, like lithium carbonate, ferrous sulfate, magnesium hydroxide, etc. Organic drugs may be weakly

acidic (aspirin, penicillin) or weakly basic (morphine, chloroquine) or nonelectrolytes (alcohol, diethyl-ether). Most drugs are normally solids, e.g. paracetamol, propranolol, furosemide, ampicillin, etc., but some such as ethanol, glyceryl trinitrate, propofol, castor oil are liquids, and few like nitrous oxide are gaseous.

The molecular weight of majority of drugs falls in the range of 100-1000 D, because molecules smaller than 100 D do not generally have sufficiently specific features in terms of shape, size, configuration, chirality, distribution of charges, etc. to selectively bind to only one/ few closely related target biomolecules, to the exclusion of others. On the other hand, larger molecules than 1000 D do not readily pass through membranes/barriers in the body to reach the target sites in various tissues/cells. However, few drugs are as small as lithium ion (7D), and some like heparin (10-20 KD), gonadotropins (>30 KD), enzymes, proteins, antibodies (>50 KD) are much bigger. Bulky molecule drugs have to be administered parenterally.

Drugs are generally perceived to be chemical substances foreign to the body (Xenobiotics). However, many endogenous chemicals like hormones, autacoids, metabolites and nutrients are also used as drugs. Chemical congeners of these metabolites/signal molecules are an important class of drugs which act by modifying the synthesis, storage, degradation or action of these metabolites/signal molecules.

SOURCES OF DRUGS

Drugs are obtained from a variety of sources:

1. *Plants* Many plants contain biologically active substances and are the oldest source of drugs. Clues about medicinal plants were obtained from traditional systems of medicine prevalent in various parts of the world; e.g. use of opium, belladonna, ephedra, cinchona, curare, foxglove, sarpagandha, qinghaosu has been learnt from Egyptian, Greek, Aztec, Ayurvedic, Chinese and other systems of medicine. Chemically the active ingredients of plants fall in several categories:

   a. *Alkaloids:* These are alkaline nitrogenous bases having potent activity, and are the most important category of vegetable origin drugs. Prominent examples are: morphine, atropine, ephedrine, nicotine, ergotamine, reserpine, quinine, vincristine, etc. They are mostly used as their water soluble hydrochloride/ sulfate salts.

   b. *Glycosides:* These compounds consist of a heterocyclic nonsugar moiety (aglycone) linked to a sugar moiety through ether linkage. Cardiac glycosides (digoxin, ouabain) are the best known glycosidic drugs. The active principle of senna and similar plant purgatives are anthraquinone glycosides. Aminoglycosides (gentamicin, etc.) are antibiotics obtained from microorganisms, and have an aminosugar in place of a sugar moiety.

   c. *Oils:* These are viscous, inflammable liquids, insoluble in water. *Fixed* (nonvolatile) oils are calorie yielding triglycerides of higher fatty acids; mostly used for food and as emollients, e.g. groundnut oil, coconut oil, sesame oil, etc. Castor oil is a stimulant purgative. *Essential* (volatile) oils, mostly obtained from flowers or leaves by steam distillation are aromatic (fragrant) terpene hydrocarbons that have no food value. They are used as flavouring agents, carminatives, counterirritants and astringents; examples are eucalyptus oil, pepermint oil, nilgiri oil, etc. Clove oil is used to allay dental pain. Menthol, thymol, camphor are volatile oils that are solids at room temperature.

   Mineral oils are not plant products, but obtained from petroleum; liquid paraffin is a lubricant laxative, soft and hard paraffin are used as emollient and as ointment bases.

Other plant products like tanins are astringent; gums are demulcents and act as suspending agents in liquid dosage forms. Glycerine is a viscous, sweet liquid used as vehicle for gum/throat paint. Resins and balsams are used as antiseptic and in

cough mixtures. The antimalarial drug artemisinin is a sesquiterpene endoperoxide obtained from a Chinese plant.

2. *Animals* Though animal parts have been used as cures since early times, it was exploration of activity of organ extracts in the late 19th and early 20th century that led to introduction of animal products into medicine, e.g. adrenaline, thyroxine, insulin, liver extract (vit. B_{12}). Antisera and few vaccines are also produced from animals.
3. *Microbes* Most antibiotics are obtained from fungi, actinomycetes and bacteria, e.g. penicillin, gentamicin, tetracycline, erythromycin, polymyxin B, actinomycin D (anticancer). Some enzymes, e.g. diastase from a fungus and streptokinase from streptococci have a microbial source. Vaccines are produced by the use of microbes.
4. *Minerals* Few minerals, e.g. iron salts, calcium salts, lithium carbonate, magnesium/aluminium hydroxide, iodine are used as medicinal substances.
5. *Synthetic chemistry* Synthetic chemistry made its debut in the 19th century, and is now the largest source of medicines. Synthetic drugs have the advantage of purity and uniformity of the product. They can be manufactured in any quantity as per need, in contrast to drugs from natural sources whose availability may be limited. Not only diverse congeners of naturally obtained drugs (atropine substitutes, adrenergic β_2 agonists, synthetic glucocorticoids/progestins/cephalosporins, etc.) have been introduced to achieve greater selectivity of action or even novel type of activity, but many entirely synthetic families of drugs, e.g. benzodiazepines, thiazides, benzimidazoles, fluoroquinolones, etc. have been produced. Many drugs are being synthesized to target specific biomolecules, e.g. ACE inhibitors, glycoprotein IIb/IIIa receptor antagonists, HIV-reverse transcriptase inhibitors, etc. Synthetic drugs that are chiral can also be produced as single active enantiomer products, which may be therapeutically superior.
6. *Biotechnology* Several drugs, especially peptides and proteins are now produced by recombinant DNA technology, e.g. human growth hormone, human insulin, altaplase, interferon, etc. Monoclonal antibodies, regulator peptides, erythropoietin and other growth factors are the newer drugs of biotechnological origin. Protein therapeutics is rapidly expanding, because specifically designed and customized proteins can now be produced.

DRUG NOMENCLATURE

A drug generally has three categories of names:

(a) *Chemical name* It describes the substance chemically, e.g. 1-(Isopropylamino)-3-(1-naphthyloxy) propan-2-ol for propranolol. This is cumbersome and not suitable for use in prescribing. A *code name,* e.g. RO 15-1788 (later named flumazenil) may be assigned by the manufacturer for convenience and simplicity before an approved name is coined.

(b) *Non-proprietary name* It is the name accepted by a competent scientific body/authority, e.g. the United States Adopted Name (USAN) by the USAN council. Similarly, there is the British Approved name (BAN) of a drug. The non-proprietary names of newer drugs are kept uniform by an agreement to use the Recommended International Nonproprietary Name (rINN) in all member countries of the WHO. The BAN of older drugs as well has now been modified to be commensurate with rINN. However, many older drugs still have more than one non-proprietary names, e.g. 'meperidine' and 'pethidine' or 'lidocaine' and 'lignocaine' for the same drugs. Until the drug is included in a pharmacopoeia, the nonproprietary name may also be called the *approved name*. After its appearance in the official publication, it becomes the *official name*.

In common parlance, the term *generic name* is used in place of nonproprietary name. Etymologically this is incorrect: 'generic'

should be applied to the chemical or pharmacological group (or genus) of the compound, e.g. phenothiazines, tricyclic antidepressants, aminoglycoside antibiotics, etc. However, this misnomer is widely accepted and used even in official parlance.

(c) *Proprietary (Brand) name* It is the name assigned by the manufacturer(s) and is his property or trade mark. One drug may have multiple proprietary names, e.g. AMCARD, AMLOGARD, AMLOCOR, AMLONG, AMLOPIN, AMLOVAS, STAMLO for amlodipine from different manufacturers. Brand names are designed to be catchy, short, easy to remember and often suggestive, e.g. LOPRESOR suggesting drug for lowering blood pressure. Brand names generally differ in different countries, e.g. timolol maleate eye drops are marketed as TIMOPTIC in USA but as GLUCOMOL in India. Even the same manufacturer may market the same drug under different brand names in different countries. In addition, combined formulations have their own multiple brand names. This is responsible for much confusion in drug nomenclature.

There are many arguments for using the nonproprietary name in prescribing: uniformity, convenience, economy and better comprehension (propranolol, sotalol, timolol, pindolol, metoprolol, acebutolol, atenolol are all β blockers, but their brand names have no such similarity). Drugs marketed under nonproprietary name (called generic products) are much cheaper than their branded counterparts, partly because the manufacturer invests a lot of money in promoting the brand name. However, when a drug is prescribed by the generic name, the chemist is free to dispense the generic product from any manufacturer, but not so when the drug is prescribed by a brand name. Thus, when it is important to ensure consistency of the product in terms of quality and bioavailability, etc. and especially when official control over quality of manufactured products is not rigorous, it is better to prescribe by the dependable brand name.

DRUG COMPENDIA

These are compilations of information on drugs in the form of monographs; without going into the theoretical concepts, mechanisms of action and other aspects which help in understanding the subject. *Pharmacopoeias* and *Formularies* are broughtout by the Government in a country, hold legal status and are called official compendia. In addition, some non-official compendia are published by professional bodies, which are supplementary and dependable sources of information about drugs.

Pharmacopoeias They contain description of chemical structure, molecular weight, physical and chemical characteristics, solubility, identification and assay methods, standards of purity, storage conditions and dosage forms of officially approved drugs in a country. They are useful to drug manufacturers and regulatory authorities, but not to doctors, most of whom never see a pharmacopoeia. Examples are Indian (IP), British (BP), European (Eur P), United States (USP) pharmacopoeias.

Formularies Generally produced in easily carried booklet form, they list indications, dose, dosage forms, contraindications, precautions, adverse effects and storage of selected drugs that are available for medicinal use in a country. Drugs are categorized by their therapeutic class. Some rational fixed-dose drug combinations are included. A brief commentary on the drug class and clinical conditions in which they are used generally precedes specifics of individual drugs. Brief guidelines for treatment of selected conditions are provided. While British National Formulary (BNF) also lists brand names with costs, the National Formulary of India (NFI) does not include these. Most formularies have informative appendices as well. Formularies can be considerably helpful to prescribers.

Martindale: The Complete Drug Reference (Extrapharmacopoeia) Published every 2–3 years by the Royal Pharmaceutical Society of Great Britain, this non-official compendium is

an exhaustive and updated compilation of unbiased information on medicines used/registered all over the world. It includes new launches and contains pharmaceutical, pharmacological as well as therapeutic information on drugs, which can serve as a reliable reference book.

Physicians Desk Reference (PDR) and *Drug: Facts and Comparisons* (both from USA), etc. are other useful non-official compendia.

ESSENTIAL MEDICINES (DRUGS) CONCEPT

The WHO has defined *Essential Medicines (drugs)* as "those that satisfy the priority healthcare needs of the population." They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times and in adequate amounts, in appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford.

It has been realized that only a handful of medicines out of the multitude available can meet the health care needs of majority of the people in any country, and that many well tested and cheaper medicines are equally (or more) efficacious and safe as their newer more expensive congeners. For optimum utilization of resources, governments (especially in developing countries) should concentrate on these medicines by identifying them as *Essential medicines*. The WHO has laid down criteria to guide selection of an essential medicine.*

(a) Adequate data on its efficacy and safety should be available from clinical studies.
(b) It should be available in a form in which quality, including bioavailability, and stability on storage can be assured.
(c) Its choice should depend upon pattern of prevalent diseases; availability of facilities and trained personnel; financial resources; genetic, demographic and environmental factors.
(d) In case of two or more similar medicines, choice should be made on the basis of their relative efficacy, safety, quality, price and availability. Cost-benefit ratio should be a major consideration.
(e) Choice may also be influenced by comparative pharmacokinetic properties and local facilities for manufacture and storage.
(f) Most essential medicines should be single compounds. Fixed ratio combination products should be included only when dosage of each ingredient meets the requirements of a defined population group, and when the combination has a proven advantage in therapeutic effect, safety, adherence or in decreasing the emergence of drug resistance.
(g) Selection of essential medicines should be a continuous process which should take into account the changing priorities for public health action, epidemiological conditions as well as availability of better medicines/formulations and progress in pharmacological knowledge.
(h) Recently, it has been emphasized to select essential medicines based on rationally developed treatment guidelines.

To guide the member countries, the WHO brought out its first *Model List of Essential Drugs* along with their dosage forms and strengths in 1977 which could be adopted after suitable modifications according to local needs. This has been revised from time to time and the current is the 20th list (2017)[§] which has 433 medicines, including 25 fixed dose drug combinations (FDCs). India produced its *National Essential Drugs List* in 1996, and has revised it in 2011, and now in 2015 with the title *"National List of Essential Medicines"*.[£] The latest list includes 376 medicines, of which 20 are FDCs. These medicines have been marked into 3 categories for being available at primary, secondary and tertiary levels of health care facility.

Adoption of the essential medicines list for procurement and supply of medicines, especially in the public sector healthcare system, has resulted in improved availability of medicines, cost saving and more rational use of drugs.

*The use of Essential Drugs (including the 8th model list of essential drugs); WHO Technical report series 850, 1995, Geneva.
[§]www.who.int>20th—essential med-list (pub. 6 Jun 2017).
[£]National list of Essential Medicines (2015) [http//www.cdsco.nic.in]

Prescription and non-prescription drugs

As per drug rules, majority of drugs including all antibiotics must be sold in retail only against a prescription issued to a patient by a registered medical practitioner. These are called 'prescription drugs', and in India they have been placed in the *schedule H* of the Drugs and Cosmetic Rules (1945) as amended from time to time. However, few drugs like simple analgesics (paracetamol aspirin), antacids, laxatives (senna, lactulose), vitamins, ferrous salts, etc. are considered relatively harmless, and can be procured without a prescription. These are 'non-prescription' or 'over-the-counter' (OTC) drugs; can be sold even by grocery stores.

Orphan Drugs These are drugs or biological products for diagnosis/treatment/ prevention of a rare disease or condition, or a more common disease (endemic only in resource poor countries or areas) for which there is no reasonable expectation that the cost of developing and marketing it will be recovered from the sales of that drug. As per Orphan Drug Amendment (1983) Act of USA, a rare disease/ condition is one that affects less than 0.2 million people in the USA. Though these drugs may be life saving for some patients, they are commercially difficult to obtain as a medicinal product. Governments in developed countries offer tax benefits and other incentives to pharmaceutical companies for developing and marketing orphan drugs. Orphan drug status has been awarded to many drugs in the USA, Europe and some other countries. Few examples of drugs granted 'Orphan Drug' status are listed in the box.

Abridged list of Orphan drugs

Azacitidine	Icatibant
Bevacizumab	Iloprost
Bortezomib	Nilotinib
Busulfan	Paromomycin
Carboprost	Rifaximin
Clofazimine	Rituximab
Colchicine	Sodium stibogluconate
Eltrombopag	Sodium thiosulfate
Fomivirsen	ThioTEPA

DOSAGE FORMS OF DRUGS

Dosage form is a product suitable for administration of a drug to a patient. Every active ingredient (drug) has to be formulated by adding other substances (excipients, diluents, preservatives, vehicles, etc.) according to a specific recipe and packaged into a specific 'dosage form' such as tablet, elixir, ointment, injection vial, etc. which is then administered to the subject. The dosage form provides body to the drug, demarkates single doses, protects the active ingredient(s), and makes it suitable for administration in various ways. The important dosage forms are briefly described below.

Solid dosage forms

1. *Powders* The drug is in a dry and finely pulverised state. If the drug is for oral administration, each dose has to be wrapped separately or packed in sachets; therefore this dosage form is inconvenient and unpopular except when the quantity is several grams, e.g. oral rehydration salts. Powders for topical application (dusting powders) are supplied as *bulk powders* in metallic or plastic containers with holes for sprinkling. *Effervescent powders* contain granulated sod. bicarbonate and citric or tartaric acid. They react when dissolved in water to liberate CO_2 causing bubbling.
2. *Tablets* The drug is powdered or granulated, mixed with binding agents, and other excipients, and compressed/moulded into discoid, oblong or other shapes suitable for swallowing. The tablet may be plain or sugar coated or film coated. Other specialized types of tablets are:

   Chewable tablets—can be chewed and swallowed, ingredients must be pleasent tasting.

   Dispersible tablets—the tablet is dropped in a small quantity of water, wherein it disperses quickly; the solution is then gulped.

   Sublingual tablets—put under the tongue, the drug is rapidly absorbed from the mouth.

   Enteric coated tablet—the tablet is coated with a material that does not dissolve in the acidic medium of the stomach; the tablet disintegrates only on reaching the duodenum.

   Sustained/Extended release tablets—These contain drug particles which are coated to

dissolve at different rates. The active ingredient is made available for absorption over a longer period of time. The duration of action of short acting (2-6 hours) drugs can be extended to 12 hours or more.

Controlled release tablets—A semipermeable membrane controls the release of the drug – prolonging its duration of action.

3. *Pills* These are archaic dosage forms in which the drug powder is mixed with honey/syrup to make a sticky mass. This is then rolled into spherical/oval bodies meant to be swallowed. The term is often loosely applied to tablets as well.
4. *Capsules* These are water soluble cylindrical containers made of gelatin which are filled with powdered or liquid medicament. The container dissolves on swallowing so that the drug is released in the stomach. Soft gelatine capsules dissolve very rapidly and generally contain liquid medicament. *Enteric coated* capsules are designed to dissolve only on reaching the ileum. *Spansules* are extended release capsules which are packed with granules of the drug having different coatings to dissolve over a range of time periods.
5. *Lozenges* These are tablet-like bodies of various shapes containing the drug along with a suitable gum, sweetening and flavouring agents. They are to be retained in the mouth and allowed to dissolve slowly, providing the drug for local action in the mouth and throat.
6. *Suppositories* These are conical bullet- shaped dosage forms for insertion into the anal canal, in which the drug is mixed with a mouldable firm base that melts at body temperature and releases the contained drug. Oval or suitably shaped bodies for vaginal insertion are called '*pessaries*', while elongated pencil-like cones meant for insertion into male or female urethra are called *bougies*.

Liquid dosage forms

1. *Aqueous solutions* They contain the drug dissolved in water, and may be meant for oral, topical or parenteral administration. Oral drug solutions often contain sweetening and flavouring agents. Preservatives have to be mostly added because shelf-life of watery solutions is short.
2. *Suspensions* are dispersion of insoluble drugs in water with the help of a suspending agent. *Emulsions* are uniform mixtures of two immiscible liquids (mostly oil and water) in which droplets of one (dispersed phase) are suspended in the other (continuous phase) with the help of an amphiphilic emulsifying agent. Milk is a naturally occurring emulsion. Both suspensions and emulsions tend to settle down on keeping; should be shaken thoroughly before use.
3. *Elixirs* are hydro-alcoholic solutions of drugs, usually sweetened with syrup and flavoured by fruit extracts. *Syrups* have higher concentration of sugar and are thicker in consistency. Drugs that deteriorate in aqueous medium can be dispensed as '*dry syrups*' which is reconstituted by adding water and shaking. The reconstituted syrup must be used within a few days. *Linctus* is a viscous syrupy liquid meant to be licked slowly for soothing the throat. It generally has menthol to impart cooling sensation, and an antitussive.
4. *Drops* These are relatively more concentrated solutions of medicaments meant for oral ingestion or external application to eye, nose or ear canal. Oral drops are the preferred dosage form for infants and young children. Eye/nasal drops should be isotonic. Eye drops need sterilization. Drops are supplied in vials with a nozzle or alongwith a dropper for accurate dosing.
5. *Lotions* These are solutions, suspensions or emulsions meant for external application to the skin without rubbing. They generally have soothing, cooling, protective or emollient property and are better suited than creams or ointments for hairy skin. *Liniments* are similar preparations which generally contain counterirritants, and are to be rubbed on the skin to relieve pain and cause rubefaction.

6. *Injections* These are sterile solutions or suspensions in aqueous or oily medium for subcutaneous or intramuscular administration. Only aqueous solutions (not suspensions) are suitable for intravenous (i.v.) injection, because particles in suspension and oils injected i.v. can cause embolism. Injections are supplied in sealed glass *ampoules* or air tight rubber capped *vials*. Ampoules are broken just before injection, and usually contain a single dose. Drug from the vial is sucked in a syringe by piercing the rubber cap. Vials may be single or multi-dose. Drugs which are unstable in solution are supplied as dry powder vials. Sterile solvent is injected in the vial just before it is to be administered, and the dissolved/suspended drug is then sucked out into the syringe. Some drugs like insulin are also supplied in prefilled syringes and pen injectors. Large volume i.v. infusions are marketed in glass/polypropylene bottles.

Semisolid dosage forms

1. *Ointments* These are greasy semisolid preparations meant for external application to the skin, eye, nasal mucosa, ear or anal canal. The drug is incorporated in an oily base, such as soft or hard paraffin, wool fat, bee's wax, etc. Ointments are not suitable for oozing surfaces, because they are more occlusive and donot allow evaporation of water. Rather they are good for dry, chronic lesions. *Creams* are similar to ointment but the base is a water in oil emulsion. The medicament is better absorbed into the skin from creams than from ointments, and creams are cosmetically more acceptable than ointments.
2. *Pastes* These are nongreasy preparations of thick consistency containing hydrophilic adhesive powders such as starch, prepared chalk, aluminium/magnesium hydroxide, zinc oxide, carboxy methylcellulose, etc. which swell by absorbing water. Pastes may contain viscous nonoily liquids like glycerol or propylene glycol. Pastes can be applied to inflamed or excoriated skin, oozing surfaces and mucous membranes. Toothpastes are items of personal hygiene, and medicated toothpastes are extensively used in dentistry.
3. *Gels* The medicament is incorporated in a viscous colloidal solution of gelatin or similar material and is usually dispensed in collapsible tubes. They are meant for external application to the skin or mucosa and provide longer duration contact, but are nongreasy and washable with water. Gels are suitable for application to hairy skin, and are commonly applied to oral ulcers because they are better retained than aqueous solutions.

Inhalations

Drugs which are gases or volatile liquids can be administered by inhalation carried into air or oxygen with the help of a mouth piece, face mask, hood or endotracheal tube. Nonvolatile liquids and fine particle solids can be aerosolized using a metered dose inhaler, jet nebulizer, rotahaler or spinhaler for inhalation through the mouth. *Pressurized metered dose inhalers* (PMDIs) are hand-held devices which use a propellant, mostly hydrofluoroalkane (HFA), and deliver a specified dose of the drug in aerosol form per actuation. *Jet nebulizers* produce a mist of the drug solution generated by pressurized air or oxygen. *Rotahaler* is also a portable device in which a capsule (rotacap) containing very fine powder of the drug is punctured during actuation and the released particles are aerosolized by the inspiratory airflow of the patient. A propellant can also be used in some *spin halers*. Efficacy of the aerosolized drug depends on the particle size: 1–5 μm diameter particles deposit on the bronchioles and effectively deliver the drug. Larger particles settle on the oropharynx, while <1 μm particles donot settle anywhere and are exhaled out.

ROUTES OF DRUG ADMINISTRATION

Most drugs can be administered by a variety of routes. The choice of appropriate route in a given situation depends both on drug as well as patient related factors. Mostly common

sense considerations, feasibility and convenience dictate the route to be used.

Routes can be broadly divided into those for (*a*) Local action and (*b*) Systemic action.

Factors governing choice of route

1. Physical and chemical properties of the drug (solid/liquid/gas; solubility, stability, pH, irritancy).
2. Site of desired action—localized and approachable or generalized and not approachable.
3. Rate and extent of absorption of the drug from different routes.
4. Effect of digestive juices and first pass metabolism on the drug.
5. Rapidity with which the response is desired (routine treatment or emergency).
6. Accuracy of dosage required (i.v. and inhalational can provide fine tuning).
7. Condition of the patient (unconscious, vomiting).

LOCAL ROUTES

These routes can only be used for localized lesions at accessible sites and for drugs whose systemic absorption from these sites is minimal or absent. Thus, high concentrations are attained at the desired site without exposing the rest of the body. Systemic side effects or toxicity are consequently absent or minimal. For drugs (in suitable dosage forms) that are absorbed from these sites/routes, the same can serve as systemic route of administration, e.g. glyceryl trinitrate (GTN) applied on the skin as ointment or transdermal patch for angina pectoris. The local routes are:

1. **Topical** This refers to external application of the drug to the surface for localized action. It is often more convenient as well as reassuring to the patient. Drugs can be efficiently delivered to the localized lesions on skin, oropharyngeal/ nasal mucosa, eyes, ear canal, anal canal or vagina in the form of lotion, ointment, cream, powder, rinse, paints, drops, spray, lozengens, suppositories or pesseries. Nonabsorbable drugs given orally for action on g.i. mucosa (sucralfate, vancomycin), inhalation of drugs for action on bronchi (salbutamol, cromolyn sodium) and irrigating solutions/jellys (povidone iodine, lidocaine) applied to urethra are other forms of topical medication.

2. **Deeper tissues** Certain deep areas can be approached by using a syringe and needle, but the drug should be in such a form that systemic absorption is slow, e.g. intra-articular injection (hydrocortisone acetate in knee joint), infiltration around a nerve or intrathecal injection (lidocaine), retrobulbar injection (hydrocortisone acetate behind the eyeball).

3. **Arterial supply** Close intra-arterial injection is used for contrast media in angiography; anticancer drugs can be infused in femoral or brachial artery to localise the effect for limb malignancies.

SYSTEMIC ROUTES

The drug administered through systemic routes is intended to be absorbed into the blood stream and distributed all over, including the site of action, through circulation (*see* Fig. 1.1).

1. **Oral**

Oral ingestion is the oldest and commonest mode of drug administration. It is safer, more convenient, does not need assistance, noninvasive, often painless, the medicament need not be sterile and so is cheaper. Both solid dosage forms (powders, tablets, capsules, spansules, dragees, moulded tablets, gastrointestinal therapeutic systems—GITs) and liquid dosage forms (elixirs, syrups, emulsions, mixtures) can be given orally.

Limitations of oral route of administration

- Action of drugs is slower and thus not suitable for emergencies.
- Unpalatable drugs (chloramphenicol) are difficult to administer; drug may be filled in capsules to circumvent this.
- May cause nausea and vomiting.
- Cannot be used for uncooperative/unconscious/ vomiting patient.
- Absorption of the drug may be variable and erratic; certain drugs are not absorbed (streptomycin).
- Others are destroyed by digestive juices (penicillin G, insulin) or in liver (GTN, testosterone, lidocaine).

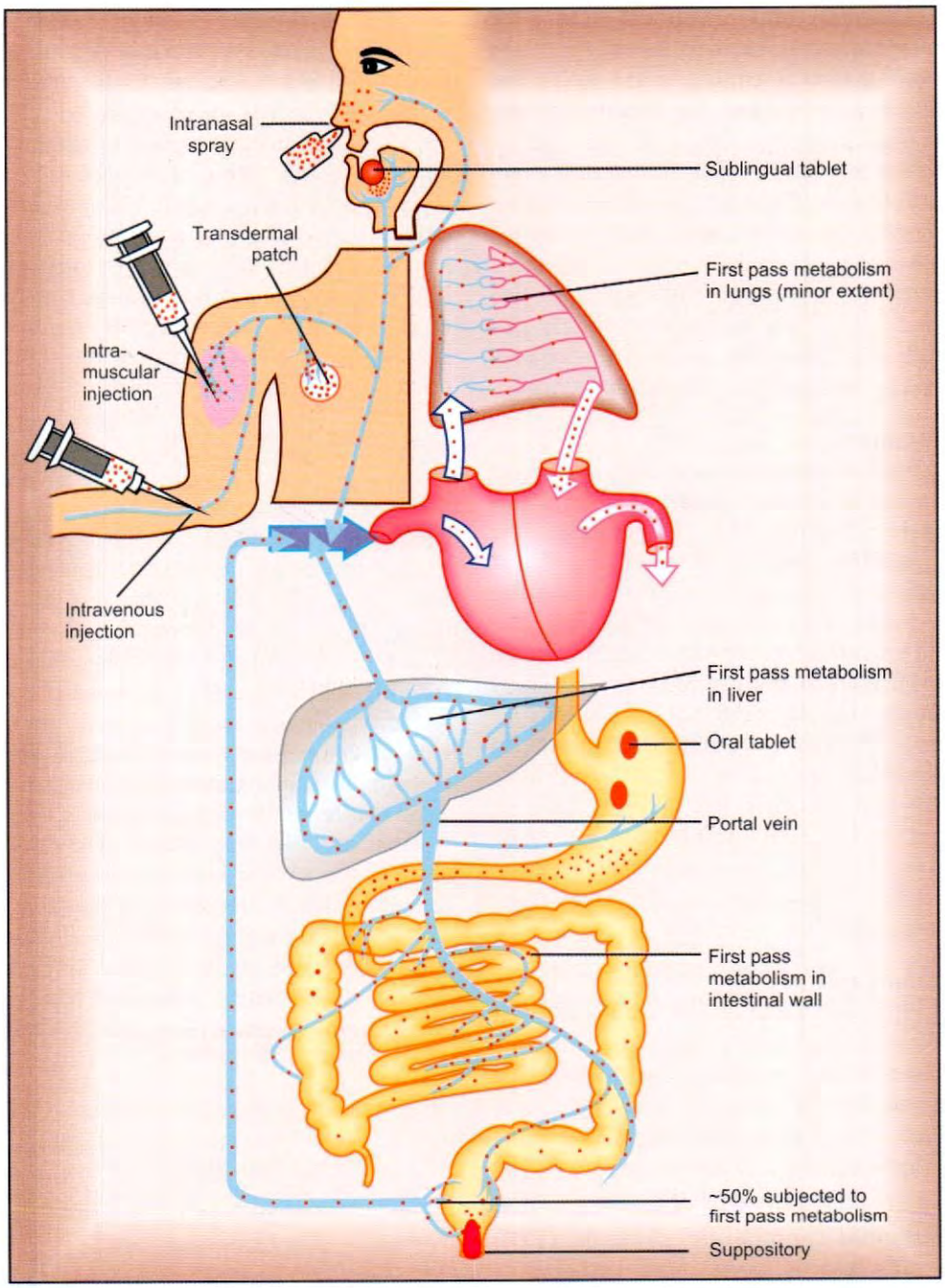


Fig. 1.1: Vascular pathway of drugs absorbed from various systemic routes of administration and sites of first pass metabolism

Note: Total drug absorbed orally is subjected to first pass metabolism in intestinal wall and liver, while approximately half of that absorbed from rectum passes through liver. Drug entering from any systemic route is exposed to first pass metabolism in lungs, but its extent is minor for most drugs.

2. Sublingual (s.l.) or buccal

The tablet or pellet containing the drug is placed under the tongue or crushed in the mouth and spread over the buccal mucosa. Only lipid soluble and non-irritating drugs can be so administered. Absorption is relatively rapid—action can be produced in minutes. Though it is somewhat inconvenient, one can spit the drug after the desired effect has been obtained. The chief advantage is that liver is bypassed and drugs with high first pass metabolism can be absorbed directly into systemic circulation. Drugs given sublingually are—GTN, buprenorphine, desamino-oxytocin.

3. Rectal

Certain irritant and unpleasant drugs can be put into rectum as suppositories or retention enema for systemic effect. This route can also be used when the patient is having recurrent vomiting or is unconscious. However, it is rather inconvenient and embarrassing; absorption is slower, irregular and often unpredictable, though diazepam solution and paracetamol suppository are rapidly and dependably absorbed from the rectum in children. Drug absorbed into external haemorrhoidal veins (about 50%) bypasses liver, but not that absorbed into internal haemorrhoidal veins. Rectal inflammation can result from irritant drugs. Diazepam, indomethacin, paracetamol, ergotamine and few other drugs are some times given rectally.

4. Cutaneous

Highly lipid soluble drugs can be applied over the skin for slow and prolonged absorption. The liver is also bypassed. The drug can be incorporated in an ointment and applied over specified area of skin. Absorption of the drug can be enhanced by rubbing the preparation, by using an oily base and by an occlusive dressing.

Transdermal therapeutic systems (TTS)

These are devices in the form of adhesive patches of various shapes and sizes (5–20 cm^2) which deliver the contained drug at a constant rate into systemic circulation via the stratum corneum (Fig. 1.2). The drug (in solution or bound to a polymer) is held in a reservoir between an occlusive backing film and a rate controlling micropore membrane, the under surface of which is smeared with an adhesive impregnated with priming dose of the drug. The adhesive layer is protected by another film that is to be peeled off just before application. The drug is delivered at the skin surface by diffusion for percutaneous absorption into circulation. The micropore membrane is such that rate of drug delivery to skin surface is less than the slowest rate of absorption from the skin. This offsets any variation in the rate of absorption according to the properties of different sites. As such, the drug is delivered at a constant and predictable rate irrespective of site of application. Usually chest, abdomen, upper arm, lower back, buttock or mastoid region are utilized.

Transdermal patches of GTN, fentanyl, nicotine and estradiol are available in India, while those of isosorbide dinitrate, hyoscine, and clonidine are marketed elsewhere. For different drugs, TTS have been designed to last for 1–3 days. Though more expensive, they provide smooth plasma concentrations of the drug without fluctuations; minimize interindividual variations (drug is subjected to little first pass metabolism) and side effects. They are also more convenient—many patients prefer transdermal patches to oral tablets of the same drug; patient compliance is better. Local irritation and erythema occurs in some subjects, but is generally mild; can be minimized by changing the site of application each time by rotation.

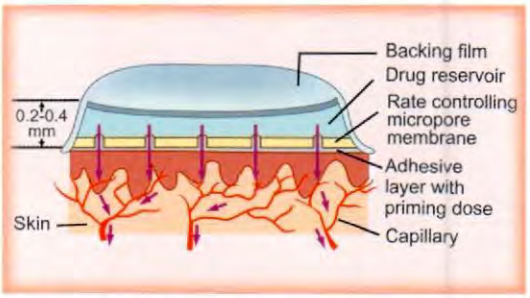


Fig. 1.2: Illustration of a transdermal drug delivery system

Discontinuation has been necessary in only 2–7% cases.

5. Inhalation

Volatile liquids and gases are given by inhalation for systemic action, e.g. general anaesthetics. Absorption takes place from the vast surface of alveoli—action is very rapid. When administration is discontinued the drug diffuses back and is rapidly eliminated in expired air. Thus, controlled administration is possible with moment to moment adjustment. Irritant vapours (ether) cause inflammation of respiratory tract and increase secretion.

6. Nasal

The mucous membrane of the nose can readily absorb many drugs; digestive juices and liver are bypassed. However, only certain drugs like GnRH agonists, calcitonin and desmopressin applied as a spray or nebulized solution have been used by this route. This route is being tried for some other peptide drugs like insulin, as well as to bypass the blood-brain barrier.

7. Parenteral

(*Par*—beyond, *enteral*—intestinal)

Conventionally, parenteral refers to administration by injection which takes the drug directly into the tissue fluid or blood without having to cross the enteral mucosa. The limitations of oral administration are circumvented.

Drug action is faster and surer (valuable in emergencies). Gastric irritation and vomiting are not provoked. Parenteral routes can be employed even in unconscious, uncooperative or vomiting patient. There are no chances of interference by food or digestive juices. Liver is bypassed.

Disadvantages of parenteral routes are—the preparation has to be sterilized and is costlier, the technique is invasive and painful, assistance of another person is mostly needed (though self injection is possible, e.g. insulin by diabetics), there are chances of local tissue injury and, in general, parenteral route is more risky than oral. The important parenteral routes are:

(i) Subcutaneous (s.c.) The drug is deposited in the loose subcutaneous tissue which is richly supplied by nerves (irritant drugs cannot be injected) but is less vascular (absorption is slower than intramuscular). Only small volumes can be injected s.c. Self-injection is possible because deep penetration is not needed. This route should be avoided in shock patients who are vasoconstricted—absorption will be delayed. Repository (depot) preparations that are aqueous suspensions can be injected for prolonged action. Some special forms of this route are:

(a) *Dermojet* In this method needle is not used; a high velocity jet of drug solution is projected from a microfine orifice using a gun like implement. The solution passes through the superficial layers and gets deposited in the subcutaneous tissue. It is essentially painless and suited for mass inoculations.

(b) *Pellet implantation* The drug in the form of a solid pellet is introduced with a trochar and cannula. This provides sustained release of the drug over weeks and months, e.g. DOCA, testosterone.

(c) *Sialistic (nonbiodegradable) and biodegradable implants* Crystalline drug is packed in tubes or capsules made of suitable materials and implanted under the skin. Slow and uniform leaching of the drug occurs over months providing constant blood levels. The nonbiodegradable implant has to be removed later on but not the biodegradable one. This has been tried for hormones and contraceptives (e.g. NORPLANT).

(ii) Intramuscular (i.m.) The drug is injected in one of the large skeletal muscles—deltoid, triceps, gluteus maximus, rectus femoris, etc. Muscle is less richly supplied with sensory nerves (mild irritants can be injected) and is more vascular (absorption of drugs in aqueous solution is faster). It is less painful, but self injection is often impracticable because deep penetration is needed. Depot preparations (oily solutions, aqueous suspensions) can be injected

by this route. Intramuscular injections should be avoided in anticoagulant treated patients, because it can produce local haematoma.

(iii) Intravenous (i.v.) The drug is injected as a bolus (Greek: *bolos*–lump) or infused slowly over hours in one of the superficial veins. The drug reaches directly into the blood stream and effects are produced immediately (great value in emergency). The intima of veins is insensitive and drug gets diluted with blood, therefore, even highly irritant drugs can be injected i.v., but hazards are—thrombophlebitis of the injected vein and necrosis of adjoining tissues if extravasation occurs. These complications can be minimized by diluting the drug or injecting it into a running i.v. line. Only aqueous solutions (not suspensions, because drug particles can cause embolism) are to be injected i.v. and there are no depot preparations for this route. Chances of causing air embolism is another risk. The dose of the drug required is smallest (bioavailability is 100%) and even large volumes can be infused. One big advantage with this route is—in case response is accurately measurable (e.g. BP) and the drug short acting (e.g. sodium nitroprusside), titration of the dose with the response is possible. However, this is the most risky route—vital organs like heart, brain, etc. get exposed to high concentrations of the drug.

(iv) Intradermal injection The drug is injected into the skin raising a bleb (e.g. BCG vaccine, sensitivity testing) or *scarring/multiple puncture* of the epidermis through a drop of the drug is done. This route is employed for specific purposes only.

☞ PROBLEM DIRECTED STUDY

1.1. A 5-year-old child is brought to the hospital with the complaint of fever, cough, breathlessness and chest pain. On examination he is found to be dull, but irritable with fast pulse (116/min), rapid breathing (RR 50/min) and indrawing of lower chest during inspiration, wheezing, crepitations and mild dehydration. Body temperature is 40°C (104°F). The paediatrician makes a provisional diagnosis of acute pneumonia and orders relevant haematological as well as bacteriological investigations. He decides to institute antibiotic therapy.

a. In case he selects an antibiotic which can be given orally as well as by i.m. or i.v. injection, which route of administration will be most appropriate in this case?
b. Should the paediatrician administer the antibiotic straight away or should he wait for the laboratory reports?

(see Appendix-1 for solution)

Chapter 2 Pharmacokinetics: Membrane Transport, Absorption and Distribution of Drugs

Pharmacokinetics is the quantitative study of drug movement in, through and out of the body. The overall scheme of pharmacokinetic processes is depicted in Fig. 2.1. The intensity of response is related to concentration of the drug at the site of action, which in turn is dependent on its pharmacokinetic properties. Pharmacokinetic considerations, therefore, determine the route(s) of administration, dose, latency of onset, time of peak action, duration of action and frequency of administration of a drug.

All pharmacokinetic processes involve transport of the drug across biological membranes.

Biological membrane This is a bilayer (about 100 Å thick) of phospholipid and cholesterol molecules, the polar groups (glyceryl phosphate attached to ethanolamine/choline or hydroxyl group of cholesterol) of these are oriented at the two surfaces and the nonpolar hydrocarbon chains are embedded in the matrix to form a continuous sheet. This imparts high electrical resistance and relative impermeability to the membrane.

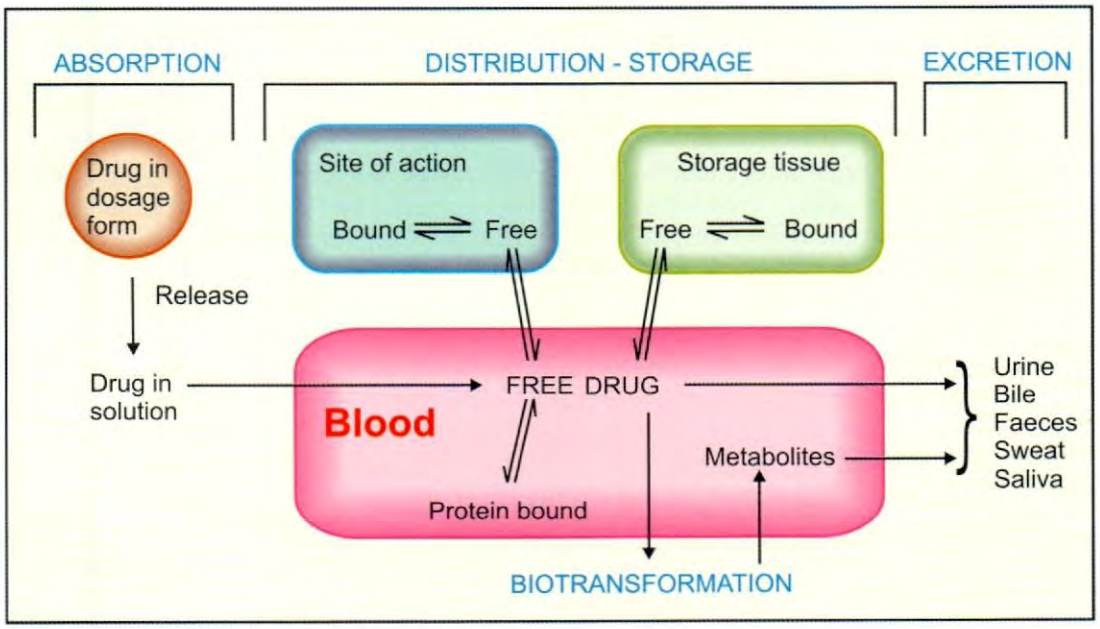


Fig. 2.1: Schematic depiction of pharmacokinetic processes

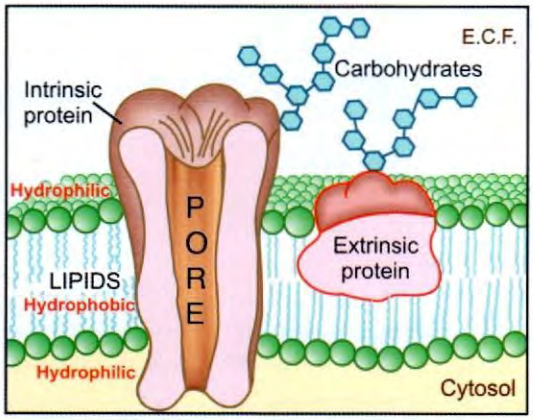


Fig. 2.2: Illustration of the organisation of biological membrane

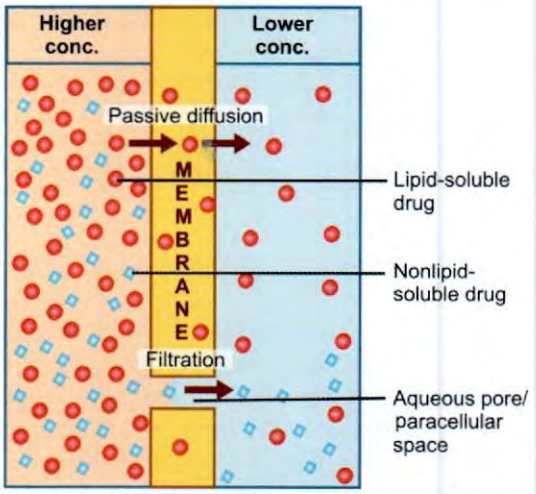


Fig. 2.3: Illustration of passive diffusion and filtration across the lipoidal biological membrane with aqueous pores

Extrinsic and intrinsic protein molecules are adsorbed on the lipid bilayer (Fig. 2.2). Glycoproteins or glycolipids are formed on the surface by attachment to polymeric sugars, aminosugars or sialic acids. The specific lipid and protein composition of different membranes differs according to the cell or the organelle type. The proteins are able to freely float through the membrane: associate and organize or vice versa. Some of the intrinsic ones, which extend through the full thickness of the membrane, surround fine aqueous pores. Paracellular spaces or channels also exist between certain epithelial/ endothelial cells. Other adsorbed proteins have enzymatic, carrier, receptor or signal transduction properties. Lipid molecules also are capable of lateral movement. Thus, biological membranes are highly dynamic structures.

Drugs are transported across the membranes by:

(a) Passive diffusion and filtration

(b) Specialized transport

Passive diffusion

The drug diffuses across the membrane in the direction of its concentration gradient (high to low), the membrane playing no active role in the process. This is the most important mechanism for majority of drugs; drugs are foreign substances (xenobiotics), and specialized mechanisms are developed by the body primarily for normal metabolites.

Lipid soluble drugs diffuse by dissolving in the lipoidal matrix of the membrane (Fig. 2.3), the rate of transport being proportional to the lipid : water partition coefficient of the drug. A more lipid-soluble drug attains higher concentration in the membrane and diffuses quickly. Also, greater the difference in the concentration of the drug on the two sides of the membrane, faster is its diffusion.

Influence of pH Most drugs are weak electrolytes, i.e. their ionization is pH dependent (contrast strong electrolytes that are nearly completely ionized at acidic as well as alkaline pH). The ionization of a weak acid HA is given by the equation:

$$pH = pKa + \log \frac{[A^-]}{[HA]} \quad ...(1)$$

pKa is the negative logarithm of acidic dissociation constant of the weak electrolyte. If the concentration of ionized drug $[A^-]$ is equal to concentration of unionized drug [HA], then

$$\frac{[A^-]}{[HA]} = 1$$

since log 1 is 0, under this condition

$$pH = pKa \quad ...(2)$$

SECTION 1

Thus, *pKa* is numerically equal to the pH at which the drug is 50% ionized.

If pH is increased by 1 scale, then—

$$\log [A^-]/[HA] = 1 \quad \text{or} \quad [A^-]/[HA] = 10$$

Similarly, if pH is reduced by 1 scale, then—

$$[A^-]/[HA] = 1/10$$

Thus, weakly acidic drugs, which form salts with cations, e.g. *sod.* phenobarbitone, *sod.* sulfadiazine, *pot.* penicillin-V, etc. ionize more at alkaline pH and 1 scale change in pH causes 10 fold change in ionization.

Weakly basic drugs, which form salts with anions, e.g. atropine *sulfate*, ephedrine *HCl*, chloroquine *phosphate*, etc. conversely ionize more at acidic pH. Ions being lipid insoluble, do not diffuse and a pH difference across a membrane can cause differential distribution of weakly acidic and weakly basic drugs on the two sides (Fig. 2.4).

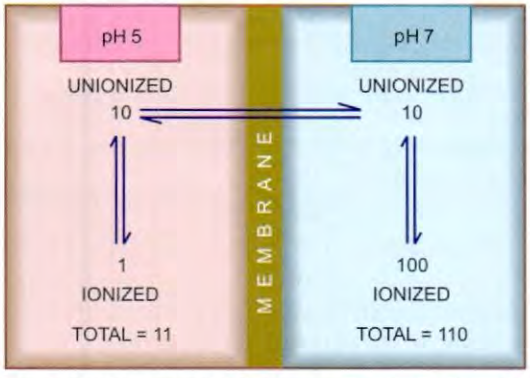


Fig. 2.4: Influence of pH difference on two sides of a biological membrane on the steady-state distribution of a weakly acidic drug with *pKa* = 6

Implications of this consideration are:

(a) Acidic drugs, e.g. aspirin (*pKa* 3.5) are largely unionized at acid gastric pH and are absorbed from stomach, while bases, e.g. atropine (*pKa* 10) are largely ionized and are absorbed only when they reach the intestines.

(b) The unionized form of acidic drugs which crosses the surface membrane of gastric mucosal cell, reverts to the ionized form within the cell (pH 7.0) and then only slowly passes to the extracellular fluid. This is called *ion trapping*, i.e. a weak electrolyte crossing a membrane to encounter a pH from which it is not able to escape easily. This may contribute to gastric mucosal cell damage caused by aspirin.

(c) Basic drugs attain higher concentration intracellularly (pH 7.0 *vs* 7.4 of plasma).

(d) Acidic drugs are ionized more in alkaline urine—do not back diffuse in the kidney tubules and are excreted faster. Accordingly, basic drugs are excreted faster if urine is acidified.

Lipid-soluble nonelectrolytes (e.g. ethanol, diethyl-ether) readily cross biological membranes and their transport is pH independent.

Filtration

Filtration is passage of drugs through aqueous pores in the membrane or through paracellular spaces. This can be accelerated if hydrodynamic flow of the solvent is occurring under hydrostatic or osmotic pressure gradient, e.g. across most capillaries including glomeruli. Lipid-insoluble drugs cross biological membranes by filtration if their molecular size is smaller than the diameter of the pores (Fig. 2.3). Majority of cells (intestinal mucosa, RBC, etc.) have very small pores (4 Å) and drugs with MW > 100 or 200 are not able to penetrate. However, capillaries (except those in brain) have large paracellular spaces (40 Å) and most drugs (even albumin) can filter through these (Fig. 2.8). As such, diffusion of drugs across capillaries is dependent on rate of blood flow through them rather than on lipid solubility of the drug or pH of the medium.

Specialized transport

This can be carrier mediated or by vesicular transport (endocytosis, exocytosis).

Carrier transport

All cell membranes express a host of transmembrane proteins which serve as carriers or transporters for physiologically important ions,

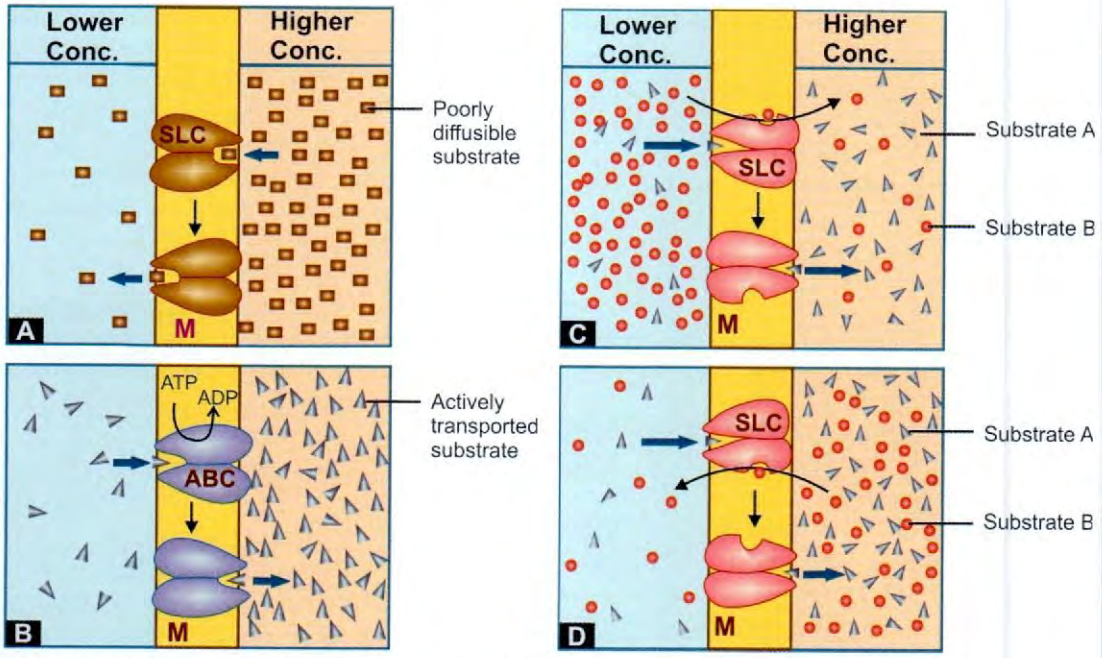


Fig. 2.5: Illustration of different types of carrier mediated transport across biological membrane
ABC—ATP-binding cassette transporter; SLC—Solute carrier transporter; M—Membrane

A. *Facilitated diffusion:* the carrier (SLC) binds and moves the poorly diffusible substrate along its concentration gradient (high to low) and does not require energy
B. *Primary active transport:* the carrier (ABC) derives energy directly by hydrolysing ATP and moves the substrate against its concentration gradient (low to high)
C. *Symport:* the carrier moves the substrate 'A' against its concentration gradient by utilizing energy from downhill movement of another substrate 'B' in the same direction
D. *Antiport:* the carrier moves the substrate 'A' against its concentration gradient and is energized by the downhill movement of another substrate 'B' in the opposite direction

nutrients, metabolites, transmitters, etc. across the membrane. At some sites, certain transporters also translocate xenobiotics, including drugs and their metabolites. In contrast to channels, which open for a finite time and allow passage of specific ions, transporters combine transiently with their substrate (ion or organic compound)—undergo a conformational change carrying the substrate to the other side of the membrane where the substrate dissociates and the transporter returns back to its original state (Fig. 2.5). Carrier transport is specific for the substrate (or the type of substrate, e.g. an organic anion), saturable, competitively inhibited by analogues which utilize the same transporter, and is much slower than the flux through channels. Depending on requirement of energy, carrier transport is of two types:

a. ***Facilitated diffusion*** The transporter, belonging to the super-family of *solute carrier* (SLC) transporters, operates passively without needing energy and translocates the substrate in the direction of its electrochemical gradient, i.e. from higher to lower concentration (Fig. 2.5A). It merely facilitates permeation of a poorly diffusible substrate, e.g. the entry of glucose into muscle and fat cells by the glucose transporter GLUT 4.

b. ***Active transport*** It requires energy, is inhibited by metabolic poisons, and transports the solute against its electrochemical gradient (low to high), resulting in selective accumulation of the

substance on one side of the membrane. Drugs related to normal metabolites can utilize the transport processes meant for these, e.g. levodopa and methyl dopa are actively absorbed from the gut by the aromatic amino acid transporter. In addition, the body has developed some relatively nonselective transporters, like *P-glycoprotein* (P-gp), to deal with xenobiotics. Active transport can be primary or secondary depending on the source of the driving force.

i. *Primary active transport* Energy is obtained directly by the hydrolysis of ATP (Fig. 2.5B). The transporters belong to the superfamily of *ATP binding cassettee* (ABC) transporters whose intracellular loops have ATPase activity. They mediate only efflux of the solute from the cytoplasm, either to extracellular fluid or into an intracellular organelli (endoplasmic reticulum, mitochondria, etc.)

Encoded by the multidrug resistance 1 (MDR1) gene, P-gp is the most well known primary active transporter expressed in the intestinal mucosa, renal tubules, bile canaliculi, choroidal epithelium, astrocyte foot processes around brain capillaries (the blood-brain barrier), testicular and placental microvessels, which pumps out many drugs/metabolites and thus limits their intestinal absorption, penetration into brain, testes and foetal tissues as well as promotes biliary and renal elimination. Many xenobiotics which induce or inhibit P-gp also have a similar effect on the drug metabolizing isoenzyme CYP3A4, indicating their synergistic role in detoxification of xenobiotics.

Other primary active transporters of pharmacological significance are multidrug resistance associated protein 2 (MRP 2) and breast cancer resistance protein (BCRP).

ii. *Secondary active transport* In this type of active transport effected by another set of SLC transporters, the energy to pump one solute is derived from the downhill movement of another solute (mostly Na^+). When the concentration gradients are such that both the solutes move in the same direction (Fig. 2.5C), it is called *symport* or *cotransport*, but when they move in opposite directions (Fig. 2.5D), it is termed *antiport* or *exchange transport*. Metabolic energy (from hydrolysis of ATP) is spent in maintaining high transmembrane electrochemical gradient of the second solute (generally Na^+). The SLC transporters mediate both uptake and efflux of drugs and metabolites.

The organic anion transporting polypeptide (OATP) and organic cation transporter (OCT), highly expressed in liver canaliculi and renal tubules, are secondary active transporters important in the metabolism and excretion of drugs and metabolites (especially glucuronides). The Na^+,Cl^- dependent neurotransmitter transporters for norepinephrine, serotonin and dopamine (NET, SERT and DAT) are active SLC transporters that are targets for action of drugs like tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), cocaine, etc. Similarly, the Vesicular monoamine transporter (VMAT-2) of adrenergic and serotonergic storage vesicles transports catecholamines and 5-HT into the vesicles by exchanging with H^+ions, and is inhibited by reserpine. The absorption of glucose in intestines and renal tubules is through secondary active transport by sodium-glucose transporters (SGLT1 and SGLT2).

As indicated earlier, carrier transport (both facilitated diffusion and active transport) is saturable and follows the Michaelis-Menten kinetics. The maximal rate of transport is dependent on the density of the transporter in a particular membrane, and its rate constant (Km), i.e. the substrate concentration at which rate of transport is half maximal, is governed by its affinity for the substrate. Genetic polymorphism can alter both the density and affinity of the transporter protein for different substrates and thus affect the pharmacokinetics of drugs. Moreover, tissue specific drug distribution can occur due to the presence of specific transporters in certain cells.

Vesicular transport (endocytosis, exocytosis)

Certain substances with very large or impermeable molecules are transported inside the cell (*endocytosis*) or extruded from it (*exocytosis*) by enclosing their particles into tiny vesicles. A binding protein located on the membrane complexes with the substance and initiates vesicle formation (Fig. 2.6). The vesicle then detaches from the membrane and may remain stored within the cell, or it may release the substance in the cytoplasm, or it may move to the opposite membrane fuse with it to release the substance across the cell (exocytosis).

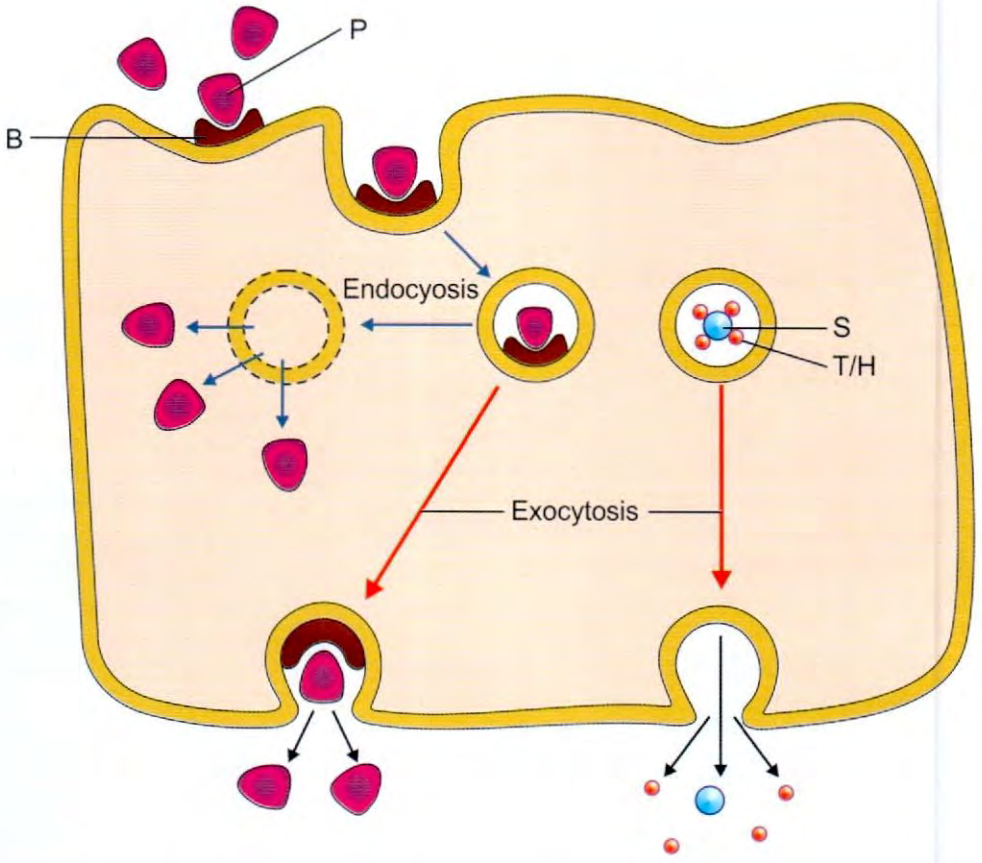


Fig. 2.6: Illustration of vesicular transport (endocytosis and exocytosis).
Endocytosis: The large molecular particle (P) binds to a binding protein (B) on the surface of the cell. The membrane invaginates to form a vesicle which nicks off, and the vesicle may remain stored within the cell, or it may disintegrate to release the substance in the cytoplasm, or be extruded across the cell by exocytosis.
Exocytosis: The particle or the transmitter/hormone(T/H) stored within intracellular vesicles, generally as a complex with a storage protein (S), is secreted by exocytosis. On activation the vesicle translocates to and fuses with the membrane. All contents of the vesicle are then poured out in the extracellular space.

Vesicular transport is applicable to proteins and other big molecules, and contributes little to transport of most drugs, barring few like vit B_{12} which is absorbed from the gut after binding to intrinsic factor (a protein). Most hormones (insulin, etc.) and neurotransmitters, like noradrenaline, are secreted/released from the cell/nerve ending by exocytosis. Activation of the secretory cell/nerve ending prompts fusion of the storage vesicle to the surface membrane followed by extrusion of its contents into the extracellular space.

ABSORPTION

Absorption is movement of the drug from its site of administration into the circulation. Not only the fraction of the administered dose that gets absorbed, but also the rate of absorption is important. Except when given i.v., the drug has to cross biological membranes; absorption is governed by the above described principles. Other factors affecting absorption are:

Aqueous solubility Drugs given in solid form must dissolve in the aqueous biophase before they are absorbed. For poorly water soluble drugs (aspirin, griseofulvin) rate of dissolution governs rate of absorption. Ketoconazole dissolves at low pH: gastric acid is needed for its absorption. Obviously, a drug given as watery solution is absorbed faster than when the same is given in solid form or as oily solution.

Concentration Passive diffusion depends on concentration gradient; drug given as concentrated solution is absorbed faster than from dilute solution.

Area of absorbing surface Larger is the surface area, faster is the absorption.

Vascularity of the absorbing surface Blood circulation removes the drug from the site of absorption and maintains the concentration gradient across the absorbing surface. Increased blood flow hastens drug absorption just as wind hastens drying of clothes.

Route of administration This affects drug absorption, because each route has its own peculiarities.

Oral

The effective barrier to orally administered drugs is the epithelial lining of the gastrointestinal tract, which is lipoidal. Nonionized lipid soluble drugs, e.g. ethanol are readily absorbed from stomach as well as intestine at rates proportional to their lipid : water partition coefficient. Acidic drugs, e.g. salicylates, barbiturates, etc. are predominantly unionized in the acid gastric juice and are absorbed from stomach, while basic drugs, e.g. morphine, quinine, etc. are largely ionized and are absorbed only on reaching the duodenum. However, even for acidic drugs absorption from stomach is slower, because the mucosa is thick, covered with mucus and the surface area is small. Absorbing surface area is much larger in the small intestine due to villi. Thus, faster gastric emptying accelerates drug absorption in general. Dissolution is a surface phenomenon, therefore, *particle size* of the drug in solid dosage form governs rate of dissolution and in turn rate of absorption.

Presence of food dilutes the drug and retards absorption. Further, certain drugs form poorly absorbed complexes with food constituents, e.g. tetracyclines with calcium present in milk; moreover food delays gastric emptying. Thus, most drugs are absorbed better if taken in empty stomach. However, there are some exceptions, e.g. fatty food greatly enhances lumefantrine absorption. Highly ionized drugs, e.g. gentamicin, neostigmine are poorly absorbed when given orally.

Certain drugs are degraded in the gastrointestinal tract, e.g. penicillin G by acid, insulin by peptidases, and are ineffective orally. Enteric coated tablets (having acid resistant coating) and sustained release preparations (drug particles coated with slowly dissolving material) can be used to overcome acid lability, gastric irritancy and brief duration of action.

The oral absorption of certain drugs is low because a fraction of the absorbed drug is extruded back into the intestinal lumen by the efflux transporter P-gp located in the gut epithelium. The low oral bioavailability of digoxin and cyclosporine is partly accounted by this mechanism. Inhibitors of P-gp like quinidine, verapamil, erythromycin, etc. enhance, while P-gp inducers like rifampin and phenobarbitone reduce the oral bioavailability of these drugs.

Absorption of a drug can be affected by other concurrently ingested drugs. This may be a *luminal effect*: formation of insoluble complexes, e.g. tetracyclines and iron preparations with calcium salts and antacids, phenytoin with sucralfate. Such interaction can be minimized by administering the two drugs at 2–3 hr intervals. Alteration of gut flora by antibiotics may disrupt the enterohepatic cycling of oral contraceptives and digoxin. Drugs can also alter absorption by *gut wall effects*: altering motility (anticholinergics, tricyclic antidepressants, opioids retard motility while metoclopramide enhances it) or causing mucosal damage (neomycin, methotrexate, vinblastine).

Subcutaneous and Intramuscular

By these routes the drug is deposited directly in the vicinity of the capillaries. Lipid soluble drugs pass readily across the whole surface of the capillary endothelium. Capillaries having large paracellular spaces do not obstruct absorption of even large lipid insoluble molecules or ions (Fig. 2.9A). Very large molecules are absorbed through lymphatics. Thus, many drugs not absorbed orally are absorbed parenterally. Absorption from s.c. site is slower than that from i.m. site, but both are generally faster and more consistent/ predictable than oral absorption. Application of heat and muscular exercise accelerate drug absorption by increasing blood flow, while vasoconstrictors, e.g. adrenaline injected with the drug (local anaesthetic) retard absorption. Incorporation of hyaluronidase facilitates drug absorption from s.c. injection by promoting spread. Many depot preparations, e.g. benzathine penicillin, protamine zinc insulin, depot progestins, etc. can be given by these routes.

Topical sites (skin, cornea, mucous membranes)

Systemic absorption after topical application depends primarily on lipid solubility of drugs. However, only few drugs significantly penetrate intact skin. Hyoscine, fentanyl, GTN, nicotine, testosterone, and estradiol (*see* p. 12) have been used in this manner. Corticosteroids applied over extensive areas of skin can produce systemic effects and pituitary-adrenal suppression. Absorption can be promoted by rubbing the drug incorporated in an olegenous base or by use of occlusive dressing which increases hydration of the skin. Organophosphate insecticides coming in contact with skin can produce systemic toxicity. Abraded surfaces readily absorb drugs, e.g. tannic acid applied over burnt skin has produced hepatic necrosis.

Cornea is permeable to lipid soluble, unionized physostigmine but not to highly ionized neostigmine. Drugs applied as eye drops may get absorbed through the nasolacrimal duct, e.g. timolol eye drops can produce bradycardia and precipitate asthma. Mucous membranes of mouth, rectum, vagina absorb lipophilic drugs: estrogen cream applied vaginally has produced gynaecomastia in the male partner.

Bioavailability

Bioavailability refers to the rate and extent of absorption of a drug from a dosage form administered by any route, as determined by its concentration-time curve in blood or by its excretion in urine (Fig. 2.7). It is a measure of the fraction (F) of administered dose of a drug that reaches the systemic circulation in the unchanged form. Bioavailability of drug injected i.v. is 100%, but is frequently lower after oral ingestion because—

(a) the drug may be incompletely absorbed.

(b) the absorbed drug may undergo first pass metabolism in the intestinal wall/liver or be excreted in bile.

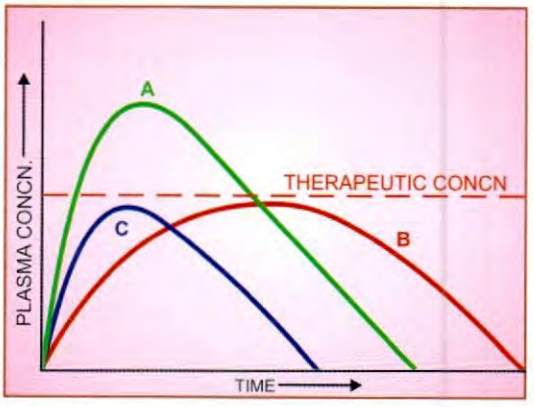


Fig. 2.7: Plasma concentration-time curves depicting bioavailability differences between three formulations of a drug containing the same amount

Note that formulation *B* is more slowly absorbed than *A*, and though ultimately both are absorbed to the same extent (area under the curve same), *B* may not produce therapeutic effect after a single dose; however average blood levels may be similar with both A and B formulations when repeated doses are given; *C* is absorbed to a lesser extent—resulting in lower bioavailability

Incomplete bioavailability after s.c. or i.m. injection is less common, but may occur due to local binding of the drug.

Bioequivalence Oral formulations of a drug from different manufacturers or different batches from the same manufacturer may have the same amount of the drug (chemically equivalent) but may not yield the same blood levels—*biologically inequivalent*. Two preparations of a drug are considered *bioequivalent* when the rate and extent of bioavailability of the active drug from them is not significantly different under suitable test conditions.

Before a drug administered orally in solid dosage form can be absorbed, it must break into individual particles of the active drug (disintegration). Tablets and capsules contain a number of other materials—diluents, stabilizing agents, binders, lubricants, etc. The nature of these as well as details of the manufacture process, e.g. force used in compressing the tablet, may affect *disintegration*. The released drug must then *dissolve* in the aqueous gastrointestinal contents. The rate of dissolution is governed by the inherent solubility, particle size, crystal form and other physical properties of the drug. Differences in bioavailability may arise due to variations in disintegration and dissolution rates.

Differences in bioavailability are seen mostly with poorly soluble and slowly absorbed drugs. Reduction in particle size increases the rate of absorption of aspirin (microfine tablets). The amount of griseofulvin and spironolactone in the tablet can be reduced to half if the drug particle is microfined. There is no need to reduce the particle size of freely water soluble drugs, e.g. paracetamol.

Bioavailability variation assumes practical significance for drugs with low safety margin (digoxin) or where dosage needs precise control (oral hypoglycaemics, oral anticoagulants). It may also be responsible for success or failure of an antimicrobial regimen.

However, in the case of a large number of drugs bioavailability differences are negligible and the risks of changing from branded to generic product or to another brand of the same drug have often been exaggerated.

DISTRIBUTION

Once a drug has gained access to the blood stream, it gets distributed to other tissues that initially had no drug, concentration gradient being in the direction of plasma to tissues. The extent of distribution of a drug and its pattern of tissue distribution depends on its:

- lipid solubility
- ionization at physiological pH (a function of its pKa)
- extent of binding to plasma and tissue proteins
- presence of tissue-specific transporters
- differences in regional blood flow.

Movement of drug proceeds until an equilibrium is established between unbound drug in the plasma and the tissue fluids. Subsequently, there is a parallel decline in both due to elimination.

Apparent volume of distribution (V) Presuming that the body behaves as a single homogeneous compartment with volume V into which the drug gets immediately and uniformly distributed

$$V = \frac{\text{dose administered i.v.}}{\text{plasma concentration}} \quad ...(3)$$

Since in the example shown in Fig. 2.8, the drug does not actually distribute into 20 L of body water, with the exclusion of the rest of it, this is only an apparent volume of distribution which can be defined as "the volume that would accommodate all the drug in the body, if the concentration throughout was the same as in plasma". Thus, it describes amount of the drug present in the body as a multiple of that contained in a unit volume of plasma. Considered together with drug clearance, this is a very useful pharmacokinetic concept.

Lipid-insoluble drugs do not enter cells—V approximates extracellular fluid volume, e.g. streptomycin, gentamicin 0.25 L/kg.

Distribution is not only a matter of dilution, but also binding and sequestration. Drugs extensively bound to plasma proteins are largely

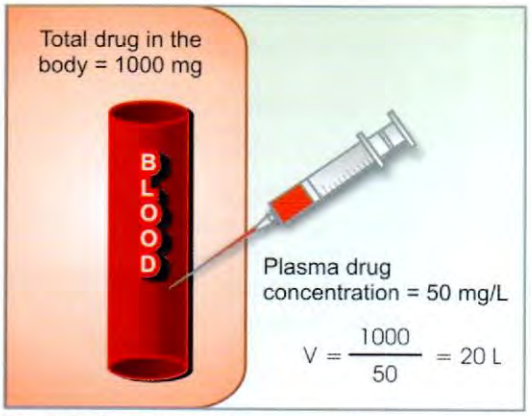


Fig. 2.8: Illustration of the concept of apparent volume of distribution (V)
In this example, 1000 mg of drug injected i.v. produces steady-state plasma concentration of 50 mg/L, apparent volume of distribution is 20 L

restricted to the vascular compartment and have low values of V, e.g. diclofenac and warfarin (99% bound) V = 0.15 L/kg.

A large value of V indicates that larger quantity of drug is present in extravascular tissue. Drugs sequestrated in other tissues may have, V much more than total body water or even body mass, e.g. digoxin 6 L/kg, propranolol 4 L/kg, morphine 3.5 L/kg, because most of the drug is present in other tissues, and plasma concentration is low. Therefore, in case of poisoning, drugs with large volumes of distribution are not easily removed by haemodialysis.

Pathological states, e.g. congestive heart failure, uraemia, cirrhosis of liver, etc. can alter the V of many drugs by altering distribution of body water, permeability of membranes, binding proteins or by accumulation of metabolites that displace the drug from binding sites.

More precise multiple compartment models for drug distribution have been worked out, but the single compartment model, described above, is simple and fairly accurate for many drugs.

Redistribution Highly lipid-soluble drugs get initially distributed to organs with high blood flow, i.e. brain, heart, kidney, etc. Later, less vascular but more bulky tissues (muscle, fat) take up the drug—plasma concentration falls and the drug is withdrawn from the highly perfused sites. If the site of action of the drug was in one of the highly perfused organs, redistribution results in termination of drug action. Greater the lipid solubility of the drug, faster is its redistribution. Anaesthetic action of thiopentone sod. injected i.v. is terminated in few minutes due to redistribution. A relatively short hypnotic action lasting 6–8 hours is exerted by oral diazepam or nitrazepam due to redistribution despite their elimination t½ of > 30 hr. However, when the same drug is given repeatedly or continuously over long periods, the low perfusion high capacity sites get progressively filled up and the drug becomes longer acting.

Factors governing volume of drug distribution

- Lipid: water partition coefficient of the drug
- *pKa* value of the drug
- Degree of plasma protein binding
- Affinity for different tissues
- Fat: lean body mass ratio, which can vary with age, sex, obesity, etc.
- Diseases like CHF, uremia, cirrhosis

Penetration into brain and CSF The capillary endothelial cells in brain have tight junctions and lack large paracellular spaces. Further, an investment of neural tissue (Fig. 2.9B) covers the capillaries. Together they constitute the so called *blood-brain barrier (BBB)*. A similar *blood-CSF barrier* is located in the choroid plexus: capillaries are lined by choroidal epithelium having tight junctions. Both these barriers are lipoidal and limit the entry of nonlipid-soluble drugs, e.g. streptomycin, neostigmine, etc. Only lipid-soluble drugs, therefore, are able to penetrate and have action on the central nervous system. In addition, efflux transporters like P-gp and anion transporter (OATP) present in brain and choroidal vessels extrude many drugs that enter brain by other processes and serve to augment the protective barrier against potentially harmful xenobiotics. Dopamine does not enter brain but its precursor levodopa does; as such,

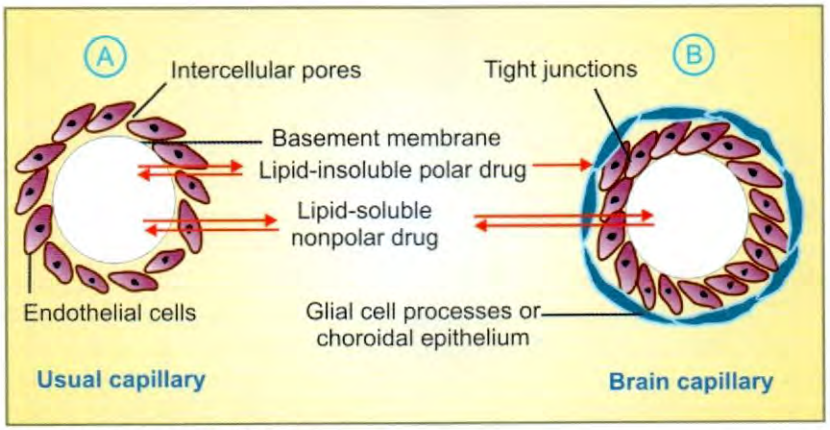


Fig. 2.9: Passage of drugs across capillaries
A. Usual capillary with large paracellular spaces through which even large lipid-insoluble molecules diffuse
B. Capillary constituting blood brain or blood-CSF barrier. Tight junctions between capillary endothelial cells and investment of glial processes or choroidal epithelium do not allow passage of nonlipid-soluble molecules/ions

the latter is used in parkinsonism. Inflammation of meninges or brain increases permeability of these barriers. It has been proposed that some drugs accumulate in the brain by utilizing the transporters for endogenous substances.

There is also an enzymatic BBB: Monoamine oxidase (MAO), cholinesterase and some other enzymes are present in the capillary walls or in the cells lining them. They do not allow catecholamines, 5-HT, acetylcholine, etc. to enter brain in the active form.

The BBB is deficient at the CTZ in the medulla oblongata (even lipid-insoluble drugs are emetic) and at certain periventricular sites—(anterior hypothalamus).

Exit of drugs from the CSF and brain, however, is not dependent on lipid-solubility and is rather unrestricted. This is due to bulk flow of CSF (alongwith the drug dissolved in it) back into blood through the arachnoid villi. Further, nonspecific organic anion and cation transport processes (similar to those in renal tubule) operate at the choroid plexus.

Passage across placenta Placental membranes are lipoidal and allow free passage of lipophilic drugs, while restricting hydrophilic drugs. The placental efflux P-gp and other transporters like BCRP, MRP3 also serve to limit foetal exposure to maternally administered drugs. Placenta is a site for drug metabolism as well, which may lower/modify exposure of the foetus to the administered drug. However, restricted amounts of nonlipid-soluble drugs, when present in high concentration or for long periods in maternal circulation, gain access to the foetus. Some influx transporters also operate at the placenta. Thus, it is an incomplete barrier and almost any drug taken by the mother can affect the foetus or the newborn (drug taken just before delivery, e.g. morphine).

Plasma protein binding

Most drugs possess physicochemical affinity for plasma proteins and get reversibly bound to these. Acidic drugs generally bind to plasma albumin and basic drugs to α_1 acid glycoprotein. Binding to albumin (which is more abundant) is quantitatively more important. Extent of binding depends on the individual compound; no generalization for a pharmacological or chemical class can be made (even small chemical change can markedly alter protein binding), for example the binding percentage of some benzodiazepines is:

Flurazepam	10%	Alprazolam	70%
Lorazepam	90%	Diazepam	99%

Increasing concentrations of the drug can progressively saturate the binding sites: fractional binding may be lower when large amounts of the drug are given. The generally expressed percentage binding refers to the usual therapeutic plasma concentrations of a drug. The clinically significant implications of plasma protein binding are:

(i) Highly plasma protein bound drugs are largely restricted to the vascular compartment because protein bound drug does not cross membranes (except through large paracellular spaces, such as in capillaries). They tend to have smaller volumes of distribution.

Drugs highly bound to plasma protein

To albumin	*To α_1-acid glycoprotein*
Barbiturates	β-blockers
Benzodiazepines	Bupivacaine
NSAIDs	Lidocaine
Valproic acid	Disopyramide
Phenytoin	Imipramine
Penicillins	Methadone
Sulfonamides	Prazosin
Tetracyclines	Quinidine
Tolbutamide	Verapamil
Warfarin	

(ii) The bound fraction is not available for action. However, it is in equilibrium with the free drug in plasma and dissociates when the concentration of the latter is reduced due to elimination. Plasma protein binding thus tantamounts to temporary storage of the drug.

(iii) High degree of protein binding generally makes the drug long acting, because bound fraction is not available for metabolism or excretion, unless it is actively extracted by liver or by kidney tubules. Glomerular filtration does not reduce the concentration of the free form in the efferent vessels, because water is also filtered. Active tubular secretion, however, removes the drug without the attendant solvent → concentration of free drug falls → bound drug dissociates and is eliminated resulting in a higher renal clearance value of the drug than the total renal blood flow (*see* Fig. 3.3). The same is true of active transport of highly extracted drugs in liver. Plasma protein binding in this situation acts as a carrier mechanism and hastens drug elimination, e.g. excretion of penicillin (elimination t½ is 30 min); metabolism of lidocaine. Highly protein bound drugs are not removed by haemodialysis and need special techniques for treatment of poisoning.

(iv) The generally expressed plasma concentrations of the drug refer to bound as well as free drug. Degree of protein binding should be taken into account while relating these to concentrations of the drug that are active *in vitro*, e.g. MIC of an antimicrobial.

(v) One drug can bind to many sites on the albumin molecule. Conversely, more than one drug can bind to the same site. This can give rise to displacement interactions among drugs bound to the same site(s). The drug bound with higher affinity will displace that bound with lower affinity and tend to increase the concentration of its free form. This, however, is often transient because the displaced drug will diffuse into the tissues as well as get metabolized or excreted: the new steady-state free drug concentration is only marginally higher unless the displacement extends to tissue binding or there is concurrent inhibition of metabolism and/or excretion reducing drug clearance. The overall impact of many displacement interactions is minimal; except when the interaction is more complex. Moreover, two highly bound drugs do not necessarily displace each other—their binding sites may not overlap, e.g. probenecid and indomethacin are highly bound to albumin but do not displace each other. Similarly, acidic drugs do not generally displace basic drugs and *vice versa*.

(vi) In hypoalbuminemia, binding may be reduced and high concentrations of free drug may be attained, e.g. phenytoin and furosemide. Other diseases may also alter drug binding, e.g. phenytoin and pethidine binding is reduced in uraemia; propranolol binding is increased in pregnant women and in patients with inflammatory disease (acute phase reactant α_1 acid-glycoprotein increases).

Drugs concentrated in tissues		
Skeletal muscle, heart	—	digoxin, emetine (bound to muscle proteins).
Liver	—	chloroquine, tetracyclines, emetine, digoxin.
Kidney	—	digoxin, chloroquine, emetine.
Thyroid	—	iodine.
Brain	—	chlorpromazine, acetazolamide, isoniazid.
Retina	—	chloroquine (bound to nucleoproteins).
Iris	—	ephedrine, atropine (bound to melanin).
Bone and teeth	—	tetracyclines, heavy metals (bound to mucopolysaccharides of connective tissue), bisphosphonates (bound to hydroxyapatite).
Adipose tissue	—	thiopentone, ether, minocycline, phenoxybenzamine, DDT dissolve in neutral fat due to high lipid-solubility; remain stored due to poor blood supply of fat.

Tissue storage Drugs may also accumulate in specific organs by active transport or get bound to specific tissue constituents (*see* box).

Drugs sequestrated in various tissues are unequally distributed, tend to have larger volume of distribution and longer duration of action. Some may exert local toxicity due to high concentration, e.g. tetracyclines on bone and teeth, chloroquine on retina, streptomycin on vestibular apparatus, emetine on heart and skeletal muscle. Drugs may also selectively bind to specific intracellular organelle, e.g. tetracycline to mitochondria, chloroquine to nuclei.

☞PROBLEM DIRECTED STUDY

2.1 A 60-year-old woman complained of weakness, lethargy and easy fatigability. Investigation showed that she had iron deficiency anaemia (Hb. 8 g/dl). She was prescribed cap. ferrous fumarate 300 mg twice daily. She returned after one month with no improvement in symptoms. Her Hb. level was unchanged. On enquiry she revealed that she felt epigastric distress after taking the iron capsules, and had started taking antacid tablets along with the capsules.
(a) What could be the possible reason for her failure to respond to the oral iron medication?

2.2 A 50-year-old type-2 diabetes mellitus patient was maintained on tab. glibenclamide (a sulfonylurea) 5 mg twice daily. He developed toothache for which he took tab. aspirin 650 mg 6 hourly. After taking aspirin he experienced anxiety, sweating, palpitation, weakness, ataxia, and was behaving abnormally. These symptoms subsided when he was given a glass of glucose solution.
(a) What could be the explanation for his symptoms?
(b) Which alternative analgesic should have been taken?
(see Appendix-1 for solutions)

Chapter 3 Pharmacokinetics: Metabolism and Excretion of Drugs, Kinetics of Elimination

BIOTRANSFORMATION (Metabolism)

Biotransformation means chemical alteration of the drug in the body. It is needed to render nonpolar (lipid-soluble) compounds polar (lipid-insoluble) so that they are not reabsorbed in the renal tubules and are excreted. In the absence of metabolism, body will not be able to get rid of lipophylic substances, and they will become very long acting. Most hydrophilic drugs, e.g. streptomycin, neostigmine, pancuronium, etc. are little biotransformed and are largely excreted unchanged. Mechanisms which metabolize drugs (essentially foreign substances or *Xenobiotics*) have developed to protect the body from ingested toxins and other environmental chemicals.

The primary site for drug metabolism is liver; others are—kidney, intestine, lungs and plasma. Biotransformation of drugs may lead to the following.

(i) *Inactivation* Most drugs and their active metabolites are rendered inactive or less active, e.g. ibuprofen, paracetamol, lidocaine, chloramphenicol, propranolol and its active metabolite 4-hydroxypropranolol. Thus, biotransformation provides an alternative method of terminating drug action to excretion.

(ii) *Active metabolite from an active drug* Many drugs have been found to be partially converted to one or more active metabolite; the effects observed are the sumtotal of that due to the parent drug and its active metabolite(s) (*see* box).

(iii) *Activation of inactive drug* Few drugs are inactive as such and need conversion in the body to one or more active metabolites. Such a drug is called a *prodrug* (*see* box). The prodrug may offer advantages over the active form in being more stable, having better bioavailability or other desirable pharmacokinetic properties or less side effects and toxicity. Some prodrugs are activated selectively at the site of action.

Active drug		Active metabolite
Morphine	—	Morphine-6-glucuronide
Cefotaxime	—	Desacetyl cefotaxime
Allopurinol	—	Alloxanthine
Procainamide	—	N-acetyl procainamide
Primidone	—	Phenobarbitone, phenylethylmalonamide
Diazepam	—	Desmethyl-diazepam, oxazepam
Digitoxin	—	Digoxin
Imipramine	—	Desipramine
Amitriptyline	—	Nortriptyline
Codeine	—	Morphine
Spironolactone	—	Canrenone
Losartan	—	E 3174

Biotransformation reactions can be classified into:

(a) *Nonsynthetic/Phase I/Functionalization reactions:* a functional group (–OH, –COOH, –CHO, $–NH_2$, –SH) is generated or exposed—metabolite may be active or inactive.

(b) *Synthetic/Conjugation/ Phase II reactions:* an endogenous radical is conjugated to the drug—metabolite is mostly inactive; except few drugs, e.g. glucuronide conjugate of morphine and sulfate conjugate of minoxidil are active. Certain drugs already have functional groups and

are directly conjugated, while others undergo a phase I reaction first followed by a phase II reaction (*see* Fig. 3.1).

Prodrug		Active form
Levodopa	—	Dopamine
Enalapril	—	Enalaprilat
α-Methyldopa	—	α-methylnorepinephrine
Dipivefrine	—	Epinephrine
Proguanil	—	Cycloguanil
Prednisone	—	Prednisolone
Clopidogrel	—	Thiol metabolite
Bacampicillin	—	Ampicillin
Sulfasalazine	—	5-Aminosalicylic acid
Cyclophosphamide	—	Aldophosphamide, phosphoramide mustard, acrolein
Fluorouracil	—	Fluorouridine monophosphate
Mercaptopurine	—	Methylmercaptopurine ribonucleotide
Acyclovir	—	Acyclovir triphosphate

Nonsynthetic reactions

(i) *Oxidation* This reaction involves addition of oxygen/negatively charged radical or removal of hydrogen/positively charged radical. Oxidations are the most important drug metabolizing reactions. Various oxidation reactions are:

hydroxylation; oxygenation at C, N or S atoms; N or O-dealkylation, oxidative deamination, etc.

In many cases the initial insertion of oxygen atom into the drug molecule produces short lived highly reactive quinone/epoxide/superoxide intermediates which then convert to more stable compounds.

Oxidative reactions are mostly carried out by a group of monooxygenases in the liver, which in the final step involve a cytochrome P-450 haemoprotein, NADPH, cytochrome P-450 reductase and molecular O_2. More than 100 cytochrome P-450 (CYP) isoenzymes differing in their affinity for various substrates (drugs), have been identified. The CYP isoenzymes important for drug metabolism in humans, along with their clinically relevant substrate drugs, inhibitors and inducers are listed in Table 3.1

Depending upon the extent of amino acid sequence homology, the cytochrome P-450 (CYP) isoenzymes are grouped into families designated by numerals (1, 2, 3.....), each having several sub-families designated by capital letters (A, B, C.....), while individual isoenzymes are again alloted numerals (1, 2, 3....). In human beings, only a few members of *three* isoenzyme families (CYP 1, 2 and 3) carryout metabolism of most of the drugs, and many drugs such as tolbutamide, barbiturates, phenytoin, paracetamol are substrates for more than one isoform. The CYP isoenzymes important in man are:

CYP3A4/5 Carryout biotransformation of largest number (nearly 50%) of drugs. In addition to liver, these isoforms are expressed in intestine (responsible for first pass metabolism at this site) and kidney as well. Inhibition of this isoenzyme by erythromycin, clarithromycin, ketoconazole, itraconazole is responsible for the important drug interaction with terfenadine, astemizole and cisapride (*see* p. 181) which are its substrates. Verapamil, ritonavir and a constituent of grape fruit juice are other important inhibitors.

CYP2D6 This is the next most important CYP isoform which metabolizes nearly 20% drugs including tricyclic antidepressants, selective serotonin reuptake inhibitors, many neuroleptics, antiarrhythmics, codeine, debrisoquine, metoprolol. Inhibition of this enzyme by quinidine results in failure of conversion of codeine to morphine → analgesic effect of codeine is lost. Human subjects can be grouped into *'extensive'* or *'poor'* metabolizers of metoprolol and debrisoquin. The poor metabolizers have an altered CYP2D6 enzyme and exhibit low capacity to hydroxylate many drugs. An ultrarapid metabolizer genotype of CYP2D6 has also been identified.

CYP2C8/9 Important in the biotransformation of >15 commonly used drugs including phenytoin, carbamazepine, warfarin which are narrow safety margin drugs.

CYP2C19 Metabolizes > 12 frequently used drugs including omeprazole, lansoprazole, phenytoin, diazepam. Omeprazole and fluconazole are its inhibitors.

CYP1A1/2 Though this subfamily participates in the metabolism of only few drugs like theophylline, caffeine, paracetamol, carbamazepine, it is more important for activation of procarcinogens. Polycyclic hydrocarbons, cigarette smoke and charbroiled meat are its potent inducers.

CYP2E1 It catalyses oxidation of alcohol, holothane, and formation of minor metabolites of few drugs, notably the hepatotoxic N-acetyl benzoquinoneimine from paracetamol; chronic alcoholism induces this isoenzyme.

The relative amount of different cytochrome P-450s differs among species and among individuals of the same species. These differences

Table 3.1: Major drug metabolizing CYP450 isoenzymes in humans with their important substrate drugs, inhibitors and inducers

CYP-450 isoenzyme	*Drugs metabolized*	*Inhibitors*	*Inducers*
CYP3A4 CYP3A5	Terfenadine, Astemizole Cisapride, Losartan Carbamazepine, Hydrocortisone Paracetamol, Diazepam Buspirone, Mifepristone Ritonavir, Saquinavir Simvastatin, Quinidine Verapamil, Lidocaine Dapsone, Nevirapine	Erythromycin Clarithromycin Ketoconazole Itraconazole Verapamil Ritonavir Fluoxetine Grape fruit juice	Barbiturates Phenytoin Carbamazepine Rifampin Glucocorticoids Nevirapine
CYP2D6	Metoprolol, Debrisoquine Nebivolol, Amitryptyline Clomipramine, Fluoxetine Paroxetine, Venlafaxine Haloperidol, Clozapine Risperidone, Codeine Propafenone, Flecainide	Qunidine Fluoxetine Paroxetine	Phenobarbitone Rifampin
CYP2C8 CYP2C9	Phenytoin, Carbamazepine Warfarin, Tolbutamide Repaglinide, Pioglitazone Diclofenac, Ibuprofem Losartan	Fluvoxamine Fluconazole Gemfibrozil Trimethoprim	Phenobarbitone Carbamazepine Rifampin
CYP2C19	Omeprazole, Lansoprazole Amitriptyline, Citalopram Phenytoin, Diazepam Propranolol, Clopidogrel	Omeprazole Fluconazole	Carbamazepine Rifampin
CYP1A1 CYP1A2	Theophylline, Caffeine Paracetamol, Warfarin Carbamazepine	Fluvoxamine Fluoxetine	Polycyclic hydrocarbons Cigarette smoke Charbroiled meat Rifampin Carbamazepine
CYP2E1	Alcohol, Halothane Paracetamol*	Disulfiram Fomepizole	Chronic alcoholism Isoniazid
CYP2B6	Efavirenz, Nevirapine Cyclophosphamide, Methadone Sertraline, Clopidogrel	Paroxetine Sertraline Clopidogrel	Phenobarbitone Cyclophosphamide

* Generates toxic metabolite N-acetyl-p-benzoquinoneimine (NABQI)

largely account for the marked interspecies and interindividual differences in rate of metabolism of drugs.

Barbiturates, phenothiazines, imipramine, propranolol, ibuprofen, paracetamol, steroids, phenytoin, benzodiazepines, theophylline and many other drugs are oxidized in this way by CYP450. In addition few drugs like cimetidine, ranitidine, clozapine are oxidized at their N, P or S atoms by a group of flavin-monooxygenases that are also located on hepatic endoplasmic reticulum, but are distinct from CYP enzymes. These enzymes are not susceptible to induction or inhibition by other drugs, and thus are not involved in drug interactions. Some other drugs, e.g. adrenaline, alcohol, mercaptopurine are oxidized by mitochondrial or cytoplasmic enzymes.

(ii) *Reduction* This reaction is the converse of oxidation and involves cytochrome P-450

enzymes working in the opposite direction. Alcohols, aldehydes, quinones are reduced. Drugs primarily reduced are chloralhydrate, chloramphenicol, halothane, warfarin.

(iii) *Hydrolysis* This is cleavage of drug molecule by taking up a molecule of water.

$$\text{Ester} + H_2O \xrightarrow{\textit{esterase}} \text{Acid} + \text{Alcohol}$$

Similarly, amides and polypeptides are hydrolysed by amidases and peptidases. In addition, there are epoxide hydrolases which detoxify epoxide metabolites of some drugs generated by CYP oxygenases. Hydrolysis occurs in liver, intestines, plasma and other tissues. Examples of hydrolysed drugs are choline esters, procaine, lidocaine, procainamide, aspirin, indomethacin, carbamazepine-epoxide, pethidine, oxytocin.

(iv) *Cyclization* This is formation of ring structure from a straight chain compound, e.g. cycloguanil from proguanil.

(v) *Decyclization* This implies opening up of ring structure of the cyclic drug molecule, such as barbiturates, phenytoin. This is generally a minor pathway.

Synthetic reactions

These reactions involve conjugation of the drug or its phase I metabolite with an endogenous substrate, usually derived from carbohydrate or amino acid, to form a polar highly ionized organic acid, which is easily excreted in urine or bile. Conjugation reactions have high energy requirement and are generally faster than phase I reactions.

(i) *Glucuronide conjugation* This is the most important synthetic reaction carriedout by a group of UDP-glucuronosyl transferases (UGTs). Compounds with a hydroxyl or carboxylic acid group are easily conjugated with glucuronic acid which is derived from glucose. Examples are—chloramphenicol, aspirin, paracetamol, diazepam, lorazepam, morphine, metronidazole. Not only drugs but endogenous substrates like bilirubin, steroidal hormones and thyroxine utilize this pathway. Glucuronidation increases the molecular weight of the drug which favours its excretion in bile. Drug glucuronides excreted in bile can be hydrolysed by bacteria in the gut—the liberated drug is reabsorbed and undergoes the same fate. This enterohepatic cycling (*see* Fig. 3.2) of the drug prolongs its action, e.g. phenolphthalein, oral contraceptives.

(ii) *Acetylation* Compounds having amino or hydrazine residues are conjugated with the help of acetyl coenzyme-A, e.g. sulfonamides, isoniazid, PAS, dapsone, hydralazine, clonazepam, procainamide. Multiple genes control the N-acetyl transferases (NATs), and rate of acetylation shows genetic polymorphism (slow and fast acetylators).

(iii) *Methylation* The amines and phenols can be methylated by methyl transferases (MT); methionine and cysteine acting as methyl donors, e.g. adrenaline, histamine, nicotinic acid, methyldopa, captopril, mercaptopurine.

(iv) *Sulfate conjugation* The phenolic compounds and steroids are sulfated by sulfotransferases (SULTs), e.g. chloramphenicol, methyldopa, adrenal and sex steroids.

(v) *Glycine conjugation* Salicylates, nicotinic acid and other drugs having carboxylic acid group are conjugated with glycine, but this is not a major pathway of metabolism.

(vi) *Glutathione conjugation* This is carried out by glutathione-S-transferase (GST) forming a mercapturate. It is normally a minor pathway. However, it serves to inactivate highly reactive quinone or epoxide intermediates formed during metabolism of certain drugs, e.g. paracetamol. When large amount of such intermediates are formed (in poisoning or after enzyme induction), glutathione supply falls short—toxic adducts are formed with tissue constituents resulting in hepatic, renal and other tissue damage.

(vii) *Ribonucleoside/nucleotide synthesis* This pathway is important for the activation of many purine and pyrimidine antimetabolites used in cancer chemotherapy.

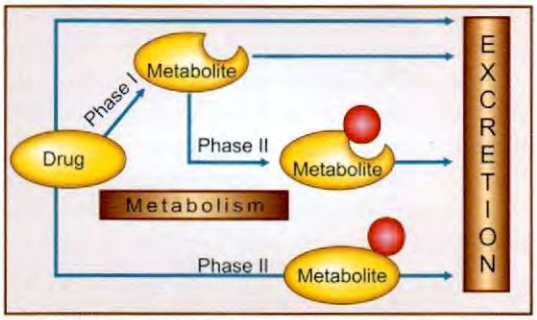


Fig. 3.1: Simultaneous and/or sequential metabolism of a drug by phase I and phase II reactions

Most drugs are metabolized by multiple pathways, simultaneously or sequentially as illustrated in Fig. 3.1. Rates of reaction by different pathways often vary considerably. A variety of metabolites (some more, some less) of a drug may be produced. Stereoisomers of a drug may be metabolized differently and at different rates, e.g. S-warfarin rapidly undergoes ring oxidation, while R-warfarin is slowly degraded by sidechain reduction.

Only a few drugs are metabolized by enzymes of intermediary metabolism, e.g. alcohol by dehydrogenase, allopurinol by xanthine oxidase, succinylcholine and procaine by plasma cholinesterase, adrenaline by monoamine oxidase. Majority of drugs are acted on by relatively nonspecific enzymes which are directed to types of molecules rather than to specific drugs. The same enzyme can metabolize many drugs. The drug metabolising enzymes are divided into two types:

Microsomal enzymes These are located on smooth endoplasmic reticulum (a system of microtubules inside the cell), primarily in liver, also in kidney, intestinal mucosa and lungs. The monooxygenases, cytochrome P450, UGTs, epoxide hydrolases, etc. are microsomal enzymes.

They catalyse most of the oxidations, reductions, hydrolysis and glucuronide conjugation. Microsomal enzymes are inducible by drugs, certain dietary constituents, and other agencies.

Nonmicrosomal enzymes These are present in the cytoplasm and mitochondria of hepatic cells as well as in other tissues including plasma. The esterases, amidases, some flavoprotein oxidases and most conjugases are nonmicrosomal. Reactions catalysed are:

> Some oxidations and reductions, many hydrolytic reactions and all conjugations except glucuronidation.

The nonmicrosomal enzymes are not inducible but many show genetic polymorphism (acetyl transferase, pseudocholinesterase) similar to the microsomal enzymes.

Both microsomal and nonmicrosomal enzymes are deficient in the newborn, especially premature, making them more susceptible to many drugs, e.g. chloramphenicol, opioids. This deficit is made up in the first few months, more quickly in case of oxidation and other phase I reactions than in case of glucuronide and other conjugations which take 3 or more months to reach adult levels.

The amount and kind of drug metabolizing enzymes is controlled genetically and is also altered by diet, environmental factors. Thus, marked interspecies and interindividual differences are seen, e.g. cats are deficient in UGTs while dogs are deficient in NATs. Upto 6-fold difference in the rate of metabolism of a drug among normal human adults may be observed. This is one of the major causes of individual variation in drug response.

Hofmann elimination This refers to inactivation of the drug in the body fluids by spontaneous molecular rearrangement without the agency of any enzyme, e.g. atracurium.

Inhibition of Drug Metabolism

Azole antifungal drugs, macrolide antibiotics and some other drugs bind to the heme iron in CYP450 and inhibit the metabolism of many drugs, as well as some endogenous substances like steroids, bilirubin. One drug can competitively inhibit the metabolism of another if it utilizes the same enzyme or cofactors. However, such interactions are not as common as one would expect, because often different drugs are substrates for different CYP-450 isoenzymes. It is thus important to

know the CYP isoenzyme(s) that carry out the metabolism of a particular drug. A drug may be the substrate as well as inhibitor of the same CYP isoenzyme. In case the drug inhibits its own metabolism, the oral bioavailability is likely to increase (for high first pass metabolism drugs), while systemic clearance is likely to decrease, prolonging plasma half life. On chronic dosing, the oral bioavailability of verapamil is nearly doubled and t½ is prolonged, because it inhibits its own metabolism. A drug may also inhibit one isoenzyme while being itself a substrate of another isoenzyme, e.g. quinidine is metabolized mainly by CYP3A4 but inhibits CYP2D6. Moreover, majority of drugs, at therapeutic concentrations, are metabolized by non-saturation kinetics, i.e. the enzyme is present in excess. Clinically significant inhibition of drug metabolism occurs in case of drugs having affinity for the same isoenzyme, specially if they are metabolized by saturation kinetics or if kinetics changes from first order to zero order over the therapeutic range (capacity limited metabolism). The 'boosted' HIV-protease inhibitor (PI) strategy utilizes the potent CYP3A4 inhibitory action of low dose ritonavir to lower the dose of other PIs like atazanavir, lopinavir, saquinavir given concurrently. Obviously, inhibition of drug metabolism occurs in a dose related manner and can precipitate toxicity of the object drug (whose metabolism has been inhibited).

Because enzyme inhibition occurs by direct effect on the enzyme, it has a fast time course (within hours) compared to enzyme induction (*see* below).

Metabolism of drugs with high hepatic extraction is dependent on liver blood flow (blood flow limited metabolism). Propranolol reduces rate of lidocaine metabolism by decreasing hepatic blood flow. Some other drugs whose rate of metabolism is limited by hepatic blood flow are morphine, propranolol, verapamil and imipramine.

Drugs that inhibit drug metabolizing enzymes

Allopurinol	Amiodarone
Omeprazole	Propoxyphene
Erythromycin	Isoniazid
Clarithromycin	Cimetidine
Chloramphenicol	Quinidine
Ketoconazole	Disulfiram
Itraconazole	Diltiazem
Metronidazole	Verapamil
Ciprofloxacin	MAO inhibitors
Fluoxetine (and other SSRIs)	Ritonavir (and other HIV protease inhibitors)

Microsomal Enzyme Induction

Many drugs, insecticides and carcinogens interact with DNA and increase the synthesis of microsomal enzyme protein, especially cytochrome P-450 and UGTs. As a result the rate of metabolism of inducing drug itself (autoinduction) and/or some other coadministered drugs is accelerated.

Different inducers are relatively selective for certain cytochrome P-450 isoenzyme families, e.g.:

- Anticonvulsants (phenobarbitone, phenytoin, carbamazepine), rifampin, glucocorticoids induce CYP3A isoenzymes.
- Phenobarbitone and rifampin also induce CYP2D6 and CYP2C8/9.
- Carbamazepine and rifampin, in addition, induce CYP2C19 and CYP1A1/2.
- Isoniazid and chronic alcohol consumption induce CYP2E1.
- Polycyclic hydrocarbons like 3-methylcholanthrene and benzopyrene found in cigarette smoke, charcoalbroiled meat, omeprazole and industrial pollutants induce CYP1A isoenzymes.
- Other enzyme inducers are: chronic alcoholism, nevirapine, griseofulvin, DDT.

Since different CYP isoenzymes are involved in the metabolism of different drugs, every inducer increases biotransformation of certain drugs but not that of others. However, phenobarbitone like inducers of CYP3A and CYP2D6 affect the metabolism of a large number of drugs, because these isoenzymes act on many drugs. On the other hand

induction by polycyclic hydrocarbons is limited to few drugs (like theophylline, warfarin) because CYP1A isoenzyme metabolizes only few drugs.

Induction involves microsomal enzymes in liver as well as other organs and increases the rate of metabolism by 2–4 fold. Induction takes 4–14 days to reach its peak and is maintained till the inducing agent is being given. Thereafter the enzymes return to their original value over 1–3 weeks.

Consequences of microsomal enzyme induction

1. Decreased intensity and/or duration of action of drugs that are inactivated by metabolism, e.g. failure of contraception with oral contraceptives and loss of anti-HIV action of nevirapine due to rifampin coadministration.
2. Increased intensity of action of drugs that are activated by metabolism. Acute paracetamol toxicity is due to one of its metabolites—toxicity occurs at lower doses in patients receiving enzyme inducers.
3. Tolerance—if the drug induces its own metabolism (autoinduction), e.g. carbamazepine, rifampin; nevirapine dose needs to be doubled after 2 weeks.
4. Some endogenous substrates (steroids, bilirubin) are also metabolized faster.
5. Precipitation of acute intermittent porphyria: enzyme induction increases porphyrin synthesis by derepressing δ-aminolevulinic acid synthetase.
6. Intermittent use of an inducer may interfere with adjustment of dose of another drug prescribed on regular basis, e.g. oral anticoagulants, oral hypoglycaemics, antiepileptics, antihypertensives.
7. Interference with chronic toxicity testing in animals.

Drugs whose metabolism is significantly affected by enzyme induction are—phenytoin, carbamazepine, antidepressants, warfarin, tolbutamide, oral contraceptives, chloramphenicol, doxycycline, theophylline, griseofulvin, nevirapine.

Possible uses of enzyme induction

1. Congenital nonhaemolytic jaundice: It is due to deficient glucuronidation of bilirubin; phenobarbitone hastens clearance of jaundice.
2. Cushing's syndrome: phenytoin may reduce the manifestations by enhancing degradation of adrenal steroids which are produced in excess.
3. Chronic poisonings: by faster metabolism of the accumulated poisonous substance.
4. Liver disease.

First-pass (Presystemic) Metabolism

This refers to metabolism of a drug during its passage from the site of absorption into the systemic circulation. All orally administered drugs are exposed to drug metabolizing enzymes in the intestinal wall and liver (where they first reach through the portal vein). Presystemic metabolism in the gut and liver can be avoided by administering the drug through sublingual, transdermal or parenteral routes. However, limited presystemic metabolism can occur in the skin (transdermally administered drug) and in lungs (for drug reaching venous blood through any route). The extent of first pass metabolism differs for different drugs (Table 3.2) and is an important determinant of oral bioavailability.

A drug can also be excreted as such into bile. The hepatic *extraction ratio* (ER_{Liver}) of a drug is the fraction of the absorbed drug prevented by the liver from reaching systemic circulation. Both presystemic metabolism as well as direct excretion into bile determine ER_{Liver}, which is given by the equation:

$$ER = \frac{CL_{Liver}}{Hepatic\ blood\ flow} \quad ..(1)$$

Accordingly the systemic bioavailability (F) of an orally administered drug will be:

$$F = fractional\ absorption \times (1\text{–}ER) \quad ..(2)$$

When a drug with high first pass metabolism is given orally at higher dose to achieve therapeutic blood levels, the plasma concentration of its metabolites will be much higher compared to those resulting from parenteral dosing of the drug for the same therapeutic level. If the metabolites contribute to the adverse effects of the drug, oral dosing will be less safe than parenteral.

Table 3.2: Extent of hepatic first pass metabolism of some important drugs

Low	*Intermediate*	*High*	
		not given orally	*high oral dose*
Phenobarbitone	Aspirin	Isoprenaline	Propranolol
Phenylbutazone	Quinidine	Lidocaine	Alprenolol
Tolbutamide	Desipramine	Hydrocortisone	Verapamil
Theophylline	Nortriptyline	Testosterone	Salbutamol
Pindolol	Chlorpromazine		Glyceryl trinitrate
Diazepam	Pentazocine		Morphine
Isosorbide mononitrate	Metoprolol		Pethidine

Attributes of drugs with high first pass metabolism:

(a) Oral dose is considerably higher than sublingual or parenteral dose.

(b) There is marked individual variation in the oral dose due to differences in the extent of first pass metabolism.

(c) Oral bioavailability is apparently increased in patients with severe liver disease.

(d) Oral bioavailability of a drug is increased if another drug competing with it in first pass metabolism is given concurrently, e.g. chlorpromazine and propranolol.

EXCRETION

Excretion is the passage out of systemically absorbed drug. Drugs and their metabolites are excreted in:

1. Urine Drug excretion in urine occurs via the kidney. It is the most important channel of excretion for majority of drugs (*see* below).

2. Faeces Apart from the unabsorbed fraction, most of the drug present in faeces is derived from bile. Liver actively transports into bile organic acids (especially drug glucuronides by OATP and MRP2), organic bases (by OCT), other lipophilic drugs (by P-gp) and steroids by distinct nonspecific active transport mechanisms. Relatively larger molecules (MW > 300) are preferentially eliminated in the bile. Most of the free drug in the gut, including that released by deconjugation of glucuronides by enteric bacteria is reabsorbed (enterohepatic cycling) and ultimate excretion occurs in urine (Fig. 3.2). Only the remaining is excreted in the faeces. Enterohepatic cycling contributes to longer stay of the drug in the body. Drugs that attain high concentrations in bile include erythromycin, ampicillin, rifampin, tetracycline, oral contraceptives, vecuronium, phenolphthalein.

Certain drugs are excreted directly in colon, e.g. anthracene purgatives, heavy metals.

3. Exhaled air Gases and volatile liquids (general anaesthetics, alcohol) are eliminated by lungs, irrespective of their lipid solubility. Alveolar transfer of the gas/vapour depends on its partial pressure in the blood. Lungs also serve to trap and extrude any particulate matter that enters circulation.

4. Saliva and sweat These are of minor importance for drug excretion. Lithium, pot. iodide, rifampin and heavy metals are present in these secretions in significant amounts. Most of the saliva along with the drug in it, is swallowed and meets the same fate as orally taken drug.

5. Milk The excretion of drug in milk is not important for the mother, but the suckling infant inadvertently receives the drug. Most drugs enter breast milk by passive diffusion. As such, more lipid soluble and less protein bound drugs cross better. Milk has a lower pH (7.0) than plasma, basic drugs are somewhat more concentrated in it. However, the total amount of

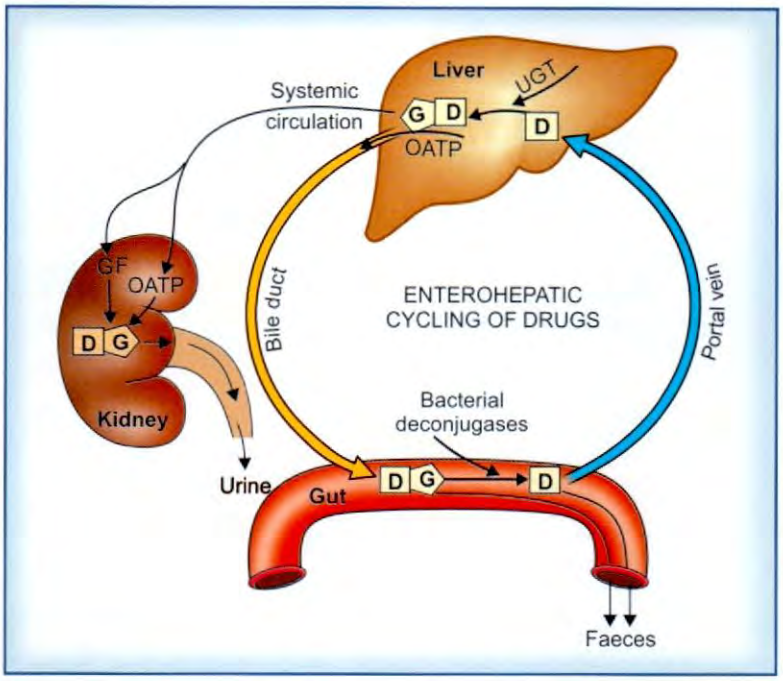


Fig. 3.2: Enterohepatic cycling of drugs
In the liver many drgus (D), including steroids, are conjugated by the enzyme UDP-glucuronosyl transferases (UGTs) to form drug-glucuronide (DG). Part of the DG enters systemic circulation and is excreted into urine by the kidney through both glomerular filtration (GF) as well as active tubular secretion involving renal organic-anion transporting peptide (OATP).

Another part of DG is actively secreted into bile by the hepatic OATP. On reaching the gut lumen via bile, a major part of DG is deconjugated by becterial hydrolytic enzymes (deconjugases) while the remaining is excreted into faeces. The released D is reabsorbed from the gut to again reach the liver through portal circulation and complete the enterohepatic cycle.

drug reaching the infant through breast feeding is generally small and majority of drugs can be given to lactating mothers without ill effects on the infant. Nevertheless, it is advisable to administer any drug to a lactating woman only when essential. Drugs that are safe, as well as those contraindicated during breast feeding or need special caution are given in Appendix-3 at the end of the book.

RENAL EXCRETION

The kidney is responsible for excreting all water soluble substances. The amount of drug or its metabolites ultimately present in urine is the sum total of glomerular filtration, tubular reabsorption and tubular secretion (Fig. 3.3).

$$\text{Net renal excretion} = (\text{Glomerular filtration} + \text{tubular secretion}) - \text{tubular reabsorption}$$

Glomerular filtration Glomerular capillaries have pores larger than usual; all nonprotein bound drug (whether lipid-soluble or insoluble) presented to the glomerulus is filtered. Thus, glomerular filtration of a drug depends on its plasma protein binding and renal blood flow. Glomerular filtration rate (g.f.r.), normally ~ 120 ml/min, declines progressively after the age of 50, and is low in renal failure. Glomerular filtration of drugs declines in parallel.

Tubular reabsorption This occurs by passive diffusion and depends on the lipid solubility

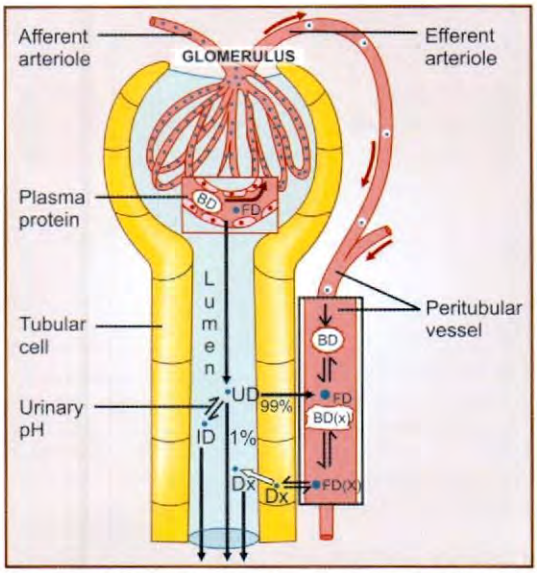


Fig. 3.3: Schematic depiction of glomerular filtration, tubular reabsorption and tubular secretion of drugs
FD—free drug; BD—bound drug; UD—unionized drug; ID—ionized drug; Dx—actively secreted organic acid (or base) drug

and ionization of the drug at the existing urinary pH. Lipid-soluble drugs filtered at the glomerulus back diffuse in the tubules because 99% of glomerular filtrate is reabsorbed, but nonlipid-soluble and highly ionized drugs are unable to do so. Thus, rate of excretion of such drugs, e.g. aminoglycoside antibiotics, quaternary ammonium compounds parallels g.f.r. (or creatinine clearance). Changes in urinary pH affect tubular reabsorption of drugs that are partially ionized—

- Weak bases ionize more and are less reabsorbed in acidic urine.
- Weak acids ionize more and are less reabsorbed in alkaline urine.

This principle is utilized for facilitating elimination of the drug in poisoning, i.e. urine is alkalinized in barbiturate and salicylate poisoning. Though elimination of weak bases (morphine, amphetamine) can be enhanced by acidifying urine, this is not practiced clinically, because acidosis can induce rhabdomyolysis, cardiotoxicity and actually worsen outcome. The effect of changes in urinary pH on drug excretion is greatest for those having pKa values between 5 to 8, because only in their case pH dependent passive reabsorption is significant.

Tubular secretion This is the active transfer of organic acids and bases by two separate classes of relatively nonspecific transporters (OAT and OCT) which operate in the proximal tubules. In addition, efflux transporters P-gp and MRP2 are located in the luminal membrane of proximal tubular cells. If renal clearance of a drug is greater than 120 mL/min (g.f.r.), additional tubular secretion can be assumed to be occurring.

Active transport of the drug across tubules reduces concentration of its free form in the tubular vessels and promotes dissociation of protein bound drug, which then becomes available for secretion (Fig. 3.3). Thus, protein binding, which is a hindrance for glomerular filtration of the drug, is not so (may even be facilitatory) to excretion by tubular secretion.

(a) *Organic acid transport* (through OATP) operates for penicillin, probenecid, uric acid, salicylates, indomethacin, sulfinpyrazone, nitrofurantoin, methotrexate, drug glucuronides and sulfates, etc.

(b) *Organic base transport* (through OCT) operates for thiazides, amiloride, triamterene, furosemide, quinine, procainamide, choline, cimetidine, etc.

Inherently both transport processes are bidirectional, i.e. they can transport their substrates from blood to tubular fluid and *vice versa*. However, for drugs and their metabolites (exogenous substances) secretion into the tubular lumen predominates, whereas an endogenous substrate like uric acid is predominantly reabsorbed.

Drugs utilizing the same active transport compete with each other. Probenecid is an organic acid which has high affinity for the tubular OATP. It blocks the active transport of both penicillin and uric acid, but whereas the net

excretion of the former is decreased, that of the latter is increased. This is because penicillin is primarily secreted while uric acid is primarily reabsorbed. Many drug interactions occur due to competition for tubular secretion, e.g.

(i) Aspirin blocks uricosuric action of probenecid and sulfinpyrazone and decrease tubular secretion of methotrexate.

(ii) Probenecid decreases the concentration of nitrofurantoin in urine, increases the duration of action of penicillin/ampicillin and impairs secretion of methotrexate.

(iii) Sulfinpyrazone inhibits excretion of tolbutamide.

(iv) Quinidine decreases renal and biliary clearance of digoxin by inhibiting efflux carrier P-gp.

Tubular transport mechanisms are not well developed at birth. As a result, duration of action of many drugs, e.g. penicillin, cephalosporins, aspirin is longer in neonates. These systems mature during infancy. Renal function again progressively declines after the age of 50 years; renal clearance of most drugs is substantially lower in the elderly (>75 yr).

KINETICS OF ELIMINATION

The knowledge of kinetics of elimination of a drug provides the basis for, as well as serves to devise rational dosage regimens and to modify them according to individual needs. There are three fundamental pharmacokinetic parameters, *viz.* bioavailability (F), volume of distribution (V) and clearance (CL) which must be understood. The first two have already been considered.

Drug elimination is the sumtotal of metabolic inactivation and excretion. As depicted in Fig. 2.1, drug is eliminated only from the central compartment (blood) which is in equilibrium with peripheral compartments including the site of action. Depending upon the ability of the body to eliminate a drug, a certain fraction of the central compartment may be considered to be totally 'cleared' of that drug in a given period of time to account for elimination over that period.

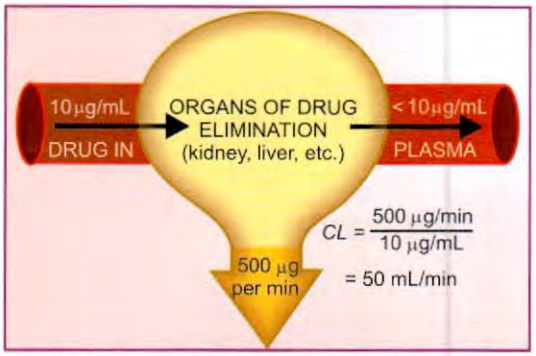


Fig. 3.4: Illustration of the concept of drug clearance. A fraction of the drug molecules present in plasma are removed on each passage through the organs of elimination. In the case shown, it requires 50 mL of plasma to account for the amount of drug being eliminated every minute: clearance is 50 mL/min

Clearance (CL) The clearance of a drug is the theoretical volume of plasma from which the drug is completely removed in unit time (analogy creatinine clearance; Fig. 3.4). It can be calculated as:

$$CL = \text{Rate of elimination}/C \quad ...(3)$$

where C is the plasma concentration.

For majority of drugs the processes involved in elimination are not saturated over the clinically obtained concentrations, they follow:

First order kinetics The rate of elimination is directly proportional to the drug concentration, CL remains constant; or a constant *fraction* of the drug present in the body is eliminated in unit time. This applies to majority of drugs which do not saturate the elimination processes (transporters, enzymes, blood flow, etc.) over the therapeutic concentration range. However, if the dose is high enough, elimination pathways of all drugs will get saturated.

Few drugs normally saturate eliminating mechanisms and are handled by—

Zero order kinetics The rate of elimination remains constant irrespective of drug concentration, CL decreases with increase in concentration; or a constant *amount* of the drug is eliminated in unit time, e.g. ethyl alcohol. This

is also called *capacity limited elimination* or *Michaelis-Menten elimination.*

The elimination of some drugs approaches saturation over the therapeutic range, kinetics changes from first order to zero order at higher doses. As a result plasma concentration increases disproportionately with increase in dose (*see* Fig. 3.6), as occurs in case of phenytoin, tolbutamide, theophylline, warfarin. Since the dose rate-plasma concentration plot in this case is curved, it is also called '*nonlinear elimination*'.

Blood flow dependent elimination For few drugs the eliminating capacity of an organ of elimination (kidney, liver) far exceeds the amount of drug normally presented to it by blood circulation. The elimination of such a drug becomes blood flow dependent. These highly extracted drugs are almost completely eliminated in a single passage through the organ of elimination.

Plasma half-life The Plasma half-life ($t\frac{1}{2}$) of a drug is the time taken for its plasma concentration to be reduced to half of its original value.

Taking the simplest case of a drug which has rapid one compartment distribution and first order elimination, and is given i.v. a semilog plasma concentration-time plot as shown in Fig. 3.5 is obtained. The plot has two slopes.

- initial rapidly declining (α) phase—due to distribution.
- later less declined (β) phase—due to elimination.

At least two half-lives (distribution $t\frac{1}{2}$ and elimination $t\frac{1}{2}$) can be calculated from the two slopes. The elimination half life derived from the β slope is simply called the 'half life' of the drug.

Most drugs infact have multicompartment distribution and multiexponential decay of plasma concentration-time plot. Half-lives calculated from the terminal slopes (when plasma concentrations are very low) are exceptionally long, probably due to release of the drug from slow equilibrating tissues, enterohepatic circulation, etc. Only the $t\frac{1}{2}$ calculated over the steady-state plasma concentration range is clinically relevant. It is this $t\frac{1}{2}$ which is commonly mentioned.

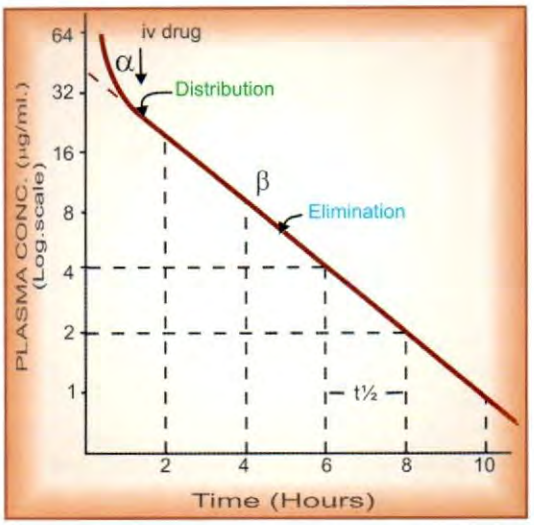


Fig. 3.5: Semilog plasma concentration-time plot of a drug eliminated by first order kinetics after intravenous injection

Since first order kinetics is an exponential process, mathematically, the elimination $t\frac{1}{2}$ is

$$t\frac{1}{2} = \frac{\ln 2}{k} \qquad ...(4)$$

Where ln2 is the natural logarithm of 2 (or 0.693) and k is the *elimination rate constant* of the drug, i.e. the fraction of the total amount of drug in the body which is removed per unit time. For example, if 2 g of the drug is present in the body and 0.1 g is eliminated every hour, then

$k = 0.1/2 = 0.05$ or 5% per hour.

It is calculated as:

$$k = \frac{CL}{V} \qquad ...(5)$$

$$\text{therefore} \quad t\frac{1}{2} = 0.693 \times \frac{V}{CL} \qquad ...(6)$$

As such, half-life is a derived parameter from two variables V and CL, both of which may change independently. It, therefore, is not an exact index of drug elimination. Nevertheless,

it is a simple and useful guide to the sojourn of the drug in the body, i.e. after

1 t½–50% drug is eliminated.
2 t½–75% (50 + 25) drug is eliminated.
3 t½–87.5% (50 + 25 + 12.5) drug is eliminated.
4 t½–93.75% (50 + 25 + 12.5 + 6.25) drug is eliminated.

Thus, nearly complete drug elimination occurs in 4–5 half lives.

For drugs eliminated by—

First order kinetics—t½ remains constant because *V* and *CL* do not change with dose.

Zero order kinetics—t½ gets prolonged with dose because *CL* progressively decreases as dose is increased. In fact, the concept of t½ is meaningless for such drugs, because, it is not a fixed value.

Half life of some representative drugs

Aspirin	4 hr	Digoxin	40 hr
Penicillin-G	30 min	Digitoxin	7 days
Doxycycline	20 hr	Phenobarbitone	90 hr

Repeated drug administration

When a drug is repeated at relatively short intervals, it accumulates in the body until elimination balances input and a *steady state* plasma concentration (*Cpss*) is attained—

$$Cpss = \frac{\text{dose rate}}{CL} \quad ...(7)$$

From this equation it is implied that doubling the dose rate would double the average *Cpss* and so on. Further, if the therapeutic plasma concentration of the drug has been worked out and its *CL* is known, the dose rate needed to achieve the target *Cpss* can be determined—

$$\text{Dose rate} = \text{target } Cpss \times CL \quad ...(8)$$

After oral administration, often only a fraction (*F*) of the dose reaches systemic circulation in the active form. In such a case—

$$\text{Dose rate} = \frac{\text{target } Cpss \times CL}{F} \quad ...(9)$$

The dose rate-*Cpss* relationship is linear only in case of drugs eliminated by first order kinetics. For drugs (e.g. phenytoin) which follow Michaelis Menten kinetics, elimination changes from first order to zero order kinetics over the therapeutic range. Increase in their dose beyond saturation levels causes an increase in *Cpss* which is out of proportion to the change in dose rate (Fig. 3.6). In their case:

$$\text{Rate of drug elimination} = \frac{(V_{max})\ (C)}{K_m + C} \quad ...(10)$$

where *C* is the plasma concentration of the drug, V_{max} is the maximum rate of drug elimination, and K_m is the plasma concentration at which elimination rate is half maximal.

Plateau principle

When constant dose of a drug is repeated before the expiry of 4 t½, it would achieve higher peak concentration, because some remnant of the previous dose will be present in the body. This continues with every dose until progressively increasing rate of elimination (which increases with increase in concentration) balances the amount administered over the dose interval. Subsequently plasma concentration plateaus

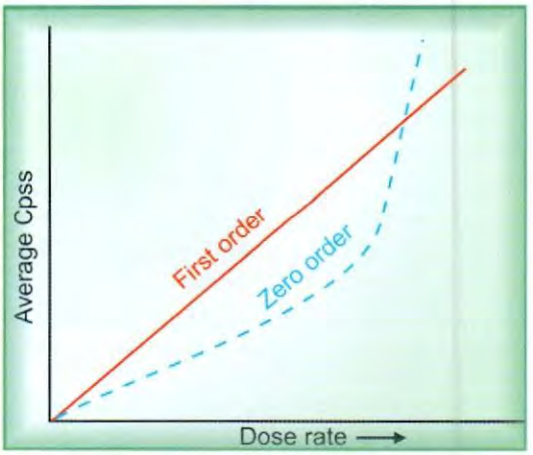


Fig. 3.6: Relationship between dose rate and average steady-state plasma concentration of drugs eliminated by first order and Michaelis Menten (zero order) kinetics

and fluctuates about an average steady-state level. This is known as the plateau principle of drug accumulation. Steady-state is reached in 4–5 half lives unless dose interval is very much longer than t½ (Fig. 3.7).

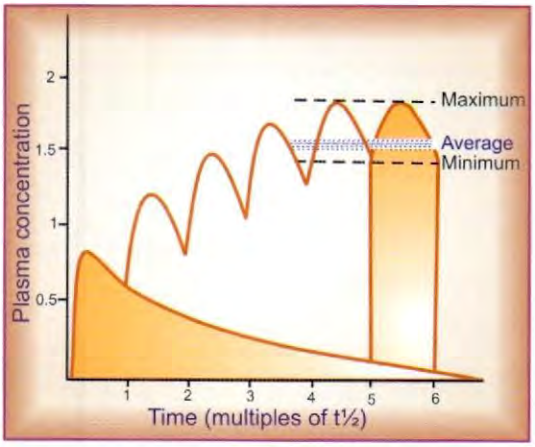


Fig. 3.7: Plateau principle of drug accumulation on repeated oral dosing.
Note. The area of the two shaded portions is equal

The amplitude of fluctuations in plasma concentration at steady-state depends on the dose interval relative to the t½, i.e. the difference between the maximum and minimum levels is less if smaller doses are repeated more frequently (dose rate remaining constant). Dose intervals are generally a compromise between what amplitude of fluctuations is clinically acceptable (because of loss of efficacy at troughs and side effects at peaks) and what frequency of dosing is convenient. However, if the dose rate is changed, a new average *Cpss* is attained over the next 4–5 half lives. When the drug is administered orally (absorption takes some time), average *Cpss* is approximately 1/3 of the way between the minimal and maximal levels in a dose interval.

Target level strategy For drugs whose effects are not easily quantifiable and safety margin is not big, e.g. anticonvulsants, antidepressants, lithium, antiarrhythmics, theophylline, some antimicrobials, etc. or those given to prevent an event, it is best to aim at achieving a certain plasma concentration which has been defined to be in the therapeutic range; such data are now available for most drugs of this type.

Drugs with short t½ (upto 2–3 hr) administered at conventional intervals (6–12 hr) achieve the target levels only intermittently and fluctuations in plasma concentration are marked. In case of many drugs (penicillin, ampicillin, chloramphenicol, erythromycin, propranolol) this however is therapeutically acceptable.

For drugs with longer t½ a dose that is sufficient to attain the target concentration after single administration, if repeated will accumulate according to plateau principle and produce toxicity later on. On the other hand, if the dosing is such as to attain target level at steady state, the therapeutic effect will be delayed by about 4 half lives (this may be clinically unacceptable). Such drugs are often administered by initial loading and subsequent maintenance doses.

Loading dose This is a single or few quickly repeated doses given in the beginning to attain target concentration rapidly. It may be calculated as—

$$\text{Loading dose} = \frac{\text{target } Cp \times V}{F} \quad ...(11)$$

Thus, loading dose is governed only by *V* and not by CL or t½.

Maintenance dose This dose is one that is to be repeated at specified intervals after the attainment of target *Cpss* so as to maintain the same by balancing elimination. The maintenance dose rate is computed by equation (9) and is governed by *CL* (or t½) of the drug. If facilities for measurement of drug concentration are available, attainment of target level in a patient can be verified subsequently and dose rate adjusted if required.

Such two phase dosing provides rapid therapeutic effect with long term safety; frequently applied to digoxin, chloroquine, long-acting sulfonamides, doxycycline, amiodarone, etc. However, if there is no urgency, maintenance

doses can be given from the beginning. The concept of loading and maintenance dose is valid also for short t½ drugs and i.v. administration in critically ill patients, e.g. lidocaine (t½ 1.5 hr) used for cardiac arrhythmias is given as an i.v. bolus dose followed by slow i.v. infusion or intermittent fractional dosing.

Monitoring of plasma concentration of drugs It is clear from the above considerations that the *Cpss* of a drug attained in a given patient depends on its *F*, *V* and *CL* in that patient. Because each of these parameters varies considerably among individuals, the actual *Cpss* in a patient may be 1/3 to 3 times that calculated on the basis of population data. Measurement of plasma drug concentration can give an estimate of the pharmacokinetic variables in that patient and the magnitude of deviation from the 'average patient', so that appropriate adjustments in the dosage regimen can be made.

In case of drugs obeying first order kinetics:

$$\text{Revised dose rate} = \frac{\text{Previous dose rate} \times \text{Target } Cpss}{\text{Measured } Cpss} \quad ...(12)$$

Therapeutic drug monitoring (TDM) is particularly useful in the following situations:

1. Drugs with low safety margin, e.g. —digoxin, anticonvulsants, antiarrhythmics, theophylline, aminoglycoside antibiotics, lithium, tricyclic antidepressants.
2. If individual variations are large, e.g.—antidepressants, lithium.
3. Potentially toxic drugs used in the presence of renal failure, e.g. —aminoglycoside antibiotics, vancomycin.
4. In case of poisoning.
5. In case of failure of response without any apparent reason, e.g. —antimicrobials.
6. To check patient compliance, e.g. —psychopharmacological agents.

Selection of the correct interval between drug administration and drawing of blood sample for TDM is critical, and depends on the purpose of TDM as well as the nature of the drug.

a. *When the purpose is dose adjustment*: In case of drugs which need to act continuously (relatively long-acting drugs), it is prudent to measure the trough steady-state blood levels, i.e. just prior to the next dose, because this is governed by both *V* and *CL*. On the other hand, for short-acting drugs which achieve therapeutic levels only intermittently (e.g. ampicillin, gentamicin), sampling is done in the immediate post-absorptive phase (usually after 1–2 hours of oral/i.m. dosing) to reflect the peak levels.
b. *In case of poisoning*: Blood for drug level estimation should be taken at the earliest to confirm the poisoning and to assess its seriousness. It should then be repeated at intervals to estimate the drug clearance in the affected patient, and the need to hasten elimination (e.g. by haemodialysis).
c. *For checking compliance to medication*: Even random blood sampling can be informative.

Monitoring of plasma concentration is of no value for

1. Drugs whose response is easily measurable, e.g.— antihypertensives, hypoglycaemics, diuretics, oral anticoagulants, inhalational general anaesthetics.
2. Drugs activated in the body, e.g.—levodopa.
3. 'Hit and run drugs' (whose effect lasts much longer than the drug itself), e.g.—reserpine, guanethidine, MAO inhibitors, omeprazole.
4. Drugs with irreversible action, e.g.—organophosphate anticholinesterases, phenoxybenzamine.

PROLONGATION OF DRUG ACTION

It is sometimes advantageous to modify a drug in such a way that it acts for a longer period. By doing so:

(i) Frequency of administration is reduced—more convenient.

(ii) Improved patient compliance—a single morning dose is less likely to be forgotten/omitted than a 6 or 8 hourly regimen; a monthly or quarterly administered contraceptive over one that has to be taken daily.

(iii) Large fluctuations in plasma concentration are avoided—side effects related to high peak

plasma level just after a dose (e.g. nifedipine) would be minimized; better round-the-clock control of blood sugar level, etc.
(iv) Drug effect could be maintained overnight without disturbing sleep, e.g. antiasthmatics, anticonvulsants, etc.

However, all drugs do not need to be made long acting, e.g. those used for brief therapeutic effect (sleep-inducing hypnotic, headache remedy) or those with inherently long duration of action (doxycycline, omeprazole, digoxin, amlodipine). Drugs with $t_{1/2} \leq 4$ hr are suitable for controlled release formulations, while there is no need of such formulations for drugs with $t_{1/2} \geq 12$ hr. Methods utilized for prolonging drug action are summarised below. Some of these have already been described.

1. By prolonging absorption from site of administration

(a) *Oral* Sustained release tablets, spansule capsules, etc.; drug particles are coated with resins, plastic materials or other substances which temporally disperse release of the active ingredient in the g.i.t. Another technique (controlled release tablet/capsule; Fig. 3.8) utilizes a semipermeable membrane to control the release of drug from the dosage form. Such preparations prolong the action by 4 to 8 hours and no more, because in that time drug particles reach the colon. Also, the drug release pattern and consequently the attained blood levels of the drug may be more variable than the regular tablet of the same drug.

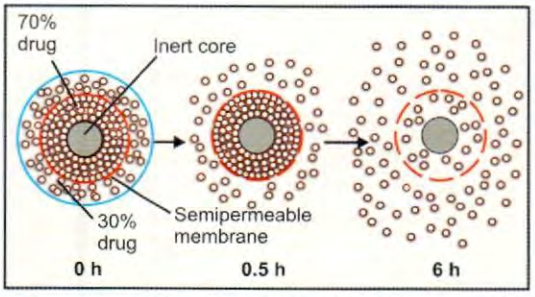


Fig. 3.8: Pattern of drug release from oral controlled release tablet/capsule; 30% of the dose outside the semipermeable membrane is released immediately, while 70% of the dose is released slowly through the membrane over the next 4–8 hours

(b) *Parenteral* The s.c. and i.m. injection of drug in insoluble form (benzathine penicillin, lente insulin) or as oily solution (depot progestins); pellet implantation, sialistic and biodegradable implants can provide for its absorption over a couple of days to several months or even years. Inclusion of a vasoconstrictor with the drug also delays absorption (adrenaline with local anaesthetics).

(c) *Transdermal drug delivery systems* The drug impregnated in adhesive patches, strips or as ointment applied on skin is utilized in some cases to prolong drug action, e.g. GTN (*see* p. 12).

2. By increasing plasma protein binding

Drug congeners have been prepared which are highly bound to plasma protein and are slowly released in the free active form, e.g. sulfadoxine.

3. By retarding rate of metabolism Small chemical modification can markedly affect the rate of metabolism without affecting the biological action, e.g. addition of ethinyl group to estradiol (ethinyl estradiol) makes it longer acting and suitable for use as oral contraceptive. Inhibition of specific enzyme by one drug can prolong the action of another drug, e.g. allopurinol inhibits the degradation of 6-mercaptopurine, ritonavir boosts the levels of atazanavir/lopinavir/saquinavir, cilastatin protects imipenem from degradation in kidney.

4. By retarding renal excretion The tubular secretion of drug being an active process, can be suppressed by a competing substance, e.g. probenecid prolongs duration of action of penicillin, ampicillin and amoxicillin.

Targeted drug delivery devices

Some new devices have been invented (and many are under development) to localise and prolong the delivery of the contained drug to a specific target organ. The ones already in use are:

1. *Liposomes* These are unilamellar or bilamellar nano-vesicles (60–80 nM) produced by sonication of lecithin or other biodegradable phospholipids. Since liposomes injected i.v. are selectively taken up by reticuloendothelial cells, especially liver and spleen, and some malignant cells, the drug incorporated in them gets selectively delivered to these cells. Liposomal amphotericin B is being used in Kala azar and some serious cases of systemic mycosis. Antibody tagging of liposomes is being tried as a means to target other specific tissues.

2. *Drug releasing implants* The implant is coated with the drug using special techniques and then placed in the target organ to provide prolonged delivery of minute quantities of the drug by slow release. Progestin impregnated intrauterine contraceptive device (IUCD) affords protection for upto 5 years. It is also being tried for other gynaecological problems. Antithrombotic drug coated stents (devices placed in the thrombosed coronary artery after balloon angioplasty to keep it patent) are in use to prevent restenosis and failure of angioplasty.

☞ PROBLEM DIRECTED STUDY

3.1 A 30-year-old mother of 2 children weighing 60 kg was taking combined oral contraceptive pill containing levonorgestrel 0.15 mg + ethinylestradiol 30 μg per day cyclically (3 weeks treatment—1 week gap). She developed fever with cough and was diagnosed as a case of pulmonary tuberculosis after sputum smear examination. She was put on isoniazid (300 mg) + rifampin (600 mg) + pyrazinamide (1.5 g) + ethambutol (1.0 g) daily for 2 months, followed by isoniazid (600 mg) + rifampin (600 mg) thrice weekly. In the 3rd month she failed to have the usual withdrawal bleeding during the gap period of contraceptive cycle. After 10 days her urinary pregnancy test was found to be positive.

(a) What could be the reason for failure of the oral contraceptive?

(b) What precaution could have prevented the unwanted pregnancy?

3.2 A 20-year-old patient weighing 60 kg has to be prescribed an antiepileptic drug (available as 200 and 400 mg tablets) for generalized tonic-clonic seizures. The pharmacokinetic parameters and therapeutic plasma concentration of the selected drug are:

Target steady-state plasma concentration (Cpss)	– 6 mg/L
Oral bioavailability (F)	– 70%
Volume of distribution (V)	– 1.4 L/kg
Clearance (CL)	– 80 ml/hr/kg
Plasma half life (t½)	– 15 hours

What should be the loading dose and the daily maintenance dose of the drug for this patient? (see Appendix-1 for solutions)

Chapter 4 Pharmacodynamics: Mechanism of Drug Action; Receptor Pharmacology

Pharmacodynamics is the study of drug effects. It starts with describing what the drugs do, and goes on to explain how they do it. Thus, it attempts to elucidate the complete action-effect sequence and the dose-effect relationship. Modification of the action of one drug by another drug is also an aspect of pharmacodynamics.

PRINCIPLES OF DRUG ACTION

Drugs (except those gene based) do not impart new functions to any system, organ or cell; they only alter the pace of ongoing activity. However, this alone can have profound medicinal as well as toxicological impact. The basic types of drug action can be broadly classed as:

1. Stimulation It refers to selective enhancement of the level of activity of specialized cells, e.g. adrenaline stimulates heart, pilocarpine stimulates salivary glands. However, excessive stimulation is often followed by depression of that function, e.g. high dose of picrotoxin, a central nervous system (CNS) stimulant, produces convulsions followed by coma and respiratory depression.

2. Depression It means selective diminution of activity of specialized cells, e.g. barbiturates depress CNS, quinidine depresses heart, omeprazole depresses gastric acid secretion. Certain drugs stimulate one type of cells but depress the other, e.g. acetylcholine stimulates intestinal smooth muscle but depresses SA node in heart. Thus, most drugs cannot be simply classed as stimulants or depressants.

3. Irritation This connotes a nonselective, often noxious effect and is particularly applied to less specialized cells (epithelium, connective tissue). Strong irritation results in inflammation, corrosion, necrosis and morphological damage. This may result in diminution or loss of function.

4. Replacement This refers to the use of natural metabolites, hormones or their congeners in deficiency states, e.g. levodopa in parkinsonism, insulin in diabetes mellitus, iron in anaemia.

5. Cytotoxic action Selective cytotoxic action on invading parasites or cancer cells, attenuating them without significantly affecting the host cells is utilized for cure/palliation of infections and neoplasms, e.g. penicillin, chloroquine, zidovudine, cyclophosphamide, etc.

MECHANISM OF DRUG ACTION

Only a handful of drugs act by virtue of their simple physical or chemical property; examples are:

- Bulk laxatives (ispaghula)—physical mass
- Dimethicone, petroleum jelly—physical form, opacity
- Paraamino benzoic acid—absorption of UV rays
- Activated charcoal—adsorptive property
- Mannitol, mag. sulfate—osmotic activity
- ^{131}I and other radioisotopes—radioactivity
- Antacids—neutralization of gastric HCl
- Pot. permanganate—oxidizing property
- Chelating agents (EDTA, dimercaprol)—chelation of heavy metals.
- Cholestyramine—sequestration of bile acids and cholesterol in the gut
- Mesna—Scavenging of vasicotoxic reactive metabolites of cyclophosphamide

Majority of drugs produce their effects by interacting with a discrete target biomolecules, which usually are proteins. Such mechanism confers selectivity of action to the drug. Functional proteins that are targets of drug action

can be grouped into *four* major categories, *viz.* enzymes, ion channels, transporters and receptors (*see* Fig. 4.1). However, a few drugs do act on other proteins (e.g. colchicine, vinca alkaloids, taxanes bind to the structural protein tubulin) or on nucleic acids (alkylating agents).

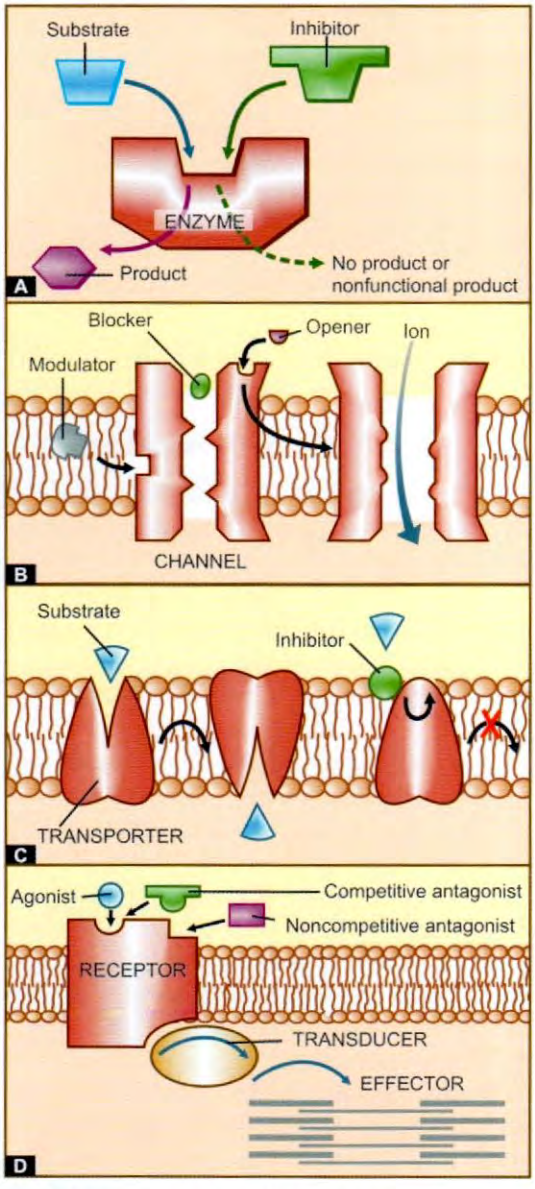


Fig. 4.1: Four major types of biomacromolecular targets of drug action.
(A) Enzyme; (B) Transmembrane ion channel; (C) Membrane bound transporter; (D) Receptor (*see* text for description)

I. ENZYMES

Almost all biological reactions are carried out under catalytic influence of enzymes; hence, enzymes are a very important target of drug action. Drugs can either increase or decrease the rate of enzymatically mediated reactions. However, in physiological systems enzyme activities are often optimally set. Thus, stimulation of enzymes by drugs, that are truly foreign substances, is unusual. Enzyme stimulation is relevant to some natural metabolites only, e.g. pyridoxine acts as a cofactor and increases decarboxylase activity. Several enzymes are stimulated through receptors and second messengers, e.g. adrenaline stimulates hepatic glycogen phosphorylase through β receptors and cyclic AMP. Stimulation of an enzyme increases its affinity for the substrate so that rate constant (*kM*) of the reaction is lowered (Fig. 4.2).

Apparent increase in enzyme activity can also occur by *enzyme induction,* i.e. synthesis

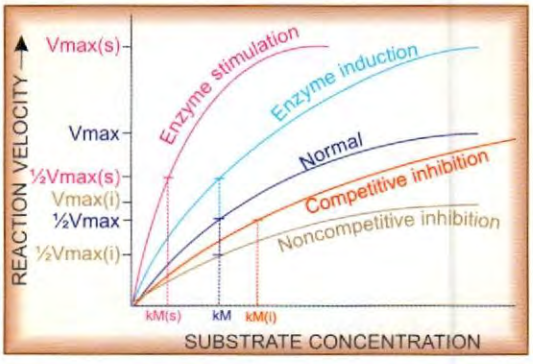


Fig. 4.2: Effect of enzyme induction, stimulation and inhibition on kinetics of enzyme reaction
Vmax—Maximum velocity of reaction; *Vmax (s)* of stimulated enzyme; *Vmax (i)*—in presence of noncompetitive inhibitor; *kM*—rate constant of the reaction; *kM (s)*—of stimulated enzyme; *kM (i)*—in presence of competitive inhibitor
Note: Enzyme induction and noncompetitive inhibition do not change the affinity of the enzyme (*kM* is unaltered), whereas enzyme stimulation and competitive inhibition respectively decrease and increase the *kM.*

Enzyme	Endogenous substrate	Competitive inhibitor
Cholinesterase	Acetylcholine	Physostigmine, Neostigmine
Monoamine-oxidase A (MAO-A)	Catecholamines	Moclobemide
Dopa decarboxylase	Levodopa	Carbidopa, Benserazide
Xanthine oxidase	Hypoxanthine	Allopurinol
Angiotensin converting enzyme (ACE)	Angiotensin-1	Captopril
5α-Reductase	Testosterone	Finasteride
Aromatase	Testosterone, Androstenedione	Letrozole, Anastrozole
Bacterial folate synthase	Para-amino benzoic acid (PABA)	Sulfadiazine

of more enzyme protein. This cannot be called stimulation because the *kM* does not change. Many drugs induce microsomal enzymes (*see* p. 33).

Enzyme inhibition

Some chemicals (heavy metal salts, strong acids and alkalies, formaldehyde, phenol, etc.) denature proteins and inhibit all enzymes nonselectively. They have limited medicinal value restricted to external application only. However, selective inhibition of a particular enzyme is a common mode of drug action. Such inhibition is either competitive or noncompetitive.

(i) Competitive *(equilibrium type)* The drug being structurally similar competes with the normal substrate for the catalytic binding site of the enzyme so that the product is not formed or a nonfunctional product is formed (Fig. 4.1A), and a new equilibrium is achieved in the presence of the drug. Such inhibitors increase the *kM* but the *Vmax* remains unchanged (Fig. 4.2), i.e. higher concentration of the substrate is required to achieve ½ maximal reaction velocity, but if substrate concentration is sufficiently increased, it can displace the inhibitor and the same maximal reaction velocity can be attained. Examples are given in the box above.

A *nonequilibrium type* of enzyme inhibition can also occur with drugs which react with the same catalytic site of the enzyme but either form strong covalent bonds or have such high affinity for the enzyme that the normal substrate is not able to displace the inhibitor, e.g.

- Organophosphates react covalently with the esteretic site of the enzyme cholinesterase.
- Methotrexate has 50,000 times higher affinity for dihydrofolate reductase than the normal substrate DHFA.

In these situations, *kM* is increased and *Vmax* is reduced.

(ii) Noncompetitive The inhibitor reacts with an adjacent site and not with the catalytic site, but alters the enzyme in such a way that it loses its catalytic property. Thus, *kM* is unchanged but *Vmax* is reduced. Examples are given in the box.

Noncompetitive inhibitor		Enzyme
Acetazolamide	—	Carbonic anhydrase
Aspirin, indomethacin	—	Cyclooxygenase
Disulfiram	—	Aldehyde dehydrogenase
Omeprazole	—	H^+ K^+ ATPase
Digoxin	—	Na^+ K^+ ATPase
Theophylline	—	Phosphodiesterase
Propylthiouracil	—	Peroxidase in thyroid
Lovastatin	—	HMG-CoA reductase
Sildenafil	—	Phosphodiesterase-5

II. ION CHANNELS

Proteins which act as ion selective channels participate in transmembrane signaling and regulate intracellular ionic composition. This makes them a common target of drug action (Fig. 4.1B). Drugs can affect ion channels, some of which actually are receptors, because they are operated by specific signal molecules either directly and are called *ligand gated channels*

(e.g. nicotinic receptor, *see* Fig. 4.4) or through G-proteins and are termed *G-protein regulated channels* (e.g. cardiac β_1 adrenergic receptor activated Ca^{2+} channel, *see* Table 4.1). Drugs can also act on *voltage operated* and *stretch sensitive* channels by directly binding to the channel and affecting ion movement through it, e.g. local anaesthetics which obstruct voltage sensitive Na^+ channels (*see* Ch. 26). In addition, certain drugs modulate opening and closing of the channels, e.g.:

- Quinidine blocks myocardial Na^+ channels.
- Dofetilide and amiodarone block myocardial delayed rectifier K^+ channel.
- Nifedipine blocks L-type of voltage sensitive Ca^{2+} channel.
- Nicorandil opens ATP-sensitive K^+ channels.
- Sulfonylurea hypoglycaemics inhibit pancreatic ATP-sensitive K^+ channels (*see* Fig. 19.6).
- Amiloride inhibits renal epithelial Na^+ channels (*see* Fig. 42.3).
- Phenytoin modulates (prolongs the inactivated state of) voltage sensitive neuronal Na^+ channel (Fig. 30.1).
- Ethosuximide inhibits T-type of Ca^{2+} channels in thalamic neurones.

III. TRANSPORTERS

Several substrates are translocated across membranes by binding to specific transporters (carriers) which either facilitate diffusion in the direction of the concentration gradient or pump the metabolite/ion against the concentration gradient using metabolic energy (*see* p. 18–19; Fig. 2.5). Many drugs produce their action by directly interacting with the solute carrier (SLC) class of transporter proteins to inhibit the ongoing physiological transport of the metabolite/ion (Fig. 4.1C). Examples are:

- Desipramine and cocaine block neuronal reuptake of noradrenaline by interacting with norepinephrine transporter (NET) as depicted in Fig. 9.4.
- Fluoxetine (and other SSRIs) inhibit neuronal reuptake of 5-HT by interacting with serotonin transporter (SERT), Fig. 33.1.
- Amphetamines selectively block dopamine reuptake in brain neurons by dopamine transporter (DAT).
- Reserpine blocks the vesicular reuptake of noradrenaline and 5-HT by the vesicular monoamine transporter (VMAT-2), see Fig. 9.4.
- Hemicholinium blocks choline uptake into cholinergic neurones and depletes acetylcholine (*see* Fig. 7.1).
- The anticonvulsant tiagabine acts by inhibiting reuptake of GABA into brain neurones by GABA transporter GAT1 (*see* Fig. 30.1).
- Furosemide inhibits the $Na^+K^+2Cl^-$ cotransporter in the ascending limb of loop of Henle (*see* Fig. 42.1).
- Hydrochlorothiazide inhibits the Na^+Cl^- symporter in the early distal tubule (*see* Fig. 42.2).
- Probenecid inhibits active transport of organic acids (uric acid, penicillin) in renal tubules by interacting with organic anion transporter (OAT).

IV. RECEPTORS

The largest number of drugs do not bind directly to the effectors, *viz.* enzymes, channels, transporters, structural proteins, template biomolecules, etc. but act through specific regulatory macromolecules which control the above listed effectors. These regulatory macromolecules or the sites on them which associate with and interact with the drug are called 'receptors'.

Receptor: It is defined as a macromolecule or binding site located on the surface or inside the effector cell that serves to recognize the signal molecule/drug and initiate the response to it, but itself has no other function.

Though, in a broad sense *all types* of target biomolecules, including the effectors (enzymes, channels, transporters, etc.) with which a drug can bind to produce its action have been denoted as 'receptors' by some authors, such designation tends to steal the specific meaning of this important term.

If so applied, xanthine oxidase would be the 'receptor' for allopurinol, L-type Ca^{2+} channel would be the 'receptor' for nifedipine, serotonin transporter (SERT) would be the 'receptor' for fluoxetine; a connotation not in consonence with the general understanding of the term 'receptor'. It is therefore better to reserve the term 'receptor' for purely regulatory macromolecules which combine with and mediate the action of signal molecules including drugs.

The following terms are used in describing drug-receptor interaction:

Agonist An agent which activates a receptor to produce an effect similar to that of the physiological signal molecule.

Inverse agonist An agent which activates a receptor to produce an effect in the opposite direction to that of the agonist.

Antagonist An agent which prevents the action of an agonist on a receptor or the subsequent response, but does not have any effect of its own.

Partial agonist An agent which activates a receptor to produce submaximal effect but antagonizes the action of a full agonist.

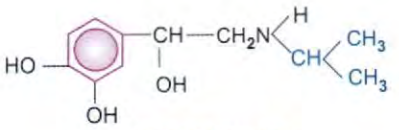
Ligand (Latin: *ligare*—to bind) Any molecule which attaches selectively to particular receptors or sites. The term only indicates affinity or ability to bind without regard to functional change: agonists and competitive antagonists are both ligands of the same receptor.

The overall scheme of drug action through receptors is depicted in Fig. 4.1D.

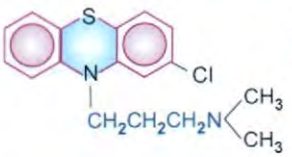
Basic evidences for drug action through receptors

(i) Many drugs exhibit structural specificity of action, i.e. specific chemical configuration is associated with a particular action, e.g. isopropyl substitution on the ethylamine side chain of sympathetic drugs produces compounds with marked cardiac and bronchial activity—most β adrenergic agonists and antagonists have this substitution. A 3 carbon internitrogen separation in the side chain of phenothiazines results in antidopaminergic-antipsychotic compounds, whereas 2 carbon separation produces anticholinergic-antihistaminic compounds. Further, chiral drugs show stereospecificity in action, e.g. *levo* noradrenaline is 10 times more potent than *dextro* noradrenaline; *d*-propranolol is about 100 times less potent in blocking β receptors than the *l*-isomer, but both are equipotent local anaesthetics.

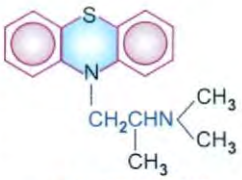
Thus, the cell must have some mechanism to recognize a particular chemical configuration and three dimensional structure.



ISOPRENALINE



CHLORPROMAZINE



PROMETHAZINE

(ii) Competitive antagonism is seen between specific agonists and antagonists. Langley in 1878 was so impressed by the mutual antagonism among two alkaloids pilocarpine and atropine that he proposed that both reacted with the same 'receptive substance' on the cell. Ehrlich (1900) observed quantitative neutralization between toxins and antitoxins and designated 'receptor' to be the anchoring group of the protoplasmic molecule for the administered compound.

(iii) It was calculated by Clark that adrenaline and acetylcholine produce their maximal effect on frog's heart by occupying only 1/6000th of the cardiac cell surface—thus, special regions of reactivity to such drugs must be present on the cell.

Receptor occupation theory

After studying quantitative aspects of drug action, Clark (1937) propounded a theory of drug action based on occupation of receptors by specific drugs and that the pace of a cellular function can be altered by interaction of these receptors with drugs which, in fact, are small molecular ligands. He perceived the interaction between the two molecular species, *viz.* drug (D) and receptor (R) to be governed by the law of mass action, and the effect (E) to be a direct function of the drug-receptor complex (DR) formed:

$$D + R \underset{K_2}{\overset{K_1}{\rightleftharpoons}} DR \longrightarrow E \quad ...(1)$$

Subsequently, it was realized that occupation of the receptor is essential but not itself sufficient to elicit a response; the agonist must also be able to activate (induce a conformational change in) the receptor. The ability to bind

CHAPTER 4

with the receptor designated as *affinity,* and the capacity to induce a functional change in the receptor designated as *intrinsic activity (IA)* or *efficacy* are independent properties.

Affinity of a drug for a receptor determines its concetration around the receptor required to form a certain number of drug-receptor associations (DRs). Higher affinity implies that the same number of DRs will be formed at lower concentrations of the drug, compared to another drug which has lower affinity.

Intrinsic activity of a drug is a measure of its ability to induce a functional change in the receptor which could vary from 0 to 1 (nil to maximal).

Competitive antagonists occupy the receptor but do not activate it, while certain drugs are partial agonists which occupy and submaximally activate the receptor. An all or none action is not a must at the receptor. A theoretical quantity (S) denoting strength of stimulus imparted to the cell was interposed in the Clark's equation:

$$D + R \underset{K_2}{\overset{K_1}{\rightleftharpoons}} DR \rightsquigarrow S \longrightarrow E \quad ...(2)$$

Depending on the agonist, DR could generate a stronger or weaker S, probably as a function of the degree of conformational change brought about by the agonist in the receptor. Accordingly:

Agonists have both affinity and maximal intrinsic activity (IA = 1), e.g. adrenaline, histamine, morphine.

Competitive antagonists have affinity but no intrinsic activity (IA = 0), e.g. propranolol, atropine, chlorpheniramine, naloxone.

Partial agonists have affinity and submaximal intrinsic activity (IA between 0 and 1), e.g. dichloroisoproterenol (on β adrenergic receptor), buspirone on 5-HT_{1A} receptor.

The lower ceiling response to a partial agonist is not because of lower affinity for the receptor. In fact some partial agonists have higher affinity and are dose-to-dose more potent than the full agonist, e.g. buprenorphine is 25 times more potent than morphine (full agonist of μ opioid receptor) but is a partial agonist and cannot relieve very severe pain or deeply depress respiration.

Partial agonists also antagonize the effects of a full agonist, because they occupy a large population of the receptors (while producing small response) and leave fewer receptors to interact with the full agonist. As such, buprenorphine precipitates withdrawal symptoms in a highly morphine dependent subject, but can substitute for it at lower levels of morphine dependence.

Inverse agonists have affinity but intrinsic activity with a minus sign (IA between 0 and –1). Inverse agonism is manifest only in case of some receptors which show certain degree of *Constitutive activation*, i.e. they are partially active even in the basal state (complete absence of any agonist). In other words they are tonically active. The benzodiazepine receptor (*see* Fig. 29.3) is one such receptor, and DMCM is its inverse agonist. However, majority of receptors (like the NM nicotinic receptor) are totally inactive in the absence of an agonist, and there is no scope for inverse agonism.

It has also been demonstrated that many full agonists can produce maximal response even while occupying <1% of the available receptors. A large receptor reserve exists in their case, or a number of *spare receptors* are present. On the other hand, for certain drugs, the total number of receptors may limit the maximal response, and there are no space receptors.

The two-state receptor model

An attractive alternative model for explaining the action of agonists, antagonists, partial agonists and inverse agonists has been proposed.

The receptor is believed to exist in two interchangeable states: *Ra* (active) and *Ri* (inactive) which are in equilibrium. In the case of majority of receptors, the *Ri* state is favoured at equilibrium—no/very weak signal is generated in the absence of the agonist—the receptor exhibits no constitutive activation (Fig. 4.3I). The agonist (A) binds preferentially to the *Ra* conformation and shifts the equilibrium → *Ra*

predominates and a response is generated (Fig. 4.3II) depending on the concentration of A. The competitive antagonist (B) binds to *Ra* and *Ri* with equal affinity → the equilibrium is not altered → no response is generated (Fig. 4.3 III), and when the agonist is applied fewer *Ra* are available to bind it—response to agonist is decreased. If an agonist has only slightly greater affinity for *Ra* than for *Ri,* the equilibrium is only modestly shifted towards *Ra* (Fig. 4.3 IV) even at saturating concentrations → a submaximal response is produced and the drug is called a partial agonist (C). The inverse agonist (D) has high affinity for the *Ri* state (Fig. 4.3V), therefore it can produce an opposite response, provided the resting equilibrium was in favour of the *Ra* state. Certain ion channel receptors such as benzodiazepine receptor and some G-protein coupled receptors like histamine H_2, angiotensin AT_1, adrenergic β_1 and cannabinoid receptors exhibit constitutive activation, i.e. an appreciable intensity signal is generated even in the basal state (no agonist present). In their case the inverse agonist stabilizes the receptor in the inactive conformation resulting in an opposite response. Only few inverse agonists are known at present.

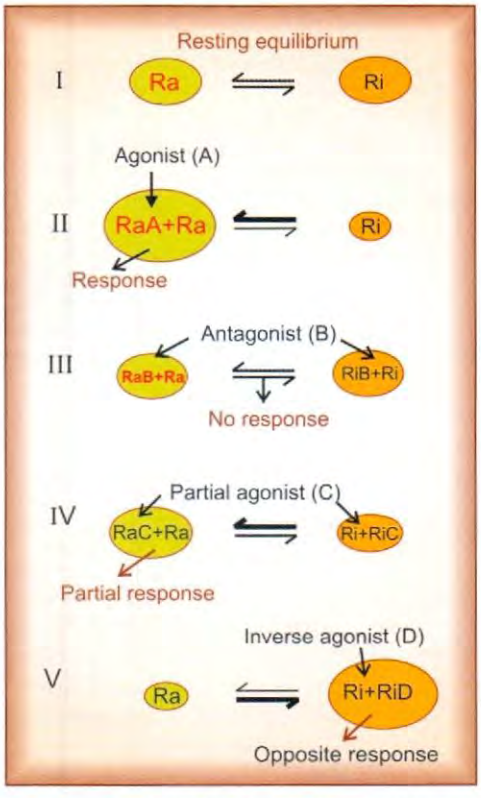


Fig. 4.3: Illustration of the two-state receptor model (*see* text for explanation)

This model provides an explanation for the phenomenon of positive cooperativity often seen with neurotransmitters, and is supported by studies of conformational mutants of the receptor with altered equilibrium. However, receptors are now known to be capable of adopting not just two, but multiple active and inactive conformations favoured by different ligands.

Nature of receptors

Receptors are regulatory macromolecules, mostly proteins, though nucleic acids may also serve as receptors. Hundreds of receptor proteins have been isolated, purified, cloned and their primary amino acid (AA) sequence has been worked out. Molecular cloning has also helped in obtaining the receptor protein in larger quantity to study its structure and properties, and in subclassifying receptors. The cell surface receptors with their coupling and effector proteins are considered to be floating in a sea of membrane lipids; the folding, orientation and topography of the system being determined by interactions between the lipophilic and hydrophilic domains of the peptide chains with solvent molecules (water on one side and lipids on the other). Nonpolar portions of the AA chain tend to bury within the membrane, while polar groups tend to come out in the aqueous medium. In such a delicately balanced system, it is not difficult to visualize that a small molecular ligand binding to one site in the receptor molecule could be capable of tripping the balance (by altering distribution of charges, etc.) and bringing about conformational changes at distant sites. Each of the five major families of receptors (described later) have a well defined common structural motif, while the individual receptors

differ in the details of amino acid sequencing, length of intra/extracellular loops, etc. Majority of receptor molecules are made up of several non-identical subunits (heteropolymeric), and agonist binding has been shown to bring about changes in their quaternary structure or relative alignment of the subunits, e.g. on activation the subunits of nicotinic receptor move apart opening a centrally located cation channel.

Many clinically useful drugs act upon *physiological receptors* which mediate responses to transmitters, hormones, autacoids and other endogenous signal molecules; examples are cholinergic, adrenergic, histaminergic, steroid, leukotriene, insulin and other such receptors. In addition, now some truly *drug receptors* have been described for which there are no known physiological ligands, e.g. benzodiazepine receptor, sulfonylurea receptor. Receptors for which no endogenous mediator or ligand is at present known are called *'Orphan receptors'*. They, nevertheless, may prove to be targets for novel drugs yet to be developed.

Receptor subtypes

The delineation of multiple types and subtypes of receptors for signal molecules has played an important role in the development of a number of targeted and more selective drugs. Even at an early stage of evolution of receptor pharmacology, it was observed that actions of acetylcholine could be grouped into 'muscarinic' and 'nicotinic' depending upon whether they were mimicked by the then known alkaloids muscarine or nicotine. Accordingly, they were said to be mediated by two types of cholinergic receptors, *viz.* muscarinic (M) or nicotinic (N); a concept strengthened by the finding that muscarinic actions were blocked by atropine, while nicotinic actions were blocked by curare. In a landmark study, Ahlquist (1948) divided adrenergic receptors into 'α' and 'β' on the basis of two distinct rankorder of potencies of adrenergic agonists. These receptors have now been further subdivided (M_1, M_2 ....M_5), (N_M, N_N) (α_1, α_2) (β_1, β_2, β_3). Multiple subtypes of receptors for practically all transmitters, autacoids, hormones, etc. are now known and have paved the way for introduction of numerous clinically superior drugs. In many cases, receptor classification has provided sound explanation for differences observed in the actions of closely related drugs.

The following criteria have been utilized in classifying receptors:

a. Pharmacological criteria Classification is based on relative potencies of selective agonists and antagonists. This is the classical and oldest approach with direct clinical bearing; was used in delineating M and N cholinergic, α and β adrenergic, H_1 and H_2 histaminergic receptors, etc.

b. Tissue distribution The relative organ/tissue distribution is the basis for designating the subtype, e.g. the cardiac β adrenergic receptors as β_1, while bronchial as β_2. This division was confirmed by selective agonists and antagonists as well as by molecular cloning.

c. Ligand binding Measurement of specific binding of high affinity radio-labelled ligand to cellular fragments (usually membranes) *in vitro*, and its displacement by various selective agonists/antagonists is used to delineate receptor subtypes. Multiple 5-HT receptors were distinguished by this approach. Autoradiography has helped in mapping distribution of receptor subtypes in the brain and other organs.

d. Transducer pathway Receptor subtypes may be distinguished by the mechanism through which their activation is linked to the response, e.g. M cholinergic receptor acts through G-proteins, while N cholinergic receptor gates influx of Na^+ ions; α adrenergic receptor acts *via* IP_3-DAG pathway and by decreasing cAMP, while β adrenergic receptor increases cAMP; $GABA_A$ receptor is a ligand gated Cl^- channel, while $GABA_B$ receptor increases K^+ conductance through a G-protein.

e. Molecular cloning The receptor protein is cloned and its detailed amino acid sequence as well as three dimentional structure is worked out. Subtypes are designated on the basis of sequence homology. This approach has in the recent years resulted in a flood of receptor subtypes and several isoforms (which do not differ in ligand selectivity) of each subtype. The functional significance of many of these subtypes/isoforms is dubious. Even receptors without known ligands (orphan receptors) have been described.

Application of so many approaches has thrown up several detailed, confusing and often conflicting classifications of receptors in the past. However, a consensus receptor classification is now decided on a continuing basis by an expert group of the International Union of Pharmacological Sciences (IUPHAR).

Silent receptors These are sites which bind specific drugs but no pharmacological response is elicited. They are better called *inert binding sites* or *sites of loss*, e.g. plasma proteins which have binding sites for many drugs. To avoid confusion, the term receptor should be restricted to those regulatory binding sites which are capable of generating a response.

ACTION-EFFECT SEQUENCE

'Drug action' and 'drug effect' are often loosely used interchangeably, but are not synonymous.

Drug action It is the initial combination of the drug with its receptor resulting in a conformational change in the latter (in case of agonists), or prevention of conformational change through exclusion of the agonist (in case of antagonists).

Drug effect It is the ultimate change in biological function brought about as a consequence of drug action, through a series of intermediate steps (transducer).

Receptors subserve two essential functions, *viz*, *recognition* of the specific ligand molecule and *transduction* of the signal into a response. Accordingly, the receptor molecule has a *ligand binding domain* (spatially and energetically suitable for binding the specific ligand) and an *effector domain* (Fig. 4.4) which undergoes a functional conformational change. These domains have now actually been identified in some receptors. The perturbation in the receptor molecule is variously translated into the response. The sequential relationship between drug action, transducer and drug effect can be seen in Fig. 4.1D and 4.6.

TRANSDUCER MECHANISMS

Considerable progress has been made in the understanding of transducer mechanisms which in most instances have been found to be highly complex multistep processes that provide for

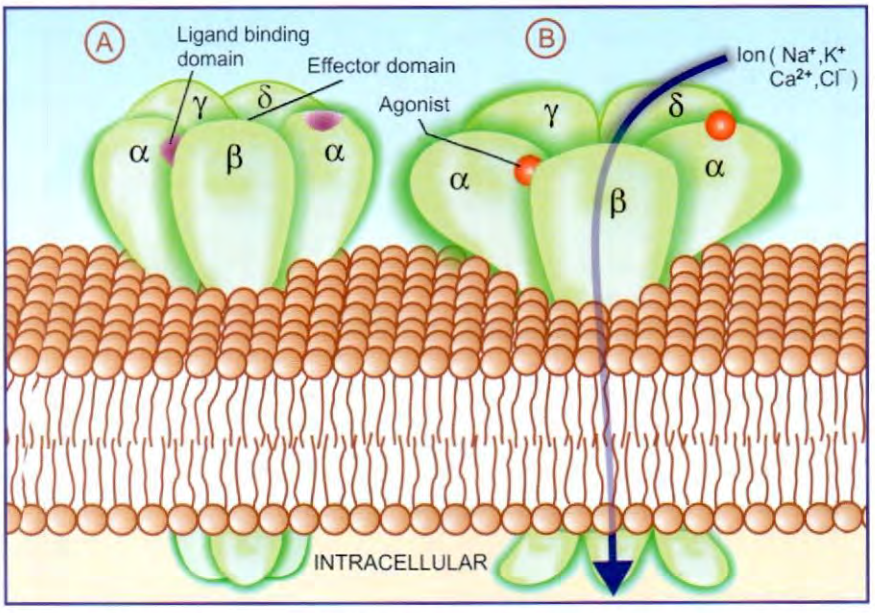


Fig. 4.4: Diagrammatic representation of receptor mediated operation of membrane ion channel
In case of nicotinic cholinergic receptor, the molecule (8 nm in diameter) is composed of 5 subunits ($2\alpha + \beta + \gamma + \delta$) enclosing a transmembrane ion channel within the α subunit. Normally the channel is closed (A). When two molecules of acetylcholine bind to the two α subunits (B), all subunits move apart opening the central pore to 0.7 nm, enough to allow passage of partially hydrated Na^+ ions. Anions are blocked from passage through the channel by positive charges lining it.
In other cases, K^+, Ca^{2+} or Cl^- ions move through the channel depending on its ion selectivity.

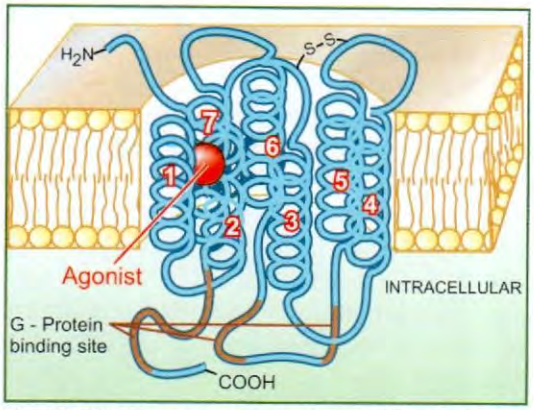


Fig. 4.5: Diagrammatic representation of G-protein coupled receptor molecule
The receptor consists of 7 membrane spanning helical segments of hydrophobic amino acids. The intervening segments connecting the helices form 3 loops on either side of the membrane. The amino terminus of the chain lies on the extracellular face, while the carboxy terminus is on the cytosolic side. The approximate location of the agonist and G-protein binding sites is indicated.

amplification of the signal, as well as integration of concurrently received extra- and intra-cellular signals at each step. Because only a handful of transducer pathways are shared by a large number of receptors, the cell is able to generate an integrated response reflecting the sum total of diverse signal inputs. The transducer mechanisms can be grouped into 5 major categories. Receptors falling in one category also possess considerable structural homology, and belong to one super-family of receptors.

1. G-protein coupled receptors (GPCRs)

These are a large family of cell membrane receptors which are linked to the effector (enzyme/channel/transporter) through one or more GTP-activated proteins (G-proteins) for response effectuation. All such receptors have a common pattern of structural organization (Fig. 4.5). The molecule has 7 α-helical membrane spanning hydrophobic amino acid (AA) segments which run into 3 extracellular and 3 intracellular loops. The agonist binding site is located somewhere between the helices on the extracellular face, while another recognition site formed by cytosolic segments binds the coupling G-protein. The G-proteins float in the membrane with their exposed domain lying in the cytosol, and are heterotrimeric in composition (α, β and γ subunits). In the inactive state GDP is bound to the α subunit at the exposed domain; activation through the receptor leads to displacement of GDP by GTP. The activated α-subunit carrying GTP dissociates from the other two subunits and either activates or inhibits the effector. The βγ diamer has also been shown to activate receptor-operated K^+ channels, to inhibit voltage gated Ca^{2+} channels and to promote GPCR desensitization at higher rates of activation.

A number of G proteins distinguished by their α subunits have been described. The important ones with their action on the effector are:

- Gs : Adenylyl cyclase activation, Ca^{2+} channel opening
- Gi : Adenylyl cyclase inhibition, K^+ channel opening
- Go : Ca^{2+} channel inhibition
- Gq : Phospholipase C activation

A limited number of G-proteins are shared between different receptors and one receptor can utilize more than one G-protein (agonist pleotropy), e.g. the following couplers have been associated with different receptors.

Receptor	*Coupler*
Muscarinic M_2	Gi, Go
Muscarinic M_1, M_3	Gq
Dopamine D2	Gi, Go
β-adrenergic	Gs
α_1-adrenergic	Gq
α_2-adrenergic	Gi, Go
$GABA_B$	Gi, Go
Serotonin 5-HT_1	Gi, Go
Serotonin 5-HT_2	Gq
Prostanoid	Gs, Gi, Gq

In addition, Gs is the coupler for histamine H_2, serotonin $5HT_{4-7}$, glucagon, thyrotropin (TSH) and many other hormones, while Gi is utilized by

opioid, cannabinoid and some other receptors. Moreover, a receptor can utilize different biochemical pathways in different tissues.

The α-subunit has GTPase activity: the bound GTP is slowly hydrolysed to GDP: the α-subunit then dissociates from the effector to rejoin its other subunits, but not before the effector has been activated/inhibited for several seconds (much longer than the life-time of the activated receptor, which is in milliseconds) and the signal has been greatly amplified. The rate of GTP hydrolysis by the α subunit and thus the period for which it remains activated is regulated by another protein called 'regulator of G protein signaling' (RGS). The onset time of response through GPCRs is in seconds.

There are three major effector pathways (Table 4.1) through which GPCRs function.

(a) Adenylyl cyclase: cAMP pathway Activation of AC results in intracellular accumulation of second messenger cAMP (Fig. 4.6) which functions mainly through cAMP-dependent protein kinase (PK_A). The PK_A phosphorylates and alters the function of many enzymes, ion channels, transporters, transcription factors and structural proteins to manifest as increased contractility/impulse generation (heart), relaxation (smooth muscle), glycogenolysis, lipolysis, inhibition of secretion/mediator release, modulation of junctional transmission, water conservation by kidney, steroid hormone synthesis, etc. In addition, cAMP directly opens a specific type of membrane Ca^{2+} channel called *cyclic nucleotide gated channel* (CNG) in the heart, brain and kidney. The other mediators of cellular actions of cAMP are: *cAMP response element binding protein (CREB)* which is a transcription factor, cAMP regulated guanine nucleotide exchange factors called EPACs and certain transporters. Responses opposite to the above are produced when AC is inhibited through inhibitory Gi-protein.

The action of cAMP is terminated intracellularly by phosphodiesterases (PDEs) which hydrolyse it to 5-AMP. Some isoforms of PDE (PDE_3, PDE_4) are selective for cAMP, while PDE_5 is selective for cGMP.

Cyclic GMP (cGMP) as a second messenger

In contrast to cAMP, the cGMP serves as an intracellular second messenger only in a limited number of tissues, such as vascular smooth muscle, intestinal mucosal cell and kidney. In these tissues it respectively mediates relaxation, inhibition of salt and water absorption as well

Table 4.1: Major functional pathways of G-protein coupled receptor transduction

Adenylyl cyclase: cAMP		*Phospholipase—IP_3/DAG*	*Channel regulation*		
activation	*inhibition*	*activation*	Ca^{2+} *opening*	Ca^{2+} *closing*	K^+ *opening*
Adrenergic-β	Adrenergic-α_2	Adrenergic-α_1	Adrenergic-β_1	Dopamine-D2	Adrenergic-α_2
Histamine-H_2	Muscarinic-M_2	Histamine-H_1		$GABA_B$	Muscarinic-M_2
Dopamine-D1	Dopamine-D2	Muscarinic-M_1, M_3		Opioid-κ	Dopamine-D2
Glucagon	5-HT_1	5-HT_2		Adenosine-A_1	5-HT_{1A}
FSH & LH	$GABA_B$	Vasopressin-Oxytocin		Somatostatin	$GABA_B$
ACTH	Opioid-μ, δ	Bradykinin-B_2			Opioid-μ, δ
TSH	Angiotensin-AT_1	Angiotensin-AT_1			Adenosine-A_1
Prostaglandin-EP_2	Prostaglandin-EP_3	Prostaglandin-FP, EP_1, EP_3			
Prostacyclin-IP	Somatostatin	Thromboxane-TP			
Adenosine-A_2	Adenosine-A_1	Leukotriene BLT_1, $_{cys}LT$			
		Cholecystokinin-Gastrin			
		PAF			

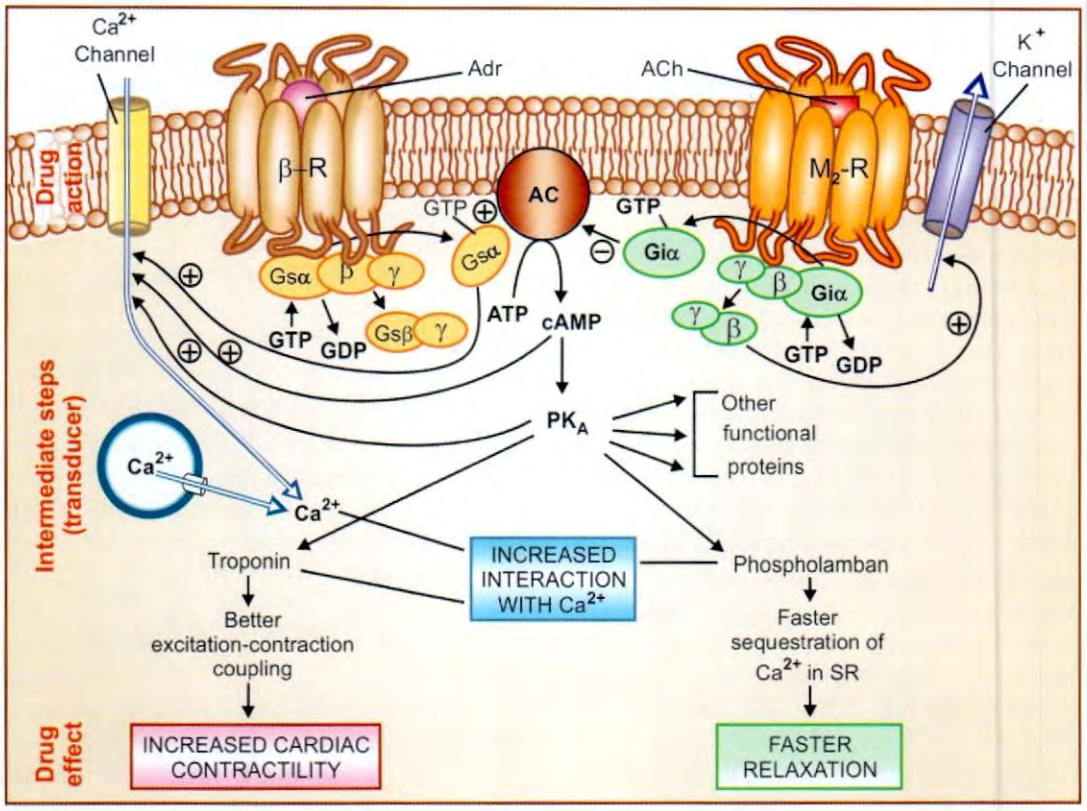


Fig. 4.6: The action-effect sequence of two G-protein coupled (β adrenergic and muscarinic M_2) receptor activation in myocardial cell

Adrenaline (Adr) binds to β-adrenergic receptor (β-R) on the cell surface inducing a conformational change which permits interaction of the G-protein binding site with the stimulatory G-protein (Gs). The activated α subunit of Gs now binds GTP (in place of GDP), and dissociates from the βγ dimer as well as from the receptor. The Gsα carrying bound GTP associates with and activates the enzyme adenylyl cyclase (AC) located on the cytosolic side of the membrane: ATP is hydrolysed to cAMP which then phosphorylates and thus activates cAMP dependent protein kinase (PK_A). The PK_A in turn phosphorylates many functional proteins including troponin and phospholamban, so that they interact with Ca^{2+}, respectively resulting in increased force of contraction and faster relaxation. Calcium is made available by entry from outside (direct activation of myocardial membrane Ca^{2+} channels by Gsα and through their phosphorylation by PK_A) as well as from intracellular stores.

One of the other proteins phosphorylated by cAMP is phosphorylase kinase which then activates the enzyme phosphorylase resulting in breakdown of glycogen to be utilized as energy source for increased contractility.

Action of acetylcholine (ACh) on muscarinic M_2 receptor (M_2-R), also located in the myocardial membrane, similarly activates an inhibitory G-protein (Gi). The GTP carrying active Giα subunit inhibits AC, and opposes its activation by Gsα. The βγ dimer of Gi activates membrane K^+ channels causing hyperpolarization which depresses impulse generation.

as anion secretion, and natriuresis (mainly due to reduced proximal tubular Na^+ reabsorption).

There are two principal forms of guanylyl cyclases (GC) which generate cGMP, one cell membrane bound and the other cytosolic. However, none of these is regulated by a GPCR. The cell membrane bound GC is regulated by a transmembrane enzyme-linked receptor (described on p.58) for atrial natriuretic peptide (ANP). The cytosolic soluble GC in vascular smooth muscle is activated by nitric oxide (NO). After generation by the vascular endothelium NO diffuses into the adjacent smooth muscle cell and stimulates the soluble GC. Increased

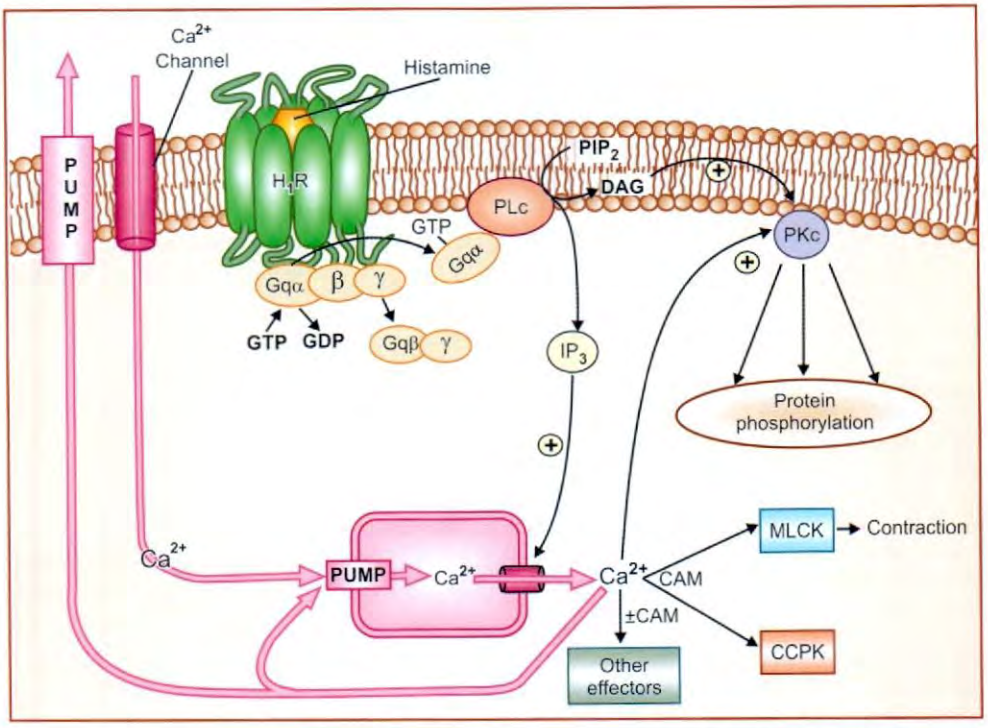


Fig. 4.7: The important steps of phospholipase cβ(PLcβ) pathway of response effectuation (in smooth muscle) The agonist, e.g. histamine binds to its H_1 receptor (H_1 R) and activates the G-protein G_q. Its α subunit binds GTP in place of GDP, dissociates from the receptor as well as from βγ dimer to activate membrane bound PLcβ that hydrolyses phosphatidyl inositol 4, 5-bisphosphate (PIP_2), a membrane bound phospholipid. The products inositol 1, 4, 5-trisphosphate (IP_3) and diacylglycerol (DAG) act as second messengers. The primary action of IP_3 is facilitation of Ca^{2+} mobilization from intracellular organellar pools, while DAG in conjunction with Ca^{2+} activates protein kinase C (PKc) which phosphorylates and alters the activity of a number of functional and structural proteins. Cytosolic Ca^{2+} is a veritable messenger: combines with calmodulin (CAM) to activate myosin light chain kinase (MLCK) inducing contraction, and another important regulator calcium-calmodulin protein kinase (CCPK). Several other effectors are regulated by Ca^{2+} in a CAM dependent or CAM- independent manner. Cytosolic Ca^{2+} is recycled by uptake into the endoplasmic reticulum as well as effluxed by membrane Ca^{2+} pump.

cGMP dephosphorylates myosin light chain kinase (MLCK) through PKG and induces relaxation (*see* Fig. 40.3). This pathway is utilized by glyceryl trinitrate, sod. nitroprusside, etc.

(b) Phospholipase C: IP_3-DAG pathway

Activation of phospholipase C_β (PLc_β) by the activated GTP carrying α subunit of Gq hydrolyses the membrane phospholipid phosphatidyl inositol 4,5-bisphosphate (PIP_2) to generate the second messengers inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). The IP_3 being water soluble diffuses to the cytosol and mobilizes Ca^{2+} from endoplasmic reticular depots (Fig. 4.7). The lipophilic DAG remains within the membrane, but recruits protein kinase C (PKc) and activates it with the help of Ca^{2+}. The activated PKc phosphorylates many intracellular proteins (depending on the type of effector cell) and mediates various physiological responses. So that it can serve signaling functions, the cytosolic concentration of Ca^{2+} is kept very low (~ 100 nM) by specific pumps located at the plasma membrane and at the endoplasmic reticulum. Triggered by IP_3, the released Ca^{2+} (third messenger in this setting) acts as a highly versatile regulator acting

through calmodulin (CAM), PKc and other effectors—mediates/modulates smooth muscle, contraction, glandular secretion/transmitter release, eicosanoid synthesis, neuronal excitability, intracellular movements, membrane function, metabolism, cell proliferation, etc. Signaling in this pathway is terminated by degradation of the second messengers. The IP_3 is dephosphorylated to inositol which is reutilized in the synthesis of PIP_2 (*see* Fig. 32.1), while DAG is partly converted back to phospholipids, and partly deacylated to arachidonic acid.

Intracellular Ca^{2+} release has been found to occur in waves (Ca^{2+} mediated Ca^{2+} release from successive pools facilitated by inositol 1, 3, 4, 5-tetrakisphosphate—IP_4) and exhibits a variety of agonist and concentration dependent oscillatory patterns. The activation of different effectors may depend on the amplitude and pattern of these oscillations. Thus, the same intracellular messenger can trigger different responses depending on the nature and strength of the extracellular signal.

(c) Channel regulation The activated G-proteins (Gs, Gi, Go) can also open or inhibit ionic channels specific for Ca^{2+} and K^+, without the intervention of any second messenger like cAMP or IP_3, and bring about hyperpolarization/depolarization/changes in intracellular Ca^{2+} concentration. The Gs opens Ca^{2+} channels in myocardium and skeletal muscles, while Gi and Go open K^+ channels in heart and smooth muscle as well as inhibit neuronal Ca^{2+} channels. Direct channel regulation is mostly the function of the $\beta\gamma$ dimer of the dissociated G protein. Physiological responses like changes in inotropy, chronotropy, transmitter release, neuronal activity and smooth muscle relaxation follow. Receptors found to regulate ionic channels through G-proteins are listed in Table 4.1.

2. Ion channel receptors

These cell surface receptors, also called *ligand gated ion channels,* enclose ion selective channels (for Na^+, K^+, Ca^{2+} or Cl^-) within their molecules. Agonist binding opens the channel (Fig. 4.4) and causes depolarization/hyperpolarization/changes in cytosolic ionic composition, depending on the ion that flows through. The nicotinic cholinergic, $GABA_A$, glycine (inhibitory AA), excitatory AA-glutamate (kainate, NMDA and AMPA) and $5HT_3$ receptors fall in this category, and a large number of clinically useful drugs act through this type of receptors.

The receptor is usually a pentameric protein; all subunits, in addition to large intra- and extracellular segments, generally have four membrane spanning helical domains. The subunits are mostly arranged round the channel like a rosette and the α subunits usually bear the agonist binding sites.

Certain receptor-operated (or ligand-gated) ion channels also have secondary ligands which bind to an allosteric site and modulate the gating of the channel by the primary ligand, e.g. the benzodiazepine receptor modulates $GABA_A$ gated Cl^- channel.

Thus, in these receptors the agonist directly operates ion channels, without the intervention of any coupling protein or second messenger. The onset and offset of responses through this class of receptors is the fastest (in milliseconds).

3. Transmembrane enzyme-linked receptors

This class of receptors are utilized primarily by peptide hormones, and are made up of a large extracellular ligand binding domain connected through a single transmembrane helical peptide chain to an intracellular subunit having enzymatic property. The enzyme at the cytosolic side is generally a protein kinase, but can also be guanylyl cyclase in few cases. The commonest protein kinases are the ones which phosphorylate tyrosine residues on the substrate proteins and are called 'receptor tyrosine kinases' (RTKs), *see* Fig. 4.8. Examples are—insulin, epidermal growth factor (EGF), nerve growth factor (NGF) and many other growth factor receptors. Inhibitors of specific RTKs involved in growth factor signaling are a new class of targeted anticancer drugs. However, the transforming growth factor (TGF) receptor and few others are serine/threonine kinases—

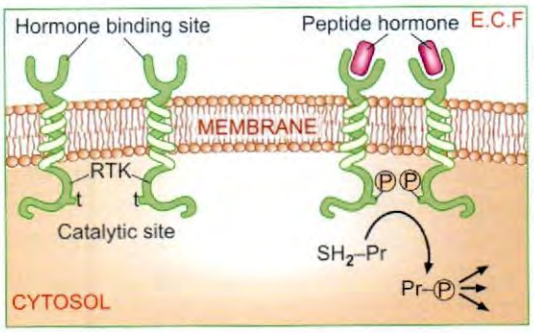


Fig. 4.8: Model of receptor tyrosine kinase, an enzyme-linked receptor
On binding the peptide hormone to the extracellular domains, the monomeric receptors move laterally in the membrane and form dimers. Dimerization activates tyrosine-kinase (RTK) activity of the intracellular domains so that they phosphorylate tyrosine (t) residues on each other, as well as on several SH_2 domain substrate proteins (SH_2-Pr). The phosphorylated substrate proteins then perform downstream signaling function.

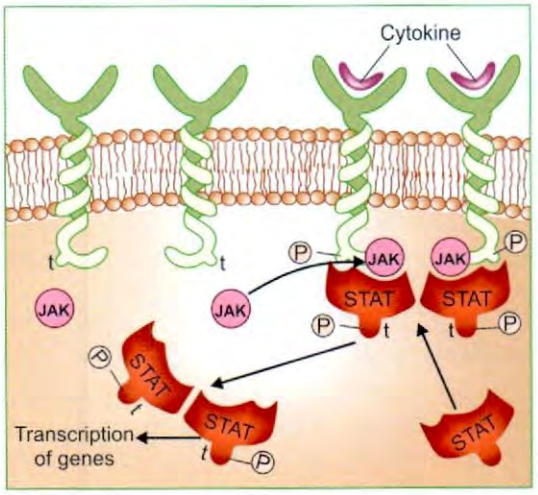


Fig. 4.9: Model of transmembrane JAK-STAT binding receptor
The intracellular domain of these receptors lacks intrinsic protein kinase activity. Cytokines/hormones binding to the extracellular domain induce receptor dimerization which activates the intracellular domain to bind free moving JAK (Janus Kinase) molecules. The activated JAK phosphorylate tyrosine residues on the receptor which then binds another protein STAT (signal transducer and activator of transcription). Tyrosine residues of STAT also get phosphorylated by JAK. The phosphorylated STAT dimerize, dissociate from the receptor and move to the nucleus to regulate transcription of target genes.

which phosphorylate serine/threonine residues of the target proteins.

In the unliganded monomeric state, the kinase remains inactive. Hormone binding induces dimerization of receptor molecules, brings about conformation changes which activate the kinase to autophosphorylate tyrosine residues on each other, increasing their affinity for binding substrate proteins which have SH_2 domains. These are then phosphorylated and released to carry forward the cascade of phosphorylations leading to the response.

A large number of intracellular signaling proteins have SH_2 domains. Thus, by controlling phosphorylation of key enzymes, ion channels, transporters, etc. the RTKs are able to regulate diverse cellular functions including metabolic reactions, cell growth and differentiation. One of the SH_2 domain enzymes is phospholipase cγ ($PLc\gamma$) which is activated by certain RTKs, and which, like $PLc\beta$, generates IP_3 and DAG as second messengers for response effectuation.

The transmembrane enzyme-linked receptors transduce responses in a matter of few minutes to few hours.

Another feature of this class of receptors is that their dimerization also promotes receptor internalization, degradation in lysosomes and down regulation if activation is fast enough. Mutations interfering with such down-regulation contribute to development of certain malignancies.

In place of protein kinase the enzyme can also be guanylyl cyclase (GC), as in the case of atrial natriuretic peptide (ANP). Agonist activation of the receptor generates cGMP in the cytosol as a second messenger, which in turn activates cGMP-dependent protein kinase (PK_G) and modulates cellular activity.

4. Transmembrane JAK-STAT binding receptors

These receptors differ from RTKs in not having any intrinsic catalytic domain. Agonist-induced dimerization alters the intracellular domain

conformation to increase its affinity for a cytosolic tyrosine protein kinase JAK (Janus Kinase). On binding, JAK gets activated and phosphorylates tyrosine residues of the receptor, which now bind another free moving protein STAT (signal transducer and activator of transcription). This is also phosphorylated by JAK. Pairs of phosphorylated STAT dimerize and translocate to the nucleus to regulate gene transcription resulting in a biological response. Many cytokines, growth hormone, prolactin, interferons, etc. act through this type of receptor.

5. Receptors regulating gene expression (Transcription factors, Nuclear receptors)

In contrast to the above 4 classes of receptors, these are intracellular (cytoplasmic or nuclear) soluble proteins which respond to lipid soluble chemical messengers that penetrate the cell (Fig. 4.10). The receptor protein (specific for each hormone/regulator) is inherently capable of binding to specific genes, but its attached proteins HSP-90 and may be some others prevent it from adopting the configuration needed for binding to DNA. When the hormone binds near the carboxy terminus of the receptor, the restricting proteins (HSP-90, etc.) are released, the receptor dimerizes and the DNA binding regulatory segment located in the middle of the molecule folds into the functionally active configuration. The liganded receptor dimer moves to the nucleus and binds other co-activator/co-repressor proteins which have a modulatory influence on its capacity to alter gene function. The whole complex then attaches to specific DNA sequences (hormone response elements) of the target genes and facilitates or represses their expression so that specific mRNA is synthesized/repressed on the template of the gene. This mRNA moves to the ribosomes and directs synthesis of specific proteins which regulate activity of the target cells.

All steroidal hormones (glucocorticoids, mineralocorticoids, androgens, estrogens, progesterone), thyroxine, vit D and vit A function in this manner. Different steroidal hormones affect different target cells and produce different effects because each one binds to its own receptor and directs a unique pattern of synthesis of specific proteins. The specificity as to which hormone will be bound is provided by the hormone binding domain, while that as to which gene will be activated or repressed is a function of the DNA binding/N-terminus domain. Different ligands of the same nuclear receptor have been found to induce ligand-specific conformations of the receptor so that different combinations of co-activators and co-repressors may be bound in different target tissues, e.g. selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene have differing patterns of action on various estrogenic target organs. Chimeric receptors have also been produced which respond to one hormone, but produce the effects of the other hormone.

This transduction mechanism is the slowest in its time course of action (takes hours) because adequate quantity of the effector protein will have to be produced before the response occurs. The effects also generally out last the signal (hormone), because majority of the generated effector proteins have slow turnover, and persist in the body even after the hormone has been eliminated.

Regulation of receptors

Receptors exist in a dynamic state; their density and efficacy to elicit the response is subject to regulation by the level of on-going activity, feedback from their own signal output and other physiopathological influences, e.g. estrogens increase the density of oxytocin receptors on the myometrium. The sensitivity of uterus to contractile action of oxytocin increases progressively during the third trimester of pregnancy, especially near term. In tonically active systems, prolonged deprivation of the agonist (by denervation or continued use of an antagonist or a drug which reduces input) results in supersensitivity of the receptor as well as the effector system to the agonist. This has

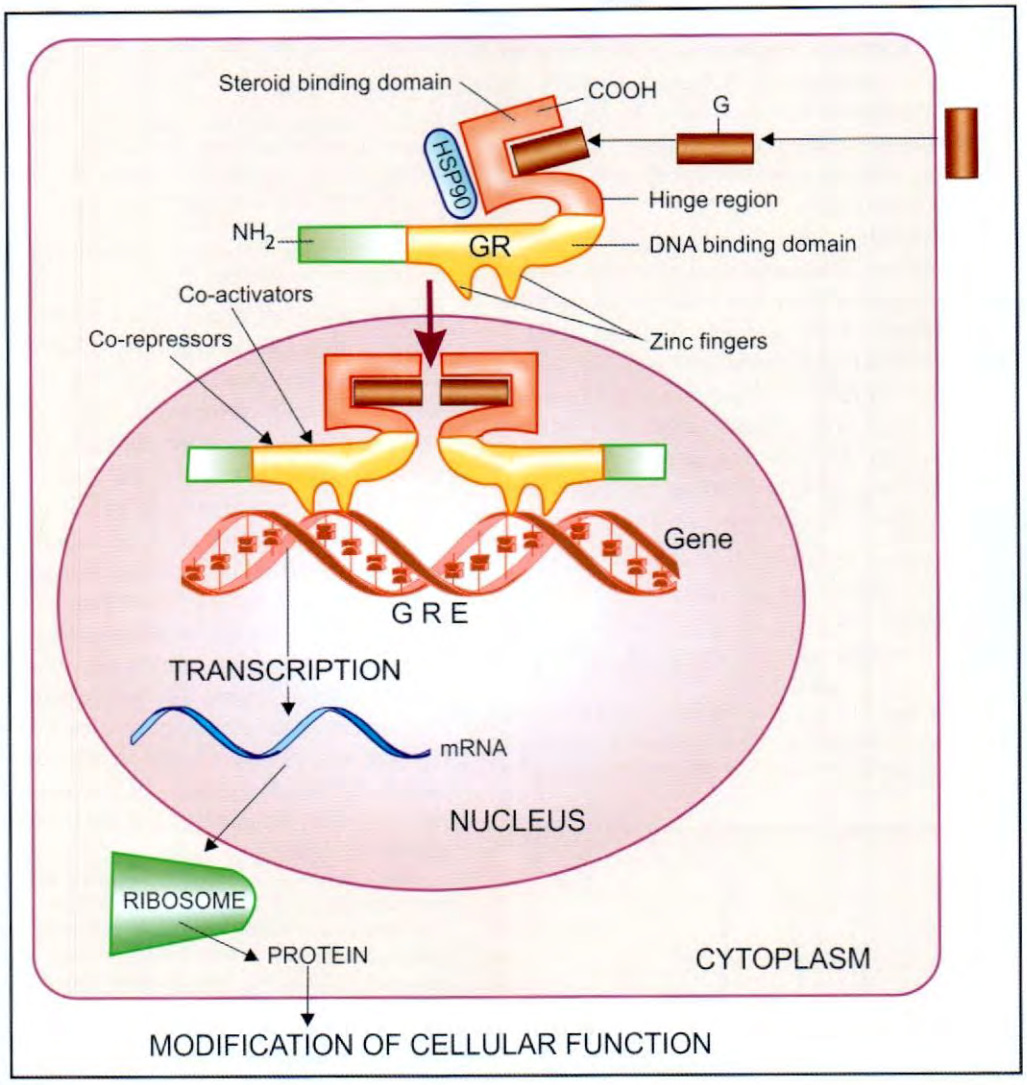


Fig. 4.10: Operational scheme of intracellular (glucocorticoid) receptor
The glucocorticoid (G) penetrates the cell membrane and binds to the glucocorticoid receptor (GR) protein that normally resides in the cytoplasm in association with heat shock protein 90 (HSP90) ± other proteins. The GR has a steroid binding domain near the carboxy terminus and a mid-region DNA binding domain joined by a 'hinge region'. The DNA binding domain has two 'zinc fingers', each made up of a loop of amino acids with chelated zinc ion. Binding of the steroid to GR dissociates the complexed proteins (HSP90, etc) removing their inhibitory influence on it. A dimerization region that overlaps the steroid binding domain is exposed, promoting dimerization of the occupied receptor. The steroid bound receptor dimer translocates to the nucleus, binds coactivator/corepressor proteins and interacts with specific DNA sequences called 'glucocorticoid responsive elements' (GREs) within the regulatory region of appropriate genes. The expression of these genes is consequently altered resulting in promotion (or suppression) of their transcription. The specific mRNA thus produced is directed to the ribosome where the message is translated into a specific pattern of protein synthesis, which inturn modifies cell function.

clinical relevance in clonidine/CNS depressant/opioid withdrawal syndromes, sudden discontinuation of propranolol in angina pectoris, etc. The mechanisms involved may be unmasking of receptors or their proliferation (*up regulation*) or accentuation of signal amplification by the transducer.

Conversely, continued/intense receptor stimulation causes desensitization or refractoriness: the receptor becomes less efficient in transducing response to the agonist. This can be easily demonstrated experimentally (Fig. 4.11); clinical examples are bronchial asthma patients treated continuously with β adrenergic agonists and parkinsonian patients treated with high doses of levodopa gradually become less responsive. The changes may be brought about by:

(i) Masking or internalization of the receptor (it becomes inaccessible to the agonist) or impaired coupling of the transducer to the receptor. In this case refractoriness develops as well as fades quickly.

In the case of β adrenergic receptor, it has been found that high rate of agonist binding promotes phosphorylation of its serine residues near the intracellular carboxy terminus by an enzyme β adrenergic receptor kinase (βARK), allowing it to bind a protein called β-arrestin (β–arr) which hinders its interaction with Gs → receptor transduction is impaired. When the β-agonist is removed, the serine residues are dephosphorylated by cellular phosphatases, and receptor mediated activation of Gs is restored. However, in case of excessive/prolonged activation, the phosphorylated β adrenergic GPCR is internalized and largely moved to the lysosomes, where they are degraded, rather than returning back to the surface membrane. This results in receptor down regulation.

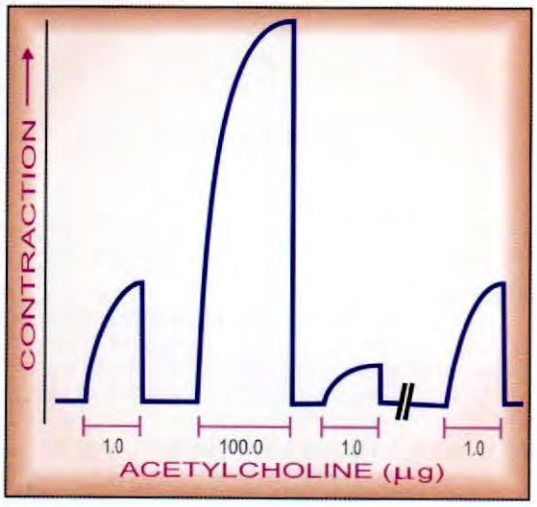


Fig. 4.11: Illustration of the phenomenon of desensitization
Contractile responses of frog's rectus abdominis muscle to acetylcholine. Note that shortly after exposure to a high (100 fold) dose of the agonist, the response is markedly attenuated, but is regained if sufficient time is allowed to elapse.

(ii) Decreased synthesis/increased destruction of the receptor (*down regulation*): refractoriness develops over weeks or months and recedes slowly. Receptor down regulation is particularly exhibited by the tyrosine kinase receptors and some GPCRs. Similarly, the transducer and effector proteins are also up or down regulated.

Some times response to all agonists which act through different receptors but produce the same overt effect (e.g. histamine and acetylcholine both contract intestinal smooth muscle) is decreased by exposure to any one of these agonists (heterologous desensitization), showing that mechanisms of response effectuation have become less efficient. However, often desensitization is limited to agonists of the same receptor that is being repeatedly activated (homologous desensitization).

Both homologous and heterologous desensitization has been observed in the case of GPCRs. The BARK β-arrestin mechanism described above produces homologous desensitization. The GPCRs transduce many responses by activating PK_A and PK_C. These kinases phosphorylate many GPCRs rather nonselectively (at a site different from that of BARK) and hinder their interaction with G-proteins, resulting in heterologous desensitization.

Functions of receptors

These can be summarized as:

(a) To propagate regulatory signals from outside to inside the effector cell when the molecular species carrying the signal cannot itself penetrate the cell membrane.

(b) To amplify the signal.

(c) To integrate various extracellular and intracellular regulatory signals.

(d) To adapt to short term and long term changes in the regulatory melieu and maintain homeostasis.

Nonreceptor-mediated drug action

This refers to drugs which do not act by binding to specific regulatory macromolecules. Drug action by purely physical or chemical means, interactions with small molecules or ions (antacids, chelating agents, cholestyramine, etc.), as well as direct interaction with enzymes, ionic channels and transporters has already been described. In addition, there are drugs like alkylating agents which react covalently with several critical biomolecules, especially nucleic acids, and have cytotoxic property useful in the treatment of cancer. Another important class of drugs are the antimetabolites (purine/pyrimidine analogues) which lead to production of nonfunctional or dysfunctional cellular components that exert antineoplastic, antiviral and immunosuppressant activity.

DOSE-RESPONSE RELATIONSHIP

When a drug is administered systemically, the dose-response relationship has two components: *dose-plasma concentration* relationship and *plasma concentration-response* relationship. The former is determined by pharmacokinetic considerations and ordinarily, descriptions of dose-response relationship refer to the latter, which can be more easily studied *in vitro*.

Generally, the intensity of response increases with increase in dose (or more precisely concentration at the receptor), but at higher doses, the increase in response progressively becomes less marked and the dose-response curve is a rectangular hyperbola (Fig. 4.12). This is because drug-receptor interaction obeys law of mass action, which is described by the equation (3) and is applicable to interaction between any two molecules having a given affinity for each other.

$$E = \frac{Emax \times [D]}{K_D + [D]} \quad ...(3)$$

Where E is the observed effect at a dose [D] of the drug, *Emax* is the maximal response, K_D is the dissociation constant of the drug-receptor

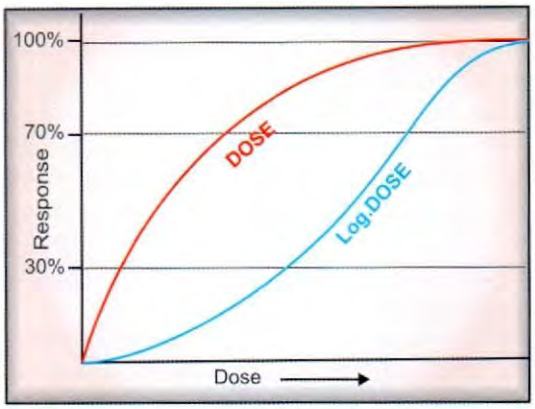


Fig. 4.12: Dose-response and log dose-response curves

complex, which is a measure of the affinity between the two, and is equal to the dose of the drug at which half maximal response is produced. If the dose is plotted on a logarithmic scale, the curve becomes sigmoid and a linear relationship between log of dose and the response is seen in the intermediate (30–70% response) zone, as can be predicted from equation (3). This is not peculiar to drugs. In fact all stimuli are graded biologically by the fractional change in stimulus intensity, e.g. 1 kg and 2 kg weights held in two hands can be easily differentiated, but not 10 kg and 11 kg weights. Though the absolute difference in both cases remains 1 kg, there is a 100% fractional change in the former case but only 10% change in the latter case. In other words, response is proportional to an exponential function (log) of the dose.

Other advantages of plotting log dose-response curves (DRC) are:

- A wide range of drug doses can be easily displayed on a graph.
- Comparison between agonists and study of antagonists becomes easier.

The log dose-response curve (DRC) can be characterized by its shape (slope and maxima) and position on the dose axis.

Drug potency and efficacy

The position of DRC on the dose axis is the index of *drug potency* which refers to the

amount of drug needed to produce a certain response. A DRC positioned rightward indicates lower potency (Fig. 4.13). Relative potency is often more meaningful than absolute potency, and is generally defined by comparing the dose (concentration) of the two agonists at which they elicit half maximal response (EC_{50}). Thus, if 10 mg of morphine = 100 mg of pethidine as analgesic, morphine is 10 times more potent than pethidine. However, a higher potency, in itself, does not confer clinical superiority unless the potency for therapeutic effect is selectively increased over potency for adverse effect. Drug potency is clearly a factor in *choosing the dose* of a drug.

The upper limit of DRC is the index of *drug efficacy* and refers to the maximal response that can be elicited by the drug, e.g. morphine produces a degree of analgesia not obtainable with any dose of aspirin—morphine is more efficacious than aspirin. Efficacy is a more decisive factor in the choice of a drug.

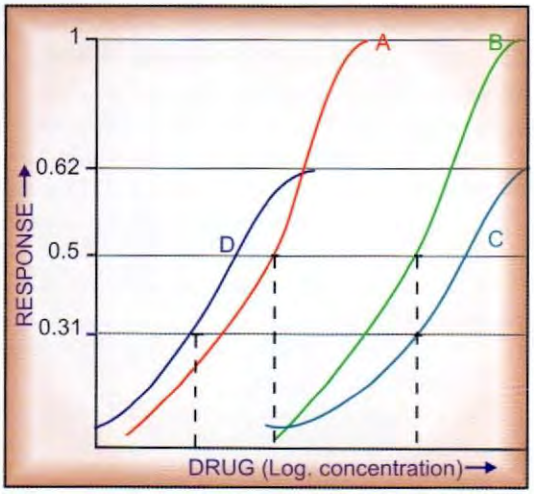


Fig. 4.13: Illustration of drug potency and drug efficacy. Dose-response curve of four drugs producing the same qualitative effect
Note:
Drug B is less potent but equally efficacious as drug A.
Drug C is less potent and less efficacious than drug A.
Drug D is more potent than drugs A, B, & C, but less effica-cious than drugs A & B, and equally efficacious as drug C.

Often the terms 'drug potency' and 'drug efficacy' are used interchangeably, but these are not synonymous and refer to different characteristics of the drug. The two can vary independently:
(a) Aspirin is less potent as well as less efficacious analgesic than morphine.
(b) Pethidine is less potent but equally efficacious analgesic as morphine.
(c) Furosemide is less potent but more efficacious diuretic than metolazone.
(d) Diazepam is more potent but less efficacious CNS depressant than pentobarbitone.

Depending on the type of drug, both higher efficacy (as in the case of furosemide confering utility for mobilizing edema fluid and in renal failure) or lower efficacy (as in the case of diazepam confering safety in over-dose) could be clinically advantageous.

The slope of the DRC is also important. A steep slope indicates that a moderate increase in dose will markedly increase the response (dose needs individualization), while a flat one implies that little increase in response will occur over a wide dose range (standard doses can be given to most patients). Hydralazine has a steep, while hydrochlorothiazide has a flat DRC of antihypertensive effect (Fig. 4.14).

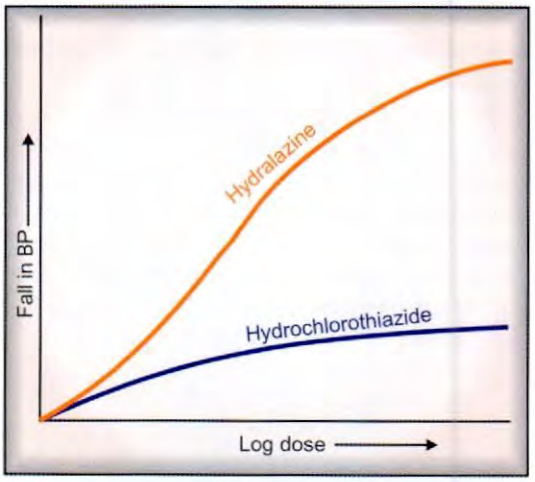


Fig. 4.14: Steep and flat dose-response curves illustrated by antihypertensive effect of hydralazine and hydrochlorothiazide

Therapeutic efficacy

The 'therapeutic efficacy' or 'clinical effectiveness' is a composite attribute of a drug different from the foregoing pharmacological description of 'potency' and 'efficacy'. It depends not only on the relative potency and efficacy of the drug, but on many pharmacokinetic and pathophysiological variables as well. It is often expressed in terms of (a) degree of benefit/relief afforded by the drug (in the recommended dose range) i.e. *graded dose-response relationship*. For example, the degree of relief in parkinsonian symptoms afforded by levodopa-carbidopa is much greater than that possible with trihexyphenidyl: the former has higher therapeutic efficacy than the latter.

The other method of expressing therapeutic efficacy is in terms of (b) success rate in achieving a defined therapeutic end point, i.e. *quantal dose-response relationship*, e.g. an antibiotic which cures 95% cases of gonorrhoea is a more efficacious antigonococcal drug than one which cures only 75% patients. Similarly, a drug which makes a higher percentage of epileptic patients totally seizure free than another drug, is the more therapeutically effective antiepileptic.

Drug selectivity

Drugs seldom produce just one action: the DRCs for different effects of a drug may be different. The extent of separation of DRCs of a drug for different effects is a measure of its selectivity, e.g. the DRCs for bronchodilatation and cardiac stimulation (Fig. 4.15) are quite similar in case of isoprenaline, but far apart in case of salbutamol—the latter is a more selective bronchodilator drug.

The gap between the therapeutic effect DRC and the adverse effect DRC defines the *safety margin* or the *therapeutic index* of a drug. In experimental animals, therapeutic index is often calculated as:

$$\text{Therapeutic index} = \frac{\text{median lethal dose}}{\text{median effective dose}}$$

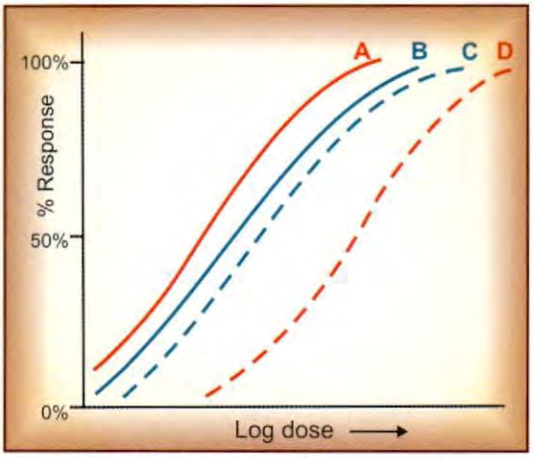


Fig. 4.15: Illustration of drug selectivity
Log dose-response curves of salbutamol for bronchodilatation (A) and cardiac stimulation (D)
Log dose-response curves of isoprenaline for bronchodilatation (B) and cardiac stimulation (C)

$$\text{or } \frac{LD_{50}}{ED_{50}}$$

where: Median effective dose (ED_{50}) is the dose which produces the specified effect in 50% individuals and median lethal dose (LD_{50}) is the dose which kills 50% of the recipients.

But this is irrelevant in the clinical set up where the *therapeutic range*, also called the *'therapeutic window'* is bounded by the dose which produces minimal therapeutic effect and the dose which produces maximal acceptable adverse effect (Fig. 4.16). Because of individual variability, the effective dose for some subjects may be toxic for others; defining the therapeutic range for many drugs is a challenging task. A drug may be capable of inducing a higher therapeutic response (have higher efficacy) but development of intolerable adverse effects may preclude use of higher doses, e.g. prednisolone in bronchial asthma.

Risk-benefit ratio This term is very frequently used, and conveys a judgement on the estimated harm (adverse effects, cost, inconvenience) *vs* expected advantages (relief of symptoms, cure, reduction of complications/mortality, improvement in quality of life). A drug should be

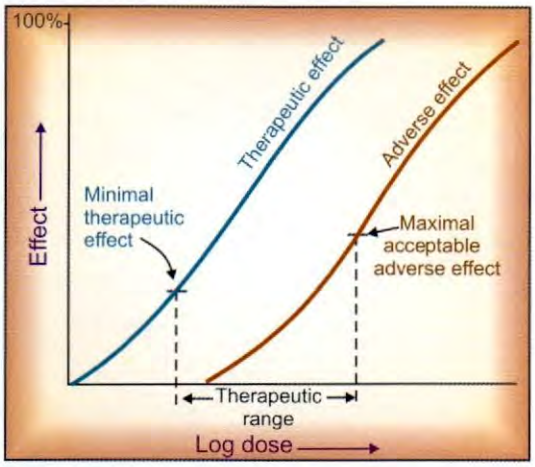


Fig. 4.16: Illustrative dose-response curves for therapeutic effect and adverse effect of the same drug

prescribed only when the benefits outweigh the risks. However, risk-benefit ratio can hardly ever be accurately measured for each instance of drug use, because 'risk' is the probability of harm; and harm has to be qualified by its nature, quantum, time-course (transient to life-long) as well as the value that the particular patient attaches to it. None of these can be precisely ascertained beforehand in an individual patient. As such, the physician has to rely on data from use of drugs in large populations (pharmacoepidemiology) and his own experience of the drug and the patient.

Drug specificity

Specificity of a drug refers to the range of actions produced by it. Certain drugs produce just one or a limited number of actions, while others have widespread effects on many organs of the body. Specificity is governed by:

(a) whether a drug acts on a single receptor/target or on many targets, and

(b) how widely the target is distributed in the body.

Omeprazole (and other proton pump inhibitors) is an example of a highly specific drug. The singular perceptible action in therapeutic doses is inhibition of gastric acid secretion, because it acts only on one target molecule H^+K^+ ATPase (proton pump) which is localized to the gastric parietal cells. An example of a drug acting on multiple targets is chlorpromazine which has antagonistic action on dopamine D2, α-adrenergic, muscarinic cholinergic, histamine H_1 and some 5-HT receptors. It also has Na^+ channel blocking action. As a result, it produces a wide range of actions. Another case is dexamethasone which is an agonist only of glucocorticoid receptor, but produces effects involving many organs and tissues, because the glucocorticoid receptor is expressed by practically every cell of the body. Drugs with all grades of specificity are available.

DRUG SYNERGISM AND ANTAGONISM

When two or more drugs are given simultaneously or in quick succession, they may be either indifferent to each other or exhibit *synergism* or *antagonism*. The interaction may take place at pharmacokinetic level (*see* Ch. 2 and 3) or at pharmacodynamic level.

SYNERGISM

(Greek: *Syn*—together; *ergon*—work)

When the action of one drug is facilitated or increased by the other, they are said to be synergistic. In a synergistic pair, both the drugs can have action in the same direction or given alone one may be inactive but still enhance the action of the other when given together. Synergism can be:

(a) *Additive* The effect of the two drugs is in the same direction and simply adds up:

effect of drugs A + B = effect of drug A + effect of drug B

Side effects of the components of an additive pair may be different—do not add up. Thus, the combination is better tolerated than higher dose of one component.

Additive drug combinations	
Aspirin + paracetamol	as analgesic/antipyretic
Nitrous oxide + halothane	as general anaesthetic
Amlodipine + atenolol	as antihypertensive
Glibenclamide + metformin	as hypoglycaemic
Ephedrine + theophylline	as bronchodilator

(b) *Supraadditive (potentiation)* The effect of combination is greater than the individual effects of the components:

effect of drug A + B > effect of drug A + effect of drug B

This is always the case when one component given alone produces no effect, but enhances the effect of the other (potentiation). Examples are given in the box. Additive synergism and potentiation are depicted diagrammatically in Fig. 4.17.

Supraadditive drug combinations	
Drug pair	*Basis of potentiation*
Acetylcholine + physostigmine	Inhibition of break down
Levodopa + carbidopa/ benserazide	Inhibition of peripheral metabolism
Adrenaline + cocaine/ desipramine	Inhibition of neuronal uptake
Sulfamethoxazole + trimethoprim	Sequential blockade
Antihypertensives (enalapril+ hydrochlorothiazide)	Tackling two contributory factors
Tyramine + MAO inhibitors	Increasing releaseable CA store

ANTAGONISM

When one drug decreases or abolishes the action of another, they are said to be antagonistic:

effect of drugs A + B < effect of drug A + effect of drug B

Usually in an antagonistic pair one drug is inactive as such but decreases the effect of the other. Depending on the mechanism involved, antagonism may be:

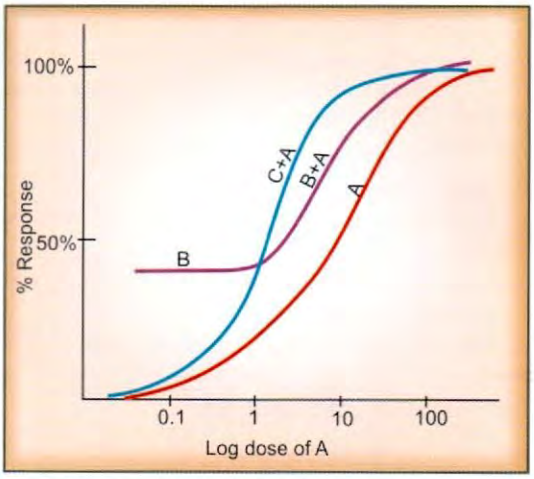


Fig. 4.17: Log dose-response curves of a drug 'A' depicting additive synergism (in purple) and potentiation (Supra-additive synergism) in blue.
A: An agonist drug.
B: Another agonist in a fixed submaximal dose producing 40% response.
C: A potentiating drug which itself has no agonistic activity.

(a) Physical antagonism

Based on the physical property of the drugs, e.g. charcoal adsorbs alkaloids and can prevent their absorption—used in alkaloidal poisonings.

(b) Chemical antagonism

The two drugs react chemically and form an inactive product, e.g.

- $KMnO_4$ oxidizes alkaloids—used for gastric lavage in poisoning.
- Tannins + alkaloids—insoluble alkaloidal tannate is formed.
- Chelating agents (BAL, Cal. disod. edetate) complex toxic metals (As, Pb).
- Nitrites form methaemoglobin which reacts with cyanide radical.

Drugs may react when mixed in the same syringe or infusion bottle:

- Thiopentone sod. + succinylcholine chloride
- Penicillin-G sod. + succinylcholine chloride
- Heparin + penicillin/tetracyclines/streptomycin/hydrocortisone

(c) Physiological/functional antagonism

The two drugs act on different receptors or by different mechanisms, but have opposite overt effects on the same physiological function, i.e. have pharmacological effects in opposite direction, e.g.

- Histamine and adrenaline on bronchial muscles and on BP.
- Hydrochlorothiazide and amiloride on urinary K^+ excretion.
- Glucagon and insulin on blood sugar level.

(d) Receptor antagonism

One drug (antagonist) blocks the receptor action of the other (agonist). This is a very important mechanism of drug action, because physiological signal molecules act through their receptors, blockade of which can produce specific and often profound pharmacological effects. Receptor antagonists are selective (relatively), i.e. an anticholinergic will oppose contraction of intestinal smooth muscle induced by cholinergic agonists, but not that induced by histamine or 5-HT (they act through a different set of receptors). Receptor antagonism can be competitive or noncompetitive.

Competitive antagonism (equilibrium type) The antagonist is chemically similar to the agonist, competes with it (Fig. 4.18 A, D) and binds to the same site to the exclusion of the agonist molecules. Because the antagonist has affinity but no intrinsic activity (*see* p. 50), no response is produced and the log DRC of the agonist is shifted to the right. Since antagonist binding is reversible and depends on the relative concentration of the agonist and antagonist molecules, higher concentration of the agonist progressively overcomes the block—a parallel shift of the agonist DRC with no suppression of maximal response is obtained (Fig. 4.19A). The extent of shift is dependent on the affinity and concentration of the antagonist.

A partial agonist (Fig. 4.18 C), having affinity for the same receptor, also competes with and antagonizes a full agonist, while producing a submaximal response of its own.

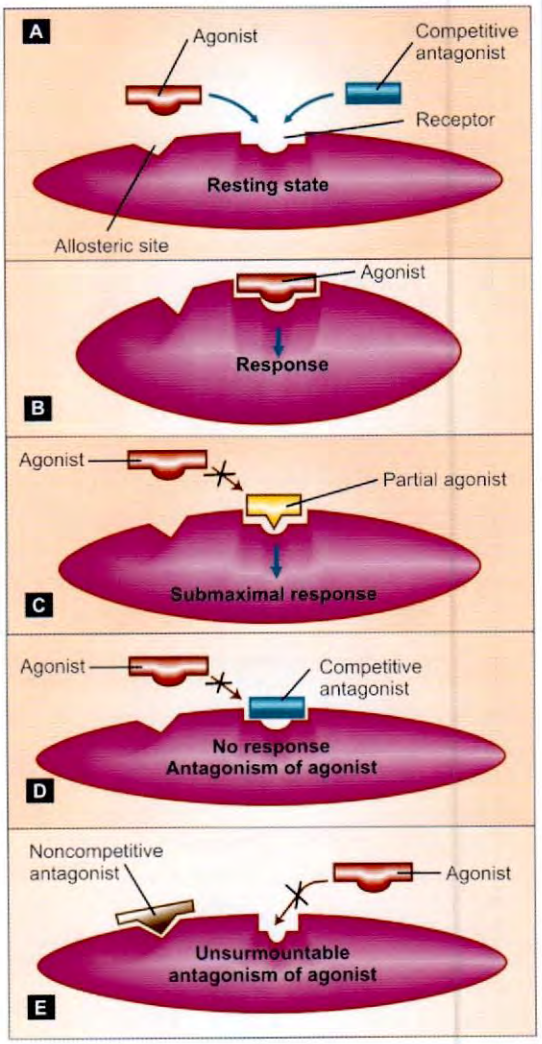


Fig. 4.18: Illustration of sites of action of agonists and antagonists (A), and the action of full agonist (B), partial agonist (C), competitive antagonist (D) and noncompetitive antagonist (E) on the receptor

Noncompetitive antagonism The antagonist is chemically unrelated to the agonist, binds to a different *allosteric site* altering the receptor in such a way that it is unable to combine with the agonist (Fig. 4.18E), or is unable to transduce

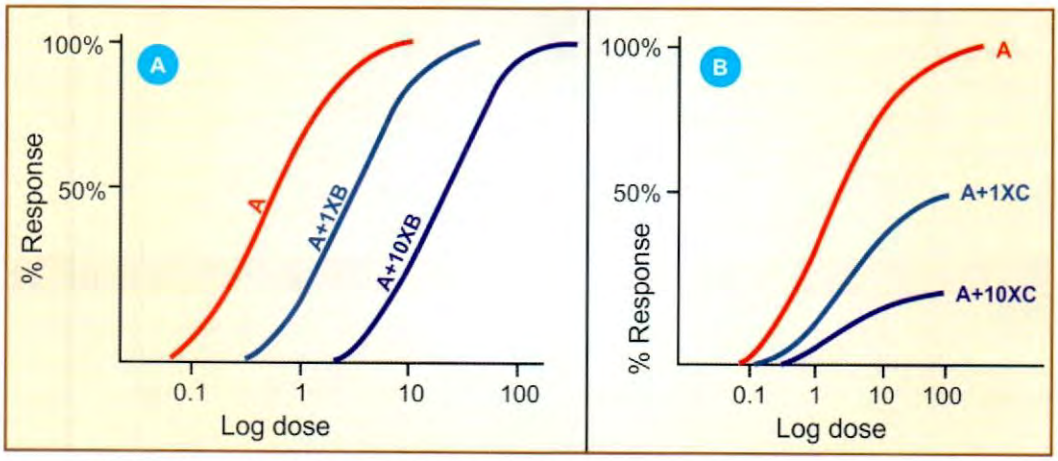


Fig. 4.19: Dose-response curves showing competitive (a) and noncompetitive (b) antagonism
A—agonist, B—competitive antagonist, C—noncompetitive antagonist

the response, so that the downstream chain of events are uncoupled. This is also called allosteric antagonism. Because the agonist and the antagonist are combining with different sites, there is no competition between them—even high agonist concentration is unable to reverse the block completely. Increasing concentrations of the antagonist progressively flatten the agonist DRC (Fig. 4.19B). Noncompetitive antagonists have been produced experimentally, but are not in clinical use.

Nonequilibrium antagonism Certain antagonists bind to the receptor with strong (covalent) bonds or dissociate from it slowly (due to very high affinity) so that agonist molecules are unable to reduce receptor occupancy of the antagonist molecules—law of mass action cannot apply—an *irreversible* or *nonequilibrium antagonism* is produced. The agonist DRC is shifted to the right and the maximal response is lowered (if spare receptors are few). Since in this situation the agonist molecules are not able to compete

Competitive (equilibrium type)	Noncompetitive
1. Antagonist binds with the same receptor as the agonist	Binds to another site of receptor
2. Antagonist resembles chemically with the agonist	Does not resemble
3. Parallel rightward shift of agonist DRC	Flattening of agonist DRC
4. The same maximal response can be attained by increasing dose of agonist (surmountable antagonism)	Maximal response is suppressed (unsurmountable antagonism)
5. Intensity of response depends on the concentration of both agonist and antagonist	Maximal response depends only on the concentration of antagonist
6. Examples: ACh—Atropine Morphine—Naloxone	Diazepam—Bicuculline

with the antagonist molecules and flattening of agonist DRC is a feature of noncompetitive antagonism; nonequilibrium antagonism has also been called 'a type of noncompetitive antagonism'. Phenoxybenzamine is a non-equilibrium antagonist of adrenaline at the α adrenergic receptors.

Features of competitive and noncompetitive antagonism are compared on previous page.

PROBLEM DIRECTED STUDY

4.1 A patient being treated with methotrexate (Mtx) developed oral ulceration, megaloblastic anaemia and other toxic symptoms. Given that (i) Mtx acts by inhibiting the enzyme dihydrofolate reductase (DHFRase) which generates the essential coenzyme tetrahydrofolic acid (THFA) from dihydrofolic acid (DHFA) needed for one carbon transfer reactions, (ii) Mtx binds to the catalytic site of DHFRase with an affinity 50,000 times greater than the natural substrate DHFA, and that (iii) two forms of folate viz. folic acid and folinic acid (N5 formyl THFA) are available for therapeutic use:

(a) Which type of enzyme inhibition will be produced by Mtx?

(b) Which form of folate should be used to treat Mtx toxicity?

(see Appendix-1 for solution)

Chapter 5 Aspects of Pharmacotherapy, Clinical Pharmacology and Drug Development

Pharmaco- (drug) therapy is dynamic and an ever evolving science. It requires understanding of the drug, the disease, the patient and the milieu in which it is undertaken. As such, in addition to knowledge of drug action, mechanisms and pharmacokinetics, several aspects like drug dosage, sources of variability in drug response, pharmacogenetics, influence of disease on drug action, etc. are important for otimum drug therapy.

DRUG DOSAGE

'Dose' is the appropriate amount of a drug needed to produce a certain degree of response in a given patient.

Accordingly, dose of a drug has to be qualified in terms of the chosen response, e.g. the analgesic dose of aspirin for headache is 0.3–0.6 g, its antiplatelet dose is 60–150 mg/day, while its antiinflammatory dose for rheumatoid arthritis is 3–5 g per day. Similarly there could be a *prophylactic dose*, a *therapeutic dose* or a *toxic dose* of the same drug.

The dose of a drug is governed by its inherent potency, i.e. the concentration at which it should be present at the target site, and its pharmacokinetic characteristics. The recommended doses are based on population data and cater to an 'average' patient. However, individual patients may not be 'average' in respect to a number of pharmacokinetic and pharmacodynamic parameters, emphasizing the need for individualizing drug dose. The strategies adopted for different types of drugs and conditions are:

1. Standard dose The same dose is appropriate for most patients—individual variations are minor or the drug has a wide safety margin so that a large enough dose can be given to cover them, e.g. oral contraceptives, penicillin, chloroquine, mebendazole, hydrochlorothiazide.

2. Regulated dose The drug modifies a finely regulated body function which can be easily measured. The dosage is accurately adjusted by repeated measurement of the affected physiological parameter, e.g. antihypertensives, hypoglycaemics, anticoagulants, diuretics, general anaesthetics. In their case, measurement of plasma drug concentration is not needed.

3. Target level dose (*see* p. 41) The response is not easily measurable but has been demonstrated to be obtained at a certain range of drug concentration in plasma. An empirical dose aimed at attaining the target level is given in the beginning and adjustments are made later by actual monitoring of plasma concentrations. When facilities for drug level monitoring are not available, crude adjustments are made by observing the patient at relatively long intervals, e.g. antidepressants, antiepileptics, digoxin, theophylline.

4. Titrated dose The dose needed to produce maximal therapeutic effect cannot be given because of intolerable adverse effects. Optimal dose is arrived at by titrating it with an acceptable level of adverse effect. Low initial dose and

upward titration (in most non-critical situations) or high initial dose and downward titration (in critical situations) can be practised. Often a compromise between submaximal therapeutic effect but tolerable side effects can be struck, e.g. anticancer drugs, corticosteroids, levodopa.

Fixed dose combinations (FDCs) of drugs

A large number of pharmaceutical preparations contain two or more drugs in a fixed dose ratio. *Advantages* offered by these are:

1. Convenience and better patient compliance—when all the components present in the FDC are actually needed by the patient and their amounts are appropriate. It may also be cost saving compared to both/all the components administered separately.
2. Certain drug combinations are synergistic, e.g. sulfamethoxazole + trimethoprim; levodopa + carbidopa/benserazide; combination oral contraceptives, isoniazid + rifampin.
3. The therapeutic effect of two components being same may add up while the side effects being different may not. For this the components of the FDC should act by different mechanisms, e.g. amlodipine + atenolol as antihypertensive.
4. The side effect of one component may be counteracted by the other, e.g. a thiazide + a potassium sparing diuretic. However, the amount of the latter may not be sufficient in all cases.
5. Combined formulation ensures that a single drug will *not* be administered. This is important in the treatment of tuberculosis, HIV-AIDS and falciparum malaria.

Before prescribing a combination, the physician must consider whether any of the ingredients is unnecessary; if it is, the combination should not be prescribed. It can never be justified that a drug is given to a patient who does not need it in order to provide him another, one that he needs.

There are many inbuilt *disadvantages* of FDCs:

1. The patient may not actually need all the drugs present in a combination: he is subjected to additional side effects and expense (often due to ignorance of the physician about the exact composition of the combined formulations).
2. The dose of most drugs needs to be adjusted and individualised. When a combined formulation is used, this cannot be done without altering the dose of the other component(s). However, few combinations are available at more than one dose ratios, e.g. levodopa (100 mg) + Carbidopa (10 mg or 25 mg), amoxicillin (250 mg or 500 mg) + clavulanic acid (125 mg).
3. The time course of action of the components may be different: administering them at the same intervals may be inappropriate.
4. Altered renal or hepatic function of the patient may differently affect the pharmacokinetics of the components.
5. Adverse effect, when it occurs, cannot be easily ascribed to the particular drug causing it.
6. Contraindication to one component (allergy, other conditions) contraindicates the whole product.
7. Confusion of therapeutic aims and false sense of superiority of two drugs over one is fostered, specially in case of antimicrobials whose combinations should be avoided. Corticosteroids should never be combined with any other drug meant for internal use. Drug combinations that are banned in India are listed in Appendix-4.

Thus, only a handful of FDCs are rational and justified, while far too many are produced and vigorously promoted by the pharmaceutical industry. In fact, the latest (2017) WHO essential medicines list incorporates only 25 FDCs, and the NLEM (2015) of India has only 20 FDCs. In addition to the previously banned FDCs, recently 344 other irrational FDCs have been banned in India.

FACTORS MODIFYING DRUG ACTION

Variation in response to the same dose of a drug between different patients and even in the same patient on different occasions is a rule rather than exception. One or more of the following categories of differences among individuals are responsible for the variations in drug response:

(1) Individuals differ in pharmacokinetic handling of drugs: attain varying plasma/target site concentration of the drug. This is more marked for drugs disposed by metabolism (e.g. propranolol) than for drugs excreted unchanged (e.g. atenolol).

(2) Variations in number or state of receptors, coupling proteins or other components of response effectuation.

(3) Variations in neurogenic/hormonal tone or concentrations of specific constituents, e.g. atropine tachycardia depends on vagal tone, propranolol bradycardia depends on sympathetic tone, captopril hypotension depends on body Na^+ status.

A multitude of host and external factors influence drug response. They fall in two categories *viz genetic* and *nongenetic* including all environmental, circumstantial and personal variables. Though individual variation cannot be totally accounted for by these factors, their understanding can guide the choice of appropriate drug and dose for an individual patient. However, final adjustments have to be made by observing the response in a given patient on a given occasion.

The factors modify drug action either:

(a) *Quantitatively* The plasma concentration and/or the action of the drug is increased or decreased. Most of the factors introduce this type of change and can be dealt with by adjustment of drug dosage.

(b) *Qualitatively* The type of response is altered, e.g. drug allergy or idiosyncrasy. This is less common but often precludes further use of that drug in the affected patient.

The various factors are discussed below—

1. Body size It influences the concentration of the drug attained at the site of action. The average adult dose refers to individuals of medium built. For exceptionally obese or lean individuals and for children dose may be calculated on body weight (BW) basis:

$$\text{Individual dose} = \frac{\text{BW (kg)}}{70} \times \text{average adult dose}$$

It has been argued that body surface area (BSA) provides a more accurate basis for dose calculation, because total body water, extracellular fluid volume and metabolic activity are better paralleled by BSA.

$$\text{Individual dose} = \frac{\text{BSA (m}^2\text{)}}{1.7} \times \text{average adult dose}$$

The BSA of an individual can be calculated from Dubois formula:

$$\text{BSA (m}^2\text{)} = \text{BW (kg)}^{0.425} \times \text{Height (cm)}^{0.725} \times 0.007184$$

or obtained from chart-form or slide-rule nomograms based on BW and height.

However, dose recommendations in terms of BSA are available only for anticancer and a handful of other drugs: for the rest BW has been used as the index. Thus, prescribing on BSA basis suffers from lack of data base, is more cumbersome and has not thrived, except in few cases.

2. Age The dose of a drug for *children* is often calculated from the adult dose. Some age based formulae for calculating child dose from the adult dose have been framed, but are not in use now. Child dose is better calculated more accurately on BW basis. For many drugs, manufacturers give dosage recommendations on mg/kg basis. Average figures for children are given in the chart below.

Age	Body weight (Kg)* Boys	Girls	% of Adult dose
Newborn	3.5	3.4	12.5
1 month	4.8	4.5	15
3 months	6.4	5.8	18
6 months	8.1	7.4	22
1 year	10.5	9.7	25
3 years	14.3	13.8	33
5 years	18.5	18.2	40
7 years	23.1	22.9	50
9 years	28.7	29.1	60
12 years	40.7	41.8	75

*50th percentile body weight of Indian boys and girls as per CDC 2000 guidelines.

However, *infants* and *children* are not small adults. They have important physiological differences from adults. The *newborn* has low g.f.r. and tubular transport is immature. As such, the t½ of drugs excreted by glomerular filtration (gentamicin) and tubular secretion (penicillin) is prolonged by 3 to 5 times. Glomerular filtration reaches adult rates by 5 month of age and tubular secretion takes about 7 months to mature. Similarly, hepatic drug metabolizing system is inadequate in newborns —chloramphenicol can produce *gray baby syndrome* (*see* Ch. 53). Blood-brain barrier is more permeable—drugs attain higher concentration in the CNS (easy entry of unconjugated bilirubin in brain causes *kernicterus*). These defects are exaggerated in the premature infant. Drug absorption may also be altered in infants because of lower gastric acidity and slower intestinal transit. Transdermal absorption however, is faster because infant skin is thin and more permeable. Rectal absorption is fast and more predictable in infants and young children. Taking advantage of this fact, diazepam solution is given rectally to control febrile seizures in children < 5 years. Therefore, infant doses must be learned as such and not derived from any formula.

After the first year of life, drug metabolism is often faster than in adults. Accordingly, the t½ of theophylline, phenytoin, carbamazepine is shorter in children than in adults. Also, higher per kg dose is needed in children for drugs which are primarily excreted unchanged by kidney, e.g. daily dose of digoxin is about 8–12 μg/kg compared to adult dose of 3–5 μg/kg.

Solid dosage forms and metered dose inhalers are difficult to administer to young children.

Children are growing and are susceptible to special adverse effects of drugs, e.g. suppression of growth can occur with corticosteroids; androgens may promote early fusion of epiphysis resulting in stunting of stature; tetracyclines get deposited in growing teeth and discolour/deform them. Dystonic reactions to phenothiazines are more common in children.

Elderly In the elderly, renal function progressively declines (intact nephron loss) so that g.f.r. is ~ 75% at 50 years and ~ 50% at 75 years age compared to young adults. Drug doses have to be reduced, e.g. daily dose of streptomycin is 0.75 g after 50 years and 0.5 g after 70 years of age compared to 1 g for young adults. There is also a reduction in the hepatic microsomal drug metabolizing activity and liver blood flow: oral bioavailability of drugs with high hepatic extraction is generally increased, but the overall effects on drug metabolism are not uniform. Due to lower renal as well as metabolic clearance, the elderly are prone to develop cumulative toxicity while receiving prolonged medication. Other affected aspects of drug handling are:

- slower absorption due to reduced gut motility as well as blood flow to intestines,
- lesser plasma protein binding due to lower plasma albumin,
- increased or decreased volume of distribution of lipophilic and hydrophilic drugs respectively.

Aged are relatively intolerant to digitalis. The responsiveness of β adrenergic receptors to both agonists and antagonists is reduced in the elderly and sensitivity to other drugs also may be altered. Due to prostatism in elderly males, even mild anticholinergic activity of the drug can accentuate bladder voiding difficulty. Elderly are also likely to be on multiple drug therapy for hypertension, ischaemic heart disease, diabetes, arthritis, etc.

which increases many fold the chances of drug interactions. They are more prone to develop postural instability, giddiness and mental confusion. In general, the incidence of adverse drug reactions is much higher in the elderly.

3. Sex Females have smaller body size and require doses that are on the lower side of the range. Subjective effects of drugs may differ in females because of their mental makeup. Maintenance treatment of heart failure with digoxin is reported to be associated with higher mortality among women than among men. A number of antihypertensives (clonidine, methyldopa, β-blockers, diuretics) have potential to interfere with sexual function in males but not in females. Gynaecomastia is a side effect (of ketoconazole, metoclopramide, chlorpromazine, digitalis) that can occur only in men. Ketoconazole causes loss of libido in men but not in women. Obviously androgens are unacceptable to women and estrogens to men. In women consideration must also be given to menstruation, pregnancy and lactation.

Drugs given during *pregnancy* can affect the foetus (*see* Ch. 6 and Appendix-2). There are marked and progressive physiological changes during pregnancy, especially in the third trimester, which can alter drug disposition.

(i) Gastrointestinal motility is reduced → delayed absorption of orally administered drug.
(ii) Plasma and extracellular fluid volume expands—volume of drug distribution may increase.
(iii) While plasma albumin level falls, that of α_1 acid glycoprotein increases—the unbound fraction of acidic drugs increases but that of basic drugs decreases.
(iv) Renal blood flow increases markedly—polar drugs are eliminated faster.
(v) Hepatic microsomal enzymes undergo induction—many drugs are metabolized faster.

Thus, the overall effect on drug disposition is complex and often difficult to predict.

4. Species and race There are many examples of differences in responsiveness to drugs among different species; rabbits are resistant to atropine, rats and mice are resistant to digitalis and rat is more sensitive to curare than cat. These differences are important while extrapolating results from experimental animals to man.

Among human beings some racial differences have been observed, e.g. blacks require higher and Mongols require lower concentrations of atropine and ephedrine to dilate their pupil. β-blockers are less effective as antihypertensive in Afro-Caribbeans. Considering the widespread use of chloramphenicol in India and Hong Kong between 1950–1980, relatively few cases of aplastic anaemia have been reported compared to its incidence in the west. Similarly, quiniodochlor related cases of subacute myelooptic neuropathy (SMON) occurred in epidemic proportion in Japan, but there is no confirmed report of its occurrence in India despite extensive use.

5. Genetics The dose of a drug to produce the same effect may vary by 4–6 fold among different individuals. All key determinants of drug response, *viz.* transporters, metabolizing enzymes, ion channels, receptors with their couplers and effectors are controlled genetically. Hence, a great deal of individual variability can be traced to the genetic composition of the subject.

Pharmacogenetics The study of genetic basis for variability in drug response is called *'Pharmacogenetics'*. It deals with genetic influences on drug action as well as on drug handling by the body. As the genomic technology has advanced and the human genome project has been undertaken, gene libraries and huge data bases (like 'pharmacogenetics and pharmacogenomics knowledge base', 'Human genome variation database', etc.) have been created aiming at improving precision in drug therapy.

Pharmacogenomics is the use of genetic information to guide the choice of drug and dose on an individual basis.

A relationship is drawn between how a patient responds to a drug with his genetic makeup.

The purpose is to identify individuals who are either more likely or less likely to respond to a drug, as well as those who require altered dose of certain drugs. Attempt is made to define the genetic basis of an individual's profile of drug response and to predict the best treatment option for him/her. So far, this has been applied largely to patients with known genetic abnormalities, but the goal is 'personalized medicine' on a wide scale. However, the basis of a large proportion of genetic variability still remains unexplained.

A continuous variation with bell-shaped Gaussian frequency distribution is seen in the case of most drugs. In addition, there are some specific genetic defects which lead to discontinuous variation in drug responses, e.g.—

1. Atypical pseudocholinesterase results in prolonged succinylcholine apnoea.
2. G-6PD deficiency is responsible for haemolysis with primaquine and other oxidizing drugs. This X-linked monogenic trait is more common in the Mediterranean, African and Southeast Asian races. The haemolysis is largely dose related. Several variants of the G-6PD gene occur in the population resulting in differing severity of haemolysis triggered by different oxidizing drugs. Haemolysis is severe in homozygous deficient individuals of certain genotypes. Important drugs reported to cause haemolysis in G-6PD deficient subjects are listed in the box.

Drugs with potential* to cause haemolysis in G-6PD deficient individuals

Primaquine	*Nalidixic acid*
Chloroquine	*Fluoroquinolones*
Quinine/Quinidine	Chloramphenicol
Proguanil	*Nitrofurantoin*
Pyrimethamine	Furazolidone
Dapsone	Menadione
Sulfonamides	*Methyldopa*
Cotrimoxazole	Hydralazine
Sulfasalazine	Procainamide
Sulfonylureas	Probenecid
Thiazide diuretics	Colchicine
Aspirin	*Methylene blue*

* Drugs carrying higher risk are italicized.

3. The low activity CYP2C9 variants metabolize warfarin at a slow rate and are at higher risk of bleeding.
4. Thiopurine methyl transferase (TPMT) deficiency increases risk of severe bone marrow toxicity of 6-mercaptopurine and azathioprine.
5. Irinotecan induced neutropenia and diarrhoea is more in patients with UGT1A1 *28 allele of glucuronyl transferase.
6. Severe 5-fluorouracil toxicity occurs in patients with dihydropyrimidine dehydrogenase (DPD) deficiency.
7. Over expression of P-gp results in tumour resistance to many cancer chemotherapeutic drugs, because it pumps out the drug from the tumour cells.
8. Polymorphism of N-acetyl transferase 2 (NAT2) gene results in rapid and slow acetylator status. Isoniazid neuropathy, procainamide and hydralazine induced lupus occurs mainly in slow acetylators.
9. Acute intermittent porphyria—precipitated by barbiturates is due to genetic defect in repression of porphyrin synthesis.
10. CYP2D6 abnormality causes poor metoprolol/debrisoquin metabolizer status. Since several antidepressants and antipsychotics also are substrates of CYP2D6, deficient patients are more likely to experience their toxicity. Codeine fails to produce analgesia in CYP2D6 deficient, because this enzyme generates morphine from codeine.
11. Malignant hyperthermia after halothane is due to abnormal Ca^{2+} release channel (ryanodine receptor) in the sarcoplasmic reticulum of skeletal muscles.
12. Inability to hydroxylate phenytoin results in toxicity at usual doses.
13. Resistance to coumarin anticoagulants is due to an abnormal enzyme vitamin K epoxide reductase (VKOR) that regenerates the reduced form of vit. K. This form has low affinity for the coumarins.
14. Attack of angle closure glaucoma is precipitated by mydriatics in individuals with narrow iridocorneal angle.

Genetic variability in drug response could be due to single gene mutation or polygenic. Genotype to phenotype predictability is much better in monogenic phenotypic traits such as G-6PD, CYP2D6, TPMT, etc., than for multigenic traits, which are clinically less significant. Majority of gene polymorphisms are due to substitution of a single base pair by another. When found in the population at a frequency of >1%, these are called 'Single neucleotide polymorphisms' (SNPs). Gene polymorphisms are often encountered at different frequencies among different ethnic/geographical groups.

Despite accumulation of considerable pharmacogenomic data and the fact that genotyping of the individual needs to be done only once, its practical application in routine patient care is at present limited due to prerequirement of multiple drug specific genotypic screening. Simple spot tests for some, e.g. G-6 PD deficiency are currently in use.

6. Route of administration Route of administration governs the speed and intensity of drug response (*see* Ch. 1). Parenteral administration is often resorted to for more rapid, more pronounced and more predictable drug action. A drug may have entirely different uses through different routes, e.g. magnesium sulfate given orally causes purgation, applied on sprained joints it decreases swelling, while intravenously it produces CNS depression and hypotension.

7. Environmental factors and time of administration Several environmental factors affect drug responses. Exposure to insecticides, carcinogens, tobacco smoke and consumption of charcoal broiled meat are well known to induce drug metabolism. Type of diet and temporal relation between drug ingestion and meals can alter drug absorption, e.g. food interferes with absorption of ampicillin, but a fatty meal enhances absorption of griseofulvin and lumefantrine. Subjective effects of a drug may be markedly influenced by the setup in which it is taken. Hypnotics taken at night and in quiet, familiar surroundings may work more easily. Statins cause greater inhibition of cholesterol synthesis when taken in the late evening. It has been shown that corticosteroids taken as a single morning dose cause less pituitary-adrenal suppression.

8. Psychological factor Efficacy of a drug can be affected by the patient's beliefs, attitudes and expectations. This is particularly applicable to centrally acting drugs, e.g. a nervous and anxious patient requires more general anaesthetic; alcohol generally impairs performance but if punishment (which induces anxiety) is introduced, it may actually improve performance by relieving anxiety.

Placebo This is an inert substance which is given in the garb of a medicine. It works by psychodynamic rather than pharmacodynamic means and often produces responses equivalent to the active drug. Some individuals are more suggestible and easily respond to a placebo: and are called 'placebo reactors'. Placebos are used in two situations:

1. As a control device in clinical trial of drugs (dummy medication).
2. To treat a patient who, in the opinion of the physician, does not require an active drug.

Placebo is a Latin word meaning 'I shall please'. A patient responds to the whole therapeutic setting; placebo-effect largely depends on the physician-patient relationship.

Placebos do induce physiological responses, e.g. they can release endorphins in brain—causing analgesia. Naloxone, an opioid antagonist, blocks placebo analgesia. When an active drug is administered, it produces effects both due to its pharmacodynamic action as well as the psychodynamic effect of the act of medication. Placebo effects can thus supplement pharmacological effects of active medicines. However, placebo effects are highly variable even in the same individual, e.g. a placebo may induce sleep on the first night, but not subsequently. Thus, it has a very limited role in practical therapeutics. Substances commonly used as placebo are lactose tablets/capsules and distilled water injection. Multivitamin preparations are often misused as placebos when no medication is needed.

Nocebo It is the converse of placebo, and refers to negative psychodynamic effect evoked by the pessimistic attitude of the patient, or by loss of faith in the medication and/or the physician. Nocebo effect can oppose the therapeutic effect of active medication.

9. Pathological states Not only drugs modify disease processes, several diseases can influence drug disposition and drug action:

Gastrointestinal (g.i.) diseases Certain g.i. diseases can alter absorption of orally administered drugs. The changes are complex and drug absorption can increase or decrease, e.g. in coeliac disease absorption of amoxicillin is decreased but that of cephalexin and cotrimoxazole is increased. Thus, malabsorption syndrome does not necessarily reduce absorption of all drugs. Gastric stasis occurring during migraine attack retards the absorption of ingested drugs. Achlorhydria decreases aspirin absorption by favouring its ionization. NSAIDs can aggravate peptic ulcer disease.

Liver disease Liver disease (especially cirrhosis) can influence drug disposition in several ways:

- Bioavailability of drugs having high first pass metabolism (*see* Ch. 3) is increased due to loss of hepatocellular function and portocaval shunting.
- Serum albumin is reduced—protein binding of acidic drugs (diclofenac, warfarin, etc.) is reduced and more drug is present in the free form.
- Metabolism and elimination of some drugs (morphine, lidocaine, propranolol) is decreased—their dose should be reduced. Alternative drugs that do not depend on hepatic metabolism for elimination and/or have shorter t½ should be preferred, e.g. oxazepam or lorazepam in place of diazepam; atenolol as β-blocker.
- Prodrugs needing hepatic metabolism for activation, e.g. bacampicillin are less effective and should be avoided.

The changes in drug metabolism due to liver disease are complex and there is no simple test (like creatinine clearance for renal disease) to estimate the extent of alteration in drug disposition. Moreover, the kinetics of different drugs is affected to different extents.

Not only disposition, but action as well of certain drugs may be altered in liver disease, e.g.

- The sensitivity of brain to depressant action of morphine and barbiturates is markedly increased in cirrhotics—normal doses can produce coma.
- Brisk diuresis can precipitate mental changes in patients with impending hepatic encephalopathy, because diuretics cause hypokalemic alkalosis which favours conversion of NH_4^+ to NH_3. Ammonia enters brain easily and causes mental derangement.
- Oral anticoagulants can markedly prolong prothrombin time, because clotting factors are already low.
- Fluid retaining action of phenylbutazone (other NSAIDs as well), and lactic acidosis due to metformin are accentuated.

Hepatotoxic drugs should be avoided in liver disease.

Kidney disease It markedly affects the pharmacokinetics of many drugs as well as alters the effects of some drugs.

Clearance of drugs that are primarily excreted unchanged (aminoglycosides, digoxin, phenobarbitone) is reduced parallel to decrease in creatinine clearance (CL_{cr}). Loading dose of such a drug is not altered (unless edema is present), but maintenance doses should be reduced or dose interval prolonged proportionately. A rough guideline is given in the box:

CL_{cr} (patient)	Dose rate to be reduced to
50–70 ml/min	70%
30–50 ml/min	50%
10–30 ml/min	30%
5–10 ml/min	20%

Dose rate of drugs only partly excreted unchanged in urine also needs reduction, but to lesser extents. If the t½ of the drug is prolonged, attainment of steady-state plasma concentration with maintenance doses is delayed proportionately.

Plasma proteins, especially albumin, are often low or altered in structure in patients with renal disease—binding of acidic drugs is reduced, but that of basic drugs is not much affected.

The permeability of blood-brain barrier is increased in renal failure; opiates, barbiturates, phenothiazines, benzodiazepines, etc. produce more CNS depression. Pethidine should be avoided because its metabolite nor-pethidine can accumulate on repeated dosing and cause seizures. The target organ sensitivity may also be increased. Antihypertensive drugs produce greater postural hypotension in patients with renal insufficiency.

Certain drugs worsen the existing clinical condition in renal failure, e.g.

- Tetracyclines have an anti-anabolic effect and accentuate uraemia.
- NSAIDs cause more fluid retention.

Antimicrobials needing dose reduction in renal failure

Even in mild failure	*Only in severe failure*
Aminoglycosides	Cotrimoxazole
Cephalexin	Carbenicillin
Ethambutol	Cefotaxime
Vancomycin	Norfloxacin
Amphotericin B	Ciprofloxacin
Acyclovir	Metronidazole

- Potentially nephrotoxic drugs, e.g. aminoglycosides, tetracyclines (except doxycycline), sulfonamides (crystalluria), vancomycin, nitrofurantoin, cyclosporine, amphotericin B should be avoided.

Thiazide diuretics tend to reduce g.f.r. They are ineffective in renal failure and can worsen uraemia; furosemide should be used instead. Potassium sparing diuretics are contraindicated because they can cause hyperkalemia → cardiac depression. Repeated doses of pethidine are likely to cause muscle twitching and seizures due to accumulation of its excitatory metabolite norpethidine.

Urinary antiseptics like nalidixic acid, nitrofurantoin and methenamine mandelate fail to achieve high concentration in urine and are likely to produce systemic toxicity.

Congestive heart failure It can alter drug kinetics by—

(i) Decreasing drug absorption from g.i.t. due to mucosal edema and splanchnic vasoconstriction. A significant reduction in procainamide and hydrochlorothiazide absorption has been documented.

(ii) Altering volume of distribution which can increase for some drugs due to expansion of extracellular fluid volume or decrease for others as a result of decreased tissue perfusion. For example, loading doses of drugs like lidocaine and procainamide should be lowered.

(iii) Retarding drug elimination as a result of decreased perfusion and congestion of liver, reduced glomerular filtration rate and increased tubular reabsorption; dosing rate of drugs may need reduction, as for lidocaine, procainamide, theophylline.

(iv) The decompensated heart is more sensitive to digitalis action.

Thyroid disease The hypothyroid patients are more sensitive to digoxin, morphine and CNS depressants. Hyperthyroid patients are relatively resistant to inotropic action of digoxin, but more prone to its arrhythmogenic action. The clearance of digoxin is roughly proportional to thyroid function, but this only partially accounts for the observed changes in sensitivity.

Other examples of modification of drug response by pathological states are:

- Antipyretics lower body temperature only when it is raised (fever).
- Thiazides induce more marked diuresis in edematous patients.
- Myocardial infarction patients are more prone to adrenaline and digitalis induced cardiac arrhythmias.
- Myasthenic patients are very sensitive to curare. In them weakness is aggravated by quinine.
- Schizophrenics tolerate large doses of phenothiazines.
- Head injury patients are prone to go into respiratory failure with normal doses of morphine.

- Atropine, tricyclic antidepressants, furosemide can cause urinary retention in individuals with prostatic hypertrophy.
- Hypnotics given to a patient in severe pain may cause mental confusion and delirium.
- Cotrimoxazole produces a higher incidence of adverse reactions in AIDS patients.

10. Other drugs Drugs can modify the response to each other by pharmacokinetic or pharmacodynamic interaction between them. Many ways in which drugs can interact have already been considered (*see* Ch. 2, 3, 4), and a comprehensive account of clinically important drug interactions is presented in Ch. 71.

11. Cumulation Any drug will cumulate in the body if rate of administration is more than the rate of elimination. However, slowly eliminated drugs are particularly liable to cause cumulative toxicity, e.g. prolonged use of chloroquine causes retinal damage.

- Full loading dose of digoxin should not be given if patient has received it within the past week.
- A course of emetine should not be repeated within 6 weeks.

12. Tolerance It refers to the requirement of higher dose of a drug to produce a given response. Tolerance is a widely occurring adaptive biological phenomenon. Loss of therapeutic efficacy after prolonged/intensive use of a drug (e.g. of sulfonylureas in type 2 diabetes, or of β_2 agonists in bronchial asthma), is generally called *'refractoriness'*. Drug tolerance may be:

Natural The species/individual is inherently less sensitive to the drug, e.g. rabbits are tolerant to atropine; black races are tolerant to mydriatics. Certain individuals in any population are hyporesponders to certain drugs, e.g. some subjects can consume large quantity of alcohol without getting inebriated; or some hypertensives do not respond to β adrenergic blockers.

Acquired Acquired tolerance occurs by repeated use of a drug in an individual who was initially responsive. Body is capable of developing tolerance to most drugs, but the phenomenon is very easily recognized in the case of CNS depressants. An uninterrupted presence of the drug in the body favours development of tolerance. However, significant tolerance does not develop to atropine, digoxin, cocaine, sodium nitroprusside, etc. Tolerance need not develop equally to all actions of a drug, consequently therapeutic index of a drug may increase or decrease with prolonged use, e.g.:

- Tolerance develops to the sedative action of chlorpromazine but not to its antipsychotic action.
- Tolerance occurs to the sedative action of phenobarbitone but not as much to its antiepileptic action.
- Tolerance occurs to analgesic and euphoric action of morphine, but not as much to its constipating and miotic actions.

Cross tolerance It is the development of tolerance to pharmacologically related drugs, e.g. alcoholics are relatively tolerant to barbiturates and general anaesthetics. Closer the two drugs are, more complete is the cross tolerance between them, e.g.—

There is partial cross tolerance between morphine and barbiturates but complete cross tolerance between morphine and pethidine.

Mechanisms of tolerance The mechanisms responsible for development of tolerance are incompletely understood. However, tolerance may be:

(i) Pharmacokinetic/drug disposition tolerance—the effective concentration of the drug at the site of action is decreased, mostly due to enhancement of drug elimination on chronic use, e.g. barbiturates and carbamazepine induce their own metabolism, while renal excretion of amphetamine is accelerated after regular intake.

(ii) Pharmacodynamic/cellular tolerance—drug action is lessened; cells of the target organ become less responsive, e.g. morphine, barbiturates, nitrates. This may be due to desensitization/down regulation of receptors (*see* p. 62), or weakening of response effectuation.

Tachyphylaxis (*Tachy*-fast, *phylaxis*-protection) It refers to rapid development of tolerance when doses of a drug repeated in quick succession result in marked reduction in response. This is usually seen with indirectly acting drugs,

such as ephedrine, tyramine, nicotine. These drugs act by releasing catecholamines in the body, synthesis of which is unable to match the rate of release: stores get depleted. Other mechanisms like slow dissociation of the drug from its receptor, desensitization/internalization or down regulation of receptor, etc. (*see* p. 62) and/or compensatory homeostatic adaptation.

Drug resistance It refers to tolerance of microorganisms to inhibitory action of antimicrobials, e.g. *Staphylococci* to penicillin. This phenomenon is described in Ch. 50).

RATIONAL USE OF MEDICINES

It is widely assumed that use of drugs by qualified doctors of modern medicine would be rational. However, in reality, irrationality abounds in almost every aspect of drug use. Medically inappropriate, ineffective and economically inefficient use of drugs occurs all over the world, more so in the developing countries.

As per the WHO — '*rational use of medicines requires that the patients receive medication appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and to their community*'.

Rational use of medicines addresses every step in the supply-use chain of drugs, i.e. selection, procurement, storage, prescribing, dispensing, monitoring and feedback. However, only rational prescribing and related aspects are dealt here.

Rational prescribing

Rational prescribing is not just the choice of a correct drug for a disease, or mere matching of drugs with diseases, but also the appropriateness of the whole therapeutic set up along with follow up of the outcome. The criteria to evaluate rational prescribing are:

- *Appropriate indication*: the reason to prescribe the medicine is based on sound medical considerations.
- *Appropriate drug* in efficacy, tolerability, safety, and suitability for the patient.
- *Appropriate dose*, *route* and *duration* according to specific features of the patient.
- *Appropriate patient*: no contraindications exist and the drug is acceptable to the patient; likelihood of adverse effect is minimal and less than the expected benefit.
- *Correct dispensing* with appropriate information/instruction to the patient.
- *Adequate monitoring* of patient's adherence to medication, as well as of anticipated beneficial and untoward effects of the medication.

There is no doubt that knowledge of the prescriber about drugs and disease is the most important determinant of his/her prescribing pattern, but it has been demonstrated time and again that simply improving knowledge has failed to promote rational drug use. A variety of other factors influence prescribing as summarized in the box.

Factors influencing prescribing

- Knowledge of the prescriber.
- Role models: one tends to follow prescribing practices of one's teachers or senior/popular physicians.
- Patient load: heavy load tends to foster routinized symptom based prescribing.
- Attitude to afford prompt symptomatic relief at all cost.
- Imprecise diagnosis: medication is given to cover all possible causes of the illness.
- Drug promotion and unrealistic claims by manufacturers.
- Unethical inducements (gifts, dinner parties, conference delegation, etc.).
- Patient's demands: many patients are not satisfied unless medication is prescribed; misconceptions, unrealistic expectations, 'pill for every ill' belief.

Irrationalities in prescribing

It is helpful to know the commonly encountered irrationalities in prescribing so that a conscious effort is made to avoid them.

- Use of drug when none is needed; e.g. antibiotics for viral fevers and nonspecific diarrhoeas.
- Compulsive coprescription of vitamins/tonics.
- Use of drugs not related to the diagnosis, e.g. ampicillin/ciprofloxacin for any fever, proton pump inhibitors for any abdominal symptom.

- Selection of wrong drug, e.g. tetracycline/ciprofloxacin for pharyngitis, β blocker as antihypertensive for asthmatic patient.
- Prescribing ineffective/doubtful efficacy drugs, e.g. antioxidants, cough mixtures, memory enhancers, oral serratiopeptidase for injuries/swellings, etc.
- Incorrect route of administration: injection when the drug can be given orally.
- Incorrect dose: either underdosing or overdosing; more prevalent in drug prescribing for children.
- Incorrect duration of treatment, e.g. prolonged postsurgical use of antibiotics or stoppage of antibiotics as soon as relief is obtained, such as in tuberculosis.
- Unnecessary use of drug combinations, e.g. ciprofloxacin + tinidazole for any case of diarrhoea, ampicillin + cloxacillin for staphylococcal infection, routine use of ibuprofen + paracetamol as analgesic.
- Unnecessary use of expensive medicines when cheaper drugs are equally effective; craze for latest drugs, e.g. routine use of newer antibiotics.
- Unsafe use of drugs, e.g. corticosteroids for fever, anabolic steroids in children, use of a single antitubercular drug.
- Polypharmacy without regard to drug interactions: each prescription on an average has 3–4 drugs, some may have as many as 10–12 drugs, of which many are combinations.

Irrational prescribing has a number of adverse consequences for the patient as well as the community. The important ones are:

Impact of irrational prescribing

- Delay/inability in affording relief/cure of disease.
- More adverse drug effects.
- Prolongation of hospitalization; loss of man days.
- Increased morbidity and mortality.
- Emergence of microbial resistance.
- Financial loss to the patient/community.
- Loss of patient's confidence in the doctor.
- Lowering of health standards of patients/community.
- Perpetuation of public health problem.

Rational prescribing is a stepwise process of scientifically analyzing the therapeutic set up based on relevant inputs about the patient as well as the drug, and then taking appropriate decisions. It does not end with handing over the prescription to the patient, but extends to subsequent monitoring, periodic evaluations and modifications as and when needed, till the therapeutic goals are achieved. The important steps are summarized in the box.

Process of rational prescribing

- Establish a diagnosis (at least provisional).
- Define therapeutic problem(s), e.g. pain, infection, etc.
- Define therapeutic goals to be achieved, e.g. symptom relief, cure, prevention of complications, etc.
- Select the class of drug capable of achieving each goal.
- Identify the drug (from the class selected) based on:
  - Efficacy
  - Safety
  - Suitability
  - Cost

  } For the particular patient
- Decide the route, dose, duration of treatment, considering patient's condition.
- Provide proper information and instructions about the medication.
- Monitor adherence to the medication (compliance).
- Monitor the extent to which therapeutic goal is achieved, e.g. BP lowering, peptic ulcer healing, etc.
- Modify therapy if needed.
- Monitor any adverse drug events that occur, and modify therapy if needed.

Information/instructions to the patient

Rational prescribing also includes giving relevant and adequate information to the patient about the drug(s) and disease, as well as necessary instructions to be followed.

Effects of the drug Which symptom is expected to disappear and when (e.g. antidepressant will take weeks to act); whether disease will be cured or not (e.g. diabetes, parkinsonism can only be ameliorated, but not cured), what happens if the drug is not taken as advised (e.g. tuberculosis will worsen and may prove fatal).

Side effects There is considerable debate as to how much the patient should be told about the side effects. Detailed descriptions may have

a suggestive effect or may scare the patient and dissuade him from taking the drug, while not informing tantamounts to negligence. The side effect, when it occurs, may upset the uninformed patient. Communicating the common side effects without discouraging the patient is a skill to be developed.

Instructions How and when to take the drug (special dosage forms like inhalers, transdermal patches, etc. may need demonstration); how long to take the drug; when to come back to the doctor; instructions about diet and exercise if needed; what laboratory tests are needed, e.g. prothrombin time with coumarine anticoagulants, leucocyte count with anticancer drugs.

Precautions/warnings What precautions to take; what not to do, e.g. driving (with conventional antihistaminics) or drinking (with metronidazole), or standing still (after sublingual glyceryl trinitrate); risk of allergy or any serious reaction, etc.

In the end it should be ensured that the instructions have been properly understood by the patient. Rational prescribing, thus, is a comprehensive process.

EXPIRY DATE OF PHARMACEUTICALS

It is a legal requirement that all pharmaceutical products must carry the date of manufacture and date of expiry on their label. The period between the two dates is called the 'life period' or 'shelf-life' of the medicine. Under specified storage conditions, the product is expected to remain stable (retain >95% potency) during this period. In India, the schedule P (Rule 96) of Drugs and Cosmetics Act (1940) specifies the life period (mostly 1–5 years) of medicinal products and the conditions of storage. The expiry of other medicines has to be specified by the manufacturer, but cannot exceed 5 years, unless permitted by the licencing authority on the basis of satisfactory stability proof.

The shelf-life of a medicine is determined by real time stability studies or by extrapolation from accelerated degradation studies. The expiry date does not mean that the medicine has actually been found to lose potency or become toxic after it, but simply that quality of the medicine is not assured beyond the expiry date, and the manufacturer is not liable if any harm arises from the use of the product. Infact, studies have shown that majority of solid oral dosage forms (tablets/capsules, etc.) stored under ordinary conditions in unopened containers remained stable for 1–5 years (some even up to 25 years) after the expiry date. Liquid formulations (oral and parenteral) are less stable. Suspensions clump by freezing. Injectable solutions may develop precipitates, become cloudy or discoloured by prolonged storage. Adrenaline injection (in ampoules) has been found to lose potency few months after the expiry date of 1 year (it gets oxidized).

There is hardly any report of toxicity of expired medicines. The degradation product of only one drug (tetracycline) has caused toxicity in man. Outdated tetracycline capsules produced renal tubular damage resembling Fanconi syndrome in the early 1960s. The capsules have now been reformulated to minimize degradation.

Loss of potency beyond the 'life period' of the formulation depends on the drug as well as the storage conditions. High humidity and temperature accelerate degradation of many drugs. Though, majority of medicines, especially solid oral dosage forms, remain safe and active years after the stated expiry date, their use cannot be legally allowed beyond this date.

EVIDENCE-BASED MEDICINE

Extensive scientific investigation of drugs in man and introduction of numerous new drugs over the past few decades is gradually transforming the practice of medicine from *'experience based'* wherein clinical decisions are made based on the experience (or rather impression) of the physician to *'evidence-based'* wherein the same are guided by scientifically credible evidence from well designed clinical studies.

Evidence-based medicine is the process of systematically finding, evaluating and using contemporary research findings as the basis of clinical decisions.

Results of well designed multicentric interventional trials are forming the basis of constantly evolving guidelines for disease management. Today's physician has to be skilled in the new techniques of searching and evaluating the literature on efficacy, safety and appropriateness of a particular therapeutic measure (drug). Therapeutic evaluation of a drug includes:

- Quantitation of benefit afforded by it.
- The best way (dosage, duration, patient selection, etc.) to use it.
- How it compares with other available drugs.
- Surveillance of adverse effects produced by it.

Clinical studies are basically of the following three types:

a. Clinical trials

b. Cohort studies
c. Case control studies.

Clinical trial

Clinical trial is a prospective ethically designed investigation in human subjects to objectively discover/verify/compare the results of two or more therapeutic measures (drugs).

Clinical trials are designed to answer one or more precisely framed questions about the value of treating equivalent groups of patients by two or more modalities (drugs, dosage regimens, other interventions). Depending on the objective of the study, clinical trial may be conducted in healthy volunteers or in volunteer patients. Healthy volunteers may be used to determine pharmacokinetic characteristics, tolerability, safety and for certain type of drugs (e.g. hypoglycaemic, hypnotic, diuretic) even efficacy. For majority of drugs (e.g. antiepileptic, antipsychotic, antiinflammatory, antitubercular, etc.) therapeutic efficacy can only be assessed in patients.

Ethical considerations All clinical trials must be conducted only after scrutiny and approval by an independent *ethics committee* as per the 'Good Clinical Practice' (GCP) guidelines. In India, the ICMR (2006) has brought out 'Ethical guidelines, for biomedical research on human participants'. A proper written *Informed consent* of the patient/trial subject must be obtained. The ethics committee has to ensure that the study does not breach the ethical principles of:

Autonomy: Freedom, dignity and confidentiality of the subject; the right to choose whether or not to participate in the trial or to continue with it.

Beneficence: Motive to do good to the subject and/or the society at large.

Non-maleficence: Not to do harm or put the participant at undue risk/disadvantage.

Justice: Observance of fairness, honesty and impartiality in obtaining, analysing and communicating the data.

Controlled trial The inclusion of a proper comparator *(control)* group in clinical trials is crucial. The control group, which should be as similar to the test group as possible, receives either a placebo (if ethically permissible) or the existing standard treatment (active control). Separate test and control groups may run simultaneously *(parallel group design)*, or all the subjects may be treated by the two options one after the other *(cross over design)* so that the same subjects serve as their own controls. Individual variation in response is thus avoided and sample size may be reduced. In the cross over design, some patients are treated first by drug 'A' followed by drug 'B', while in others the order is reversed. This nullifies the effect (if any) of order of treatment. However, there may still be 'carry over' effects. This design is applicable only to certain chronic diseases which remain stable over long periods.

When one drug is compared to another drug or to a placebo, the dosage regimen (dose, frequency, duration) of the drug is decided in advance. The trial results are applicable only to this chosen regimen. No conclusions can be drawn about a higher or a lower dose. To determine the most appropriate dose, separate dose-ranging studies (trials) have to be performed.

It is well known that both the participants and the investigators of the trial are susceptible to conscious as well as unconscious bias in favour of or against the test drug. The greatest challenge in the conduct of clinical trial is the elimination of bias. The credibility of the trial depends on the measures that are taken to minimize bias. The two basic strategies for minimizing bias are 'randomization' and concealment or 'blinding'.

Randomization The subjects are allocated to either group using a preselected random number table or computer programme so that any subject has equal chance of being assigned to the test or the control group. Discretion (and likely bias) of the investigator/subject in treatment allocation is thus avoided. If considered

necessary, *stratified randomization* according to age/sex/disease severity/other patient variable may be adopted.

Blinding (masking) This refers to concealment of the nature of treatment (test or control) from the subject (single blind) or both the subject as well as the investigator (double blind). For this purpose the two medications have to appear similar in looks, number, weight, taste, etc. and are to be supplied in unlabelled packets marked for each patient. In double blind, the key/code to treatment allocation is kept by a third 'data management' party who is not involved in treating or recording observations. The code is broken at the completion of the trial and the results are analysed according to prespecified statistical method. However, all clinical trials need not be blinded. Those in which the nature of treatment is not concealed are called *'open'* trials.

Randomized controlled double blind trial (RCT) is the most credible method of obtaining evidence of efficacy, safety or comparative value of treatments.

Inclusion/exclusion criteria The characteristics of the subject/patient (age, sex, disease/symptom, severity and/or duration of illness, coexistent and past diseases, concurrent/preceeding drug therapy, etc.) who are to be recruited in the trial or excluded from it must be decided in advance. The trial results are applicable only to the population specified by these criteria.

End point The primary and secondary (if any) end points (cure, degree of improvement, symptom relief, surrogate marker, avoidance of complication, curtailment of hospitalization, survival, quality of life, etc.) of the trial must be specified in advance. The results are analysed in relation to the specified end points.

Higher efficacy may not always be the aim of a clinical trial. A trial may be designed to prove 'non-inferiority' (of the new drug) to the existing treatment, and possibly afford advantages in terms of tolerability, safety, convenience, cost or applicability to special patient subgroup(s).

Sample size: Both financial and ethical considerations demand that the number of subjects in the trial be the minimum needed for a valid result. The minimum number of subjects for obtaining a decisive conclusion (test better than control/control better than test/no difference between the two) must be calculated statistically beforehand. Because the trial is conducted on a sample of the whole patient population, there is always a chance that the sample was *not* representative of the population. Thus, the results cannot be absolutely conclusive.

Two types of errors are possible:

Type I (α) error: a difference is found between the two groups while none exists. Its possibility is called *'significance'* of the result, e.g. if test drug is found to be better than control at a significance level of 0.05, it means that there is 5% chance that this is not real.

Type II (β) error: no difference is found while it really exists. The probability of failing to detect an actual difference is expressed by the *'power'* of the trial. A power of 0.9 means that there is 10% chance of missing a real difference.

The sample size of the trial depends on the desired level of significance and power. The other input needed for calculation of sample size is the magnitude of difference between the two groups that is expected or is considered clinically significant, e.g. a 10% reduction in pain intensity may not be considered clinically significant, while a 10% reduction in mortality may be worthwhile. Larger sample size is required to detect smaller difference. Also, higher the significance and power level desired, greater is the number of subjects. The variability of response in terms of the primary end point also affects the sample size. Responses that show greater individual variation need larger number of subjects to achieve the desired significance and power levels.

Many large scale trials are subjected to interim analysis from time to time as the trial progresses by an independent committee which can order an early termination if a decisive result (positive or negative) is obtained; because it would be unethical to subject some of the remaining patients to a treatment (test or control) which has been found inferior.

Multicentric trial Many large trials are conducted at more than one centre by as many teams of investigators, sometimes spread over several countries. The advantages are:

- Larger number of patients can be recruited in a shorter period of time.
- Results are applicable to a wider population base which may cover several countries/ethnic groups.
- Regulatory requirements of several countries may be satisfied.
- Credibility of the trial is enhanced.

The phase III trials are generally multicentric.

Sequential trial

This design attempts to detect a significant result as soon as it is achieved, minimizing the number of subjects. The trial is conducted on matched pairs of subjects and is scored as 'A' treatment better than 'B' or 'B' better than 'A' or no difference. This is plotted continuously as the trial proceeds till the boundries of predetermined level of significant superiority/inferiority/no difference are touched. The trial is then terminated. This design is applicable only to certain types of drugs and diseases for which clinical end points are achieved quickly and paired comparisons are possible. Moreover, it may not always be practicable to recruit matching pairs of trial subjects.

Meta-analysis

This is an exercise in which data from several similarly conducted randomized controlled clinical trials with the same drug (or class of drugs) examining the same clinical end point(s) is pooled to bring out the overall balance of evidence by enlarging the number of test and control subjects and increasing the significance and power of the conclusions. Because individual trials are often conducted on relatively smaller number of patients, some may fail to detect a significant difference, while others may find it. Discordant results are published which confuse the medical practitioner. There are many criticisms of meta-analysis, such as:

a. bias in the selection of trials for analysis (selection bias);
b. unintentional exclusion of negative results which are less likely to be published (publication bias);
c. nonuniformity of the trials in details of methodology and conduct.

Nevertheless, meta-analysis is a useful tool to arrive at conclusions that may influence medical practice. For example, meta-analysis of trials has strongly supported the use of β-adrenergic blockers in heart failure and use of statins to reduce risk of coronary artery disease.

To be reliable, the meta-analysis should observe the following:

- Comprehensive search of the literature to identify all eligible trials.
- Use objective criteria in selecting the trials for inclusion.
- Include only randomized trials of assured quality.
- Employ proper statistical methods in pooling and treating the data from individual trials.

Meta-analysis are now frequently published on contemporary therapeutic issues.

Cohort study

This is a type of observational study in which no intervention for the sake of the study is done. 'Cohort' is a group of individuals having some common features. In the context of drug research, the common feature is that all study subjects have taken a particular drug. Occurrence of events (beneficial or adverse) in users and nonusers of the drug is compared. *Prescription event monitoring* is a cohort study. The cohort study can be a prospective or a retrospective study. In the prospective design, all patients who receive the study drug are followed up for therapeutic outcomes or adverse effects. A matching group of patients who have not received the drug is identified and followed up to serve as control. Cohort studies are primarily used to discover uncommon adverse effects that may be missed during formal therapeutic trials which involve fewer patients and often exclude certain type of patients who may be susceptible to that adverse effect. Its value for defining therapeutic outcomes is less credible. The limitations of cohort studies are that controls included may not be appropriate, and relatively long period of follow up is needed.

In the retrospective cohort study, health records of a population are scrutinized for exposure to the study drug and the subsequent

Grades of strength of evidence		
Grade I	Systematic reviews/Meta-analysis	Most reliable, may form the basis of clinical decisions
Grade II	Well powered randomized controlled trial/more than one trials	Reliable, but may be supported or refuted by similar studies
Grade III	Open label trials/pilot studies/observational (cohort and case-control) studies (prospective or retrospective)	Less reliable, need more rigorous testing, may indicate further investigation
Grade IV	Case reports/anecdotal reports/clinical experience	Least reliable; may serve as pointers to initiate formal studies

beneficial/adverse events. Its value is questionable because many events may have been missed in the records and several unknown factors may have contributed to the findings. However, it may serve as pointer, or to arouse suspicion.

Case control study

This type of observational study is used mainly to reveal association of a suspected rare adverse event with the use of a particular drug. Cases of the suspected adverse event (e.g. agranulocytosis) are collected from hospital records or disease registries, etc. A matched control group similar in other respects but not having the adverse event is selected. Drug histories of both groups are traced backwards to compare exposure to the indicated drug (e.g. phenylbutazone) among patients with the adverse event to those without it. The suspicion is strengthened if high association is found. Though case control studies can be performed rather quickly because the number of patients analysed is small compared to the cohort design, they do not prove causality. Moreover, the causative drug and the adverse event have to be suspected first to plan the study, whereas cohort study can reveal unsuspected adverse events. Variable accuracy of retrospective records, non-randomly selected control group, chances of bias and a variety of unknown factors make the case control study a weak instrument for affording convincing evidence.

Grading strength of evidence

The strength of evidence from the conclusions of various kinds of trials, studies and reports has been graded from strong to weak as presented in the box.

NEW DRUG DEVELOPMENT

In this era of bewildering new drug introduction and rapid attrition of older drugs, the doctor needs to have an overall idea of the manner in which new drugs are developed and marketed. Drug development now is a highly complex, tedious, competitive, costly and commercially risky process. From the synthesis/identification of the molecule to marketing, a new drug takes at least 10 years and costs 500–1000 million US$. As such, invention and development of new drugs is now possible only in the set up of big pharmaceutical houses that alone have the resources, infrastructure and dedicated teams of scientists to carry out the multiple specialized stages of the process. Though the pharmaceutical industry is often regarded cunning, greedy, unscrupulous, deceptive and fleecing the people, there is no denying that it is responsible for most of the progress in therapeutics as well as pharmacological knowledge of today.

The major steps/stages in the development of a new drug are given in the box.

Stages in new drug development	
Synthesis/isolation of the compound:	(1–2 years)
Preclinical studies: screening, evaluation, pharmacokinetic and short-term toxicity testing in animals:	(2–4 years)
Scrutiny and grant of permission for clinical trials:	(3–6 months)
Pharmaceutical formulation, standardization of chemical/ biological/immuno-assay of the compound:	(0.5–1 year)
Clinical studies: phase I, phase II, phase III trials; long-term animal toxicity testing:	(3–10 years)
Review and grant of marketing permission:	(0.5–2 years)
Postmarketing surveillance:	(phase IV studies)

Approaches to drug discovery/ invention

Exploration of natural sources *Plants* are the oldest source of medicines. Clues about these have been obtained from traditional systems of medicine prevalent in various parts of the world; Opium (morphine), *Ephedra* (ephedrine), *Cinchona* (quinine), curare (tubocurarine), belladonna (atropine), Quinghaosu (artemisinin) are the outstanding examples. Though *animal* parts have been used as cures since early times, it was physiological experiments performed in the 19th and early 20th century that led to introduction of some animal products into medicine, e.g. adrenaline, thyroxine, insulin, liver extract, antisera, etc. Few *minerals* (iron/calcium salts, etc.) are the other natural medicinal substances. The discovery of penicillin (1941) opened the flood-gates of a vast source—*microorganisms*—of a new kind of drugs (antibiotics). The use of microbes for production of vaccines is older than their use to produce antibiotics.

Though few drugs are now produced from plants, animals or microbes, these sources of medicines are by no means exhausted. However, they mostly serve as lead compounds.

Random or targeted chemical synthesis Synthetic chemistry made its debut in the 19th century and is now the largest source of medicines. Randomly synthesized compounds can be tested for a variety of pharmacological activities. Though some useful drugs (barbiturates, chlorpromazine) have been produced serendipitously by this approach, it has very low probability of hitting at the right activity in the right compound; rarely employed now.

Lead optimization A more practical approach is to synthesize chemical congeners of natural products/synthetic compounds with known pharmacological activity in the hope of producing more selective/superior drugs. Many families of clinically useful drugs have been fathered by a *'lead compound'*. Often only 'me too' drugs are produced, but sometimes breakthroughs are achieved, e.g. thiazide diuretics from acetazolamide, tricyclic antidepressants from phenothiazines.

Study of several congeners of the lead compound can delineate molecular features responsible for a particular property. Application of this *structure-activity relationship* information has proven useful on many occasions, e.g. selective β_2 agonists (salbutamol) and β blockers (propranolol, etc.) have been produced by modifying the structure of isoprenaline, H_2 blockers by modifying the side chain of histamine, ethinyl-estradiol by introducing a substitution that resists metabolic degradation, mesoprostol (more stable) by esterifying PGE_1.

More commonly now, as described later in the rational approach, identification of the target biomolecule is the starting point for new drug invention. A lead compound capable of interacting with the target is searched by applying diverse approaches described above and below. The affinity and selectivity of the lead compound for the target is determined. It is then chemically modified to optimise these parameters as well as pharmacokinetic, pharmaceutical, toxicological and other characteristics. More suitable candidate drug(s) may thus emerge for further development.

Single enantiomers Many drugs are *chiral* compounds. Because pharmacological activity depends on three dimensional interaction of drug molecules with their target biomolecules, the *enantiomers* (R and S forms or *d* and *l* isomers) of chiral drugs differ in biological activity, metabolic degradation, etc. Often only one of the enantiomers is active. Single enantiomer drug could be superior to its racemate, because the additional enantiomer may not only be a 'silent passenger' but contribute to side effects, toxicity (dextro-dopa is more toxic than levo-dopa), load on metabolism or even antagonize the active enantiomer. Regulatory authorities in many countries, led by US-FDA, have mandated separate investigation of the enantiomers in case the new drug is a chiral molecule. Approval is withheld unless the pure enantiomers are shown to be no better than the racemate. Several drugs, originally introduced as racemates, have now been made available as *single enantiomer* preparations as well (*see* box).

Rational approach This depends on sound physiological, biochemical, pathological knowledge and identification of specific target for drug action. Truly new classes of drugs generally follow the identification of a novel target for drug action, such as H^+K^+ATPase for gastric acid suppression or glycoprotein IIa/IIIb receptor for platelet function inhibition. The drug is aimed at mitigating the derangement caused by the disease, e.g. levodopa was tried in parkinsonism based on the finding that the condition resulted from deficiency of dopamine in the striatum. The purine, pyrimidine, folate antimetabolites were introduced in cancer chemotherapy after elucidation of key role of these metabolites in cell proliferation. Because virus directed reverse transcriptase is unique to retroviruses, its inhibitors have been developed as anti-HIV drugs. This approach is very attractive but requires a lot of basic research.

Drugs marketed as single enantiomers

Enantiomer	*Advantage claimed*
(S) atenolol	half dose, better tolerated
(S) metoprolol	half dose
(S) amlodipine	half dose, less peripheral edema
(S) omeprazole (esomeprazole)	better oral bioavailability
(S) pantoprazole	more potent
(R) salbutamol	more active, (S) may antagonize (R)
(S) citalopram (escitalopram)	lower dose, less side effects
(S) naproxen	less burden on kidney (but inversion occurs *in vivo*)
cisatracurium	4× more potent, less histamine release
levofloxacin	more active, slower elimination
levocetirizine (R)	half dose, only (R) form active
desloratadine	half dose

Molecular modelling Advances in protein chemistry and computer aided elucidation of three-dimensional structure of key receptors, enzymes, etc. has permitted designing of targeted compounds. Suitable computer programmes are being used to optimise the three-dimensional structure of the candidate drug to fit the identified target site(s) and/or have optimum pharmacokinetics. The designing of selective COX-2 inhibitors was prompted by the comparative configuration of COX-1 and COX-2 isoenzyme molecules. Study of drug binding to mutated receptors and elucidation of configuration of drug-receptor complexes is now guiding production of improved drugs. Attempts are being made to produce individualized drugs according to pharmacogenomic suitability.

Combinatorial chemistry Chemical groups are combined in a random manner to yield innumerable compounds and subjected to *high-throughput screening* on cells, genetically engineered microbes, receptors, enzymes, etc. in robotically controlled automated assay systems. Computerized analysis is used to identify the so called 'hits.' These compounds are then subjected to conventional tests. This new approach has vast potentials, but failure rates are high.

Biotechnology Several drugs are now being produced by recombinant DNA technology, e.g. human growth hormone, human insulin, interferon, etc. Some monoclonal and chimeral antibodies have been introduced as drugs.

New molecules, especially antibiotics, regulatory peptides, growth factors, cytokines, etc. produced by biotechnological methods can be evaluated as putative drugs. Other experimental approaches in new drug development are antisense oligonucleotides and gene therapy.

Preclinical studies

After synthesizing/identifying a prospective compound, it is tested on animals to expose the whole pharmacological profile. Experiments are generally performed on a rodent (mouse, rat, guinea pig, hamster, rabbit) and then on a larger animal (cat, dog, monkey). As the evaluation progresses unfavourable compounds get rejected at each step, so that only a few out of thousands reach the stage when administration to man is considered. The following types of tests are performed.

1. *Screening tests* These are simple and rapidly performed tests to indicate presence or absence of a particular pharmacodynamic activity that is sought for, e.g. analgesic or hypoglycaemic activity.
2. *Tests on isolated organs, bacterial cultures, etc.* These also are preliminary tests to detect specific activity, such as antihistaminic, antisecretory, vasodilator, antibacterial, etc.
3. *Tests on animal models of human disease* Such as kindled seizures in rats, spontaneously (genetically) hypertensive rats, experimental tuberculosis in mouse, alloxan induced diabetes in rat or dog, etc.
4. *Confirmatory tests and analogous activities* Compounds found active are taken up for detailed study by more elaborate tests which confirm and characterize the activity. Other related activities, e.g. antipyretic and anti-inflammatory activity in an analgesic are tested.
5. *Systemic pharmacology* Irrespective of the primary action of the drug, its effects on major organ systems such as nervous, cardiovascular, respiratory, renal, g.i.t are worked out. Mechanism of action, including additional mechanisms, e.g. α adrenergic blockade, calcium channel blockade, nitro-vasodilatation, etc. in a β adrenergic blocker antihypertensive, are elucidated.
6. *Quantitative tests* The dose-response relationship, maximal effect and comparative potency/efficacy with existing drugs is ascertained.
7. *Pharmacokinetics* The absorption, volume of distribution, metabolism, excretion, pattern of tissue distribution and plasma half-life of the drug are quantified.
8. *Toxicity tests* The aim is to determine safety of the compound in at least 2 animal species, one rodent and one nonrodent, e.g. mouse/rat and dog by oral and parenteral routes.

Acute toxicity: Single escalating doses are given to small groups of animals that are observed for overt effects and mortality for 1–3 days. The dose which kills 50% animals (LD_{50}) is calculated. Organ toxicity is examined by histopathology on all animals.

Subacute toxicity: Repeated doses are given for 2–12 weeks depending on the duration of intended treatment in man. Doses are selected on the basis of ED_{50} and LD_{50}. Animals are examined for overt effects, food intake, body weight, haematology, etc. and organ toxicity.

Chronic toxicity: The drug is given for 6–12 months and effects are studied as in subacute toxicity. This is generally undertaken concurrently with early clinical trials.

Reproduction and teratogenicity: Effects on spermatogenesis, ovulation, fertility and developing foetus are studied.

Mutagenicity: Ability of the drug to induce genetic damage is assessed in bacteria (Ames test), mammalian cell cultures and in intact rodents.

Carcinogenicity: Drug is given for long-term, even the whole life of the animal and they are watched for development of tumours.

Standardised procedures under *'Good Laboratory Practices'* (GLP) have been laid down for the conduct of animal experiments, especially toxicity testing.

Clinical trials

When a compound deserving trial in man is identified by animal studies, the regulatory authorities are approached who on satisfaction issue an 'investigational new drug' (IND) licence. The drug is formulated into a suitable dosage form and clinical trials are conducted in a logical phased manner. To minimize any risk, initially few subjects receive the drug under close supervision. Later, larger numbers are treated with only relevant monitoring. Standards for the design, ethics, conduct, monitoring, auditing, recording and analyzing data and reporting of clinical trials have been laid down in the form of *'Good Clinical Practice'* (GCP) guidelines by an International Conference on Harmonization (ICH). National agencies in most countries, including ICMR in India, have also framed ethical guidelines for clinical trials. Adherence to these provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected as enunciated in the *Helsinki Declaration* of the World Medical Association. The requirements and regulations for the conduct of clinical trials on a new drug in India have been laid down in the schedule Y of the Drugs and Cosmetics Rules.

The clinical studies are conventionally divided into 4 phases.

Phase I: Human pharmacology and safety

The first human administration of the drug is carried out by qualified clinical pharmacologists/trained physicians in a setting where all vital functions are monitored and emergency/resuscitative facilities are available. Subjects (mostly healthy volunteers, sometimes patients) are exposed to the drug one by one (total 20–80 subjects), starting with the lowest estimated dose (generally 1/100 to 1/10 of the highest dose producing no toxicity in animals) and increasing stepwise to achieve the effective dose. An attempt is made to determine the dose range that may be used in further studies. The emphasis is on safety, tolerability, and to detect any potentially dangerous effects on vital functions, such as precipitous fall/rise in blood pressure or heart rate, arrhythmias, bronchospasm, seizures, kidney/liver damage, etc. Unpleasant side effects are noted and an attempt is made to observe the pharmacodynamic effects in man. The human pharmacokinetic parameters of the drug are measured for the first time. No blinding is done: the study is open label.

Phase 0: Microdosing study

This is a new strategy being developed to reduce the cost and time of the drug development process. The rate of rejection of candidate drugs at various stages of clinical development has progressively increased recently, discouraging pharmaceutical companies to venture into the risky business of new drug invention. This has alarmed the FDA (USA) and the European Medicines Agency to encourage novel cost-cutting approaches in drug development. One such tool is the *microdosing* human study undertaken before phase-1 trial, and is also called *phase '0' study.*

Many candidate drugs fail during clinical trials due to sub-optimal human pharmacokinetics. Very low doses, generally about 1/100th of the estimated human dose, or a maximum of 100 µg total dose of candidate drug, are administered to healthy volunteers and pharmacokinetics is worked out using highly sophisticated instrumentation, such as Accelerator mass spectrometry (AMS) with radiolabelled drug, or LC-Tandem mass spectrometry (LC-MS-MS) to measure ultra low drug levels. These subpharmacological doses are not expected to produce any therapeutic or toxic effects, but yield human pharmacokinetic information. These studies may obviate the need for animal pharmacokinetic studies and can be undertaken before extensive animal toxicity tests. Thus, elaborate animal studies and costly phase 1 human trials could be avoided for candidate drugs which would have later failed due to unsuitable human pharmacokinetics. Moreover, the pharmacokinetic 0 phase data could be useful in more precise selection of doses for phase 1 study.

The major objection against phase '0' study is that the microdose pharmacokinetics may be quite different from that at pharmacological doses, since body may handle such divergent doses in different ways. The phase 0 studies have not yet been technically fully developed or adequately evaluated. They are neither established nor mandatory. However, they are promising, and most regulatory authorities are willing to allow and consider them.

Phase II: Therapeutic exploration and dose ranging

This is conducted by physicians who are trained as clinical investigators, and involve 100–500 patients selected according to specific inclusion and exclusion criteria. The primary aim is establishment of therapeutic efficacy, dose range and ceiling effect in a controlled setting. Tolerability and pharmacokinetics are studied as extension of phase I. The study is mostly controlled and randomized, and may be blinded or open label. It is generally carried out at 2–4 centres. The candidate drug may get dropped at this stage if the desired level of clinical efficacy is not obtained.

Phase III: Therapeutic confirmation/ comparison

Generally these are randomized double blind comparative trials conducted on a larger patient population (500–3000) by several physicians (usually specialists in treating the target disease) at many centres. The aim is to establish the value of the drug in relation to existing therapy. Safety and tolerability are assessed on a wider scale, while pharmacokinetic studies may be conducted on some of the participants to enlarge the population base of pharmacokinetic data. Indications are finalized and guidelines for therapeutic use are formulated. A 'new drug application' (NDA) is submitted to the licencing authority (like FDA), who if convinced give marketing permission. Restricted marketing permission for use only in hospitals with specific monitoring facilities, or only by specially trained physicians may be granted in case of toxic drugs which are found useful in serious or otherwise incurable diseases.

Phase IV: Postmarketing surveillance/data gathering studies

After the drug has been marketed for general use, practicing physicians are identified through whom data are collected on a structured proforma about the efficacy, acceptability and adverse effects of the drug in the real field situation (similar to prescription event monitoring). Patients treated in the normal course form the study population: numbers therefore are much larger. Uncommon/idiosyncratic adverse effects, or those that occur only after long-term use and unsuspected drug interactions are detected at this stage. Patterns of drug utilization and additional indications may emerge from the surveillance data.

Further therapeutic trials involving special groups like children, elderly, pregnant/lactating women, patients with renal/hepatic disease, etc. (which are generally excluded during clinical trials) may be undertaken at this stage. Modified release dosage forms, additional routes of administration, fixed dose drug combinations, etc. may be explored.

As such, most drugs continue their development even after marketing.

☞PROBLEM DIRECTED STUDY

5.1 A 65-year-old male hepatic cirrhosis patient was admitted to the hospital for treatment of gross ascites. He was administered inj. furosemide 40 mg i.m. three times a day to excrete the ascitic fluid. He responded with brisk diuresis, but on the 3rd day he was found to be talking irrelevant, was weak and partly disoriented. He had a fainting episode on getting up from the bed. His serum K^+ was 2.8 mEq/L (low) and blood pH was 7.6 (raised).

(a) What is the likely cause of his condition on the 3rd day?

(b) What should be the principles of management of this complication?

(see Appendix-1 for solution)

Chapter 6 Adverse Drug Effects

Adverse effect is 'any undesirable or unintended consequence of drug administration'. It is a broad term, includes all kinds of noxious effect—trivial, serious or even fatal.

For the purposes of detecting and quantifying only those adverse effects of a drug which are of some import and occur in ordinary therapeutic setting, the term *adverse drug reaction* (ADR) has been defined as 'any noxious change which is suspected to be due to a drug, occurs at doses normally used in man, requires treatment or decrease in dose or indicates caution in the future use of the same drug'. This definition excludes trivial or expected side effects and poisonings or overdose.

Another term *'adverse drug event'* (ADE) has been used to mean 'any untoward medical occurrence that may present during treatment with a medicine, but which does not necessarily have a causal relationship with the treatment'. The idea is to record all adverse events first, and look for causality only while analyzing pooled data.

All drugs are capable of producing adverse effects, and whenever a drug is given a risk is taken. The magnitude of risk has to be considered along with the magnitude of expected therapeutic benefit in deciding whether to use or not to use a particular drug in a given patient, e.g. even risk of bone marrow depression may be justified in treating cancer, while mild drowsiness caused by an antihistaminic in treating common cold may be unacceptable.

Adverse effects may develop promptly or only after prolonged medication or even after stoppage of the drug. Adverse effects are not rare; an incidence of 10–25% has been documented in different clinical settings. They are more common with multiple drug therapy and in the elderly. Adverse effects have been classified in many ways. One may divide them into:

Predictable (Type A or Augmented) reactions (mechanism based adverse reactions) These are based on the pharmacological properties of the drug, which means that they are augmented, but qualitatively normal response to the drug; include side effects, toxic effects and consequences of drug withdrawal. They are more common, dose related and mostly preventable and reversible.

Unpredictable (Type B or Bizarre) reactions These are based on peculiarities of the patient and not on drug's known actions; include allergy and idiosyncrasy. They are less common, often non-dose related, generally more serious and require withdrawal of the drug. Some of these reactions can be predicted and prevented if their genetic basis is known and suitable test to characterize the individual's phenotype is performed.

Severity of adverse drug reactions has been graded as:

Minor: No therapy, antidote or prolongation of hospitalization is required.

Moderate: Requires change in drug therapy, specific treatment or prolongs hospital stay by at least one day.

Severe: Potentially life-threatening, causes permanent damage or requires intensive medical treatment.

Lethal: Directly or indirectly contributes to death of the patient.

Pharmacovigilance

Pharmacovigilance has been defined by the WHO (2002) as the 'science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.' The information generated by pharmacovigilance is useful in educating doctors about ADRs and in the official regulation of drug use. Its main purpose is to reduce the risk of drug-related harm to the patient. It has an important role in the rational use of medicines, as it provides the basis for assessing safety of medicines.

The activities involved in pharmacovigilance are:

a. Postmarketing surveillance and other methods of ADR monitoring such as voluntary reporting by doctors (e.g. yellow card system of UK), prescription event monitoring, computerized medical record linkage and other cohort/case control studies as well as anecdotal case reports by doctors.

   Voluntary reporting depends on the initiative and willingness of the health professionals. It is minimal in India, while even in the developed countries only ~10% ADRs are reported voluntarily. Immediately occurring reactions and those that are dramatic are mostly reported. Though even rare reactions can be detected by this method, it does not provide incidence of the reaction.

b. Dissemination of ADR data through 'drug alerts', 'medical letters', advisories sent to doctors by pharmaceuticals and regulatory agencies (such as FDA in USA, committee on safety of medicines in UK).

c. Changes in the labelling of medicines indicating restrictions in use or statuary warnings, precautions, or even withdrawal of the drug, by the regulatory decision making authority.

Pharmacovigilance centres have been set up in most countries. The Uppsala Monitoring Centre (Sweden) is the international collaborating centre. In India, the Central Drugs Standard Control Organization (CDSCO) is coordinating the pharmacovigilance programme, under which peripheral, regional and zonal monitoring centres have been set up along with a National Pharmacovigilance advisory committee. The pharmacovigilance centres collect, communicate and disseminate ADR data by linking with hospitals as well as practitioners and are also expected to provide expertise for assessing causality and severity of ADRs by using standard algorithms and rating scales like the 'Naranjo algorithm' (causalilty assessment) and modified Hartwig scale (severity grading).

Causality assessment

When a patient undergoing drug therapy experiences an adverse event, it may be due to the drug, or the disease or some other causes. Most of the time, a clear-cut 'yes/no' cause and effect relationship between a drug and the adverse event cannot be pronounced. Causality is assessed on the basis of:

- *Temporal relationship:* How the time-sequence of the event is related to drug administration.
- *Previous knowledge:* Whether the drug is known to produce the event in earlier recipients with a certain degree of consistency.
- *Dechallenge:* Whether the event subsided on stopping the drug.
- *Rechallenge:* Whether the event reappeared when the drug was administered again after a gap during which the event had subsided. Many times rechallenge is unethical/dangerous, and is not done.

Assessed on the basis of the above criteria, causality has been graded as:

1. *Definite:* Causality is proven.
2. *Probable:* Though not proven, drug is the likely cause of the event.
3. *Possible:* Drug as well as other causes could be responsible for the event.
4. *Doubtful:* Drug unlikely to be the cause, but cannot be ruled out.

Prevention of adverse effects to drugs

Adverse drug effects can be minimized but not altogether eliminated by observing the following practices:

1. Avoid all inappropriate use of drugs in the context of patient's clinical condition.
2. Use appropriate dose, route and frequency of drug administration based on patient's specific variables.
3. Elicit and take into consideration previous history of drug reactions.

4. Elicit history of allergic diseases and exercise caution (drug allergy is more common in patients with allergic diseases).
5. Rule out possibility of drug interactions when more than one drug is prescribed.
6. Adopt correct drug administration technique (e.g. intravenous injection of vancomycin must be slow).
7. Carry out appropriate laboratory monitoring (e.g. prothrombin time with warfarin, serum drug levels with lithium).

Adverse drug effects may be categorized into:

1. Side effects

These are unwanted but often unavoidable pharmacodynamic effects that occur at therapeutic doses. Generally, they are not serious but may occasionally be hazardous, e.g. postural hypotension caused by prazosin as a side effect may result in fall and fracture neck femur in an elderly patient. Side effects can be predicted from the pharmacological profile of a drug and are known to occur in a given percentage of drug recipients. Reduction in dose, usually ameliorates the symptoms.

A side effect may be based on the same action as the therapeutic effect, e.g. atropine is used in preanaesthetic medication for its antisecretory action. The same action produces dryness of mouth as a side effect. Glyceryl trinitrate relieves angina pectoris by dilating peripheral vasculature which is also responsible for postural hypotension and throbbing headache.

The side effect may also be based on a different facet of action, e.g. promethazine produces sedation which is unrelated to its antiallergic action; estrogens cause nausea which is unrelated to their antiovulatory action.

An effect may be therapeutic in one context but side effect in another context, e.g. codeine used for cough produces constipation as a side effect, but the latter is its therapeutic effect in traveller's diarrhoea; depression of A-V conduction is the desired effect of digoxin in atrial fibrillation, but the same may be undesirable when it is used for CHF.

Many drugs have been developed from observation of side effects, e.g. early sulfonamides used as antibacterial were found to produce hypoglycaemia and acidosis as side effects which directed research resulting in the development of hypoglycaemic sulfonylureas and the carbonic anhydrase inhibitor—acetazolamide.

2. Secondary effects

These are indirect consequences of a primary action of the drug, e.g. suppression of bacterial flora by tetracyclines paves the way for superinfections; corticosteroids weaken host defence mechanisms so that latent tuberculosis gets activated.

3. Toxic effects

These are the result of excessive pharmacological action of the drug due to overdosage or prolonged use. Overdosage may be absolute (accidental, homicidal, suicidal) or relative (i.e. usual dose of gentamicin in presence of renal failure). The manifestations are predictable and dose related. They result from functional alteration (high dose of atropine causing delirium) or drug induced tissue damage (hepatic necrosis from paracetamol overdosage). The CNS, CVS, kidney, liver, lung, skin and blood forming organs are most commonly involved in drug toxicity.

Toxicity may result from extension of the therapeutic effect itself, e.g. coma by barbiturates, complete A-V block by digoxin, bleeding due to heparin.

Another action of the drug can also be responsible for toxicity, e.g.—

- Morphine (analgesic) causes respiratory failure in overdosage.
- Imipramine (antidepressant) overdose causes cardiac arrhythmia.
- Streptomycin (antitubercular) causes vestibular damage on prolonged use.

Poisoning In a broad sense, poisoning implies harmful effects of a chemical on a biological system. It may result from large doses of drugs because 'it is the dose which distinguishes a

drug from a poison'. *Poison* is a 'substance which endangers life by severely affecting one or more vital functions'. Poisons derived from biologic sources are also referred to as '*toxins*'. Not only drugs, but other household, environmental and industrial chemicals, insecticides, etc. are frequently involved in poisonings. Specific antidotes such as receptor antagonists, chelating agents or specific antibodies are available only for few poisons. General supportive and symptomatic treatment, as the need arises, is all that can be done for others, and this is also important for poisons which have a selective antagonist.

The general detoxification and supportive measures are:

1. *Resuscitation and maintenance of vital functions*

a. Ensure patent airway, adequate ventilation, give artificial respiration/100% oxygen inhalation as needed. This is important because severe poisoning often makes the patient comatose; protective airway reflexes and respiratory drive are lost.
b. Maintain blood pressure and heart beat by fluid and crystalloid infusion, pressor agents, cardiac stimulants, pacing, defibrillation, etc, as needed. Hypotension, often prolonged, is common in severe poisonings.
c. Prevent and manage seizures (with i.v. lorazepam).
d. Maintain body temperature.
e. Maintain blood sugar level by dextrose infusion, especially in patients with altered sensorium.

2. *Termination of exposure (decontamination)* Decontamination procedures should be started concurrently with the above supportive measures. It is done by removing the patient to fresh air (for inhaled poisons), removing contaminated clothing and washing the skin and eyes (for poisons entering from the surface), induction of emesis with syrup ipecac or gastric lavage (for ingested poisons). Emesis should not be attempted in comatose or haemodynamically unstable patient, as well as for kerosene poisoning due to risk of aspiration into lungs. These procedures are also contraindicated in corrosive and CNS stimulant poisoning. Emesis/gastric lavage is not recommended if the patient presents > 2 hours after ingesting the poison; if the poison/its dose ingested are known to be non-life-threatening, or if the patient has vomited after consuming the poison. Thus, induction of vomiting or gastric lavage is useful only in very few cases of poisoning.

3. *Prevention of absorption of ingested poisons* A suspension of 20–40 g (or 1g/ kg body weight) of activated charcoal, which has large surface area and can adsorb many chemicals, should be administered in 200 ml of water. However, strong acids and alkalies, metallic salts, iodine, cyanide, caustics, alcohol, hydrocarbons and other organic solvents are not adsorbed by charcoal. Charcoal should not be administered if there is paralytic ileus or intestinal obstruction or when the patient reports > 2 hours after ingesting the poison.

4. *Hastening elimination* of the poison by inducing diuresis (furosemide, mannitol) or altering urinary pH (alkalinization for acidic drugs, e.g. barbiturates, aspirin). However, excretion of many poisons, especially those which are eliminated mainly by hepatic metabolism, is not enhanced by forced diuresis and risk of fluid overload/electrolyte imbalance outweighs the benefit. This procedure is generally not employed now. Haemodialysis is more efficacious in hastening elimination of many drugs, including phenobarbitone, carbamazepine, valproate, lithium, salicylate, theophylline, etc.

4. Intolerance

It is the appearance of characteristic toxic effects of a drug in an individual at therapeutic doses. It is the converse of tolerance and indicates a low threshold of the individual to the action of a drug. Such subjects are individuals who fall on the extreme left side of the Gaussian

frequency distribution curve for sensitivity to the drug. Examples are:

- A single dose of triflupromazine induces muscular dystonias in some individuals, specially children.
- Only few doses of carbamazepine may cause ataxia in some people.
- One tablet of chloroquine may cause vomiting and abdominal pain in an occasional patient.

5. Idiosyncrasy

Idiosyncrasy refers to genetically determined abnormal reactivity to a chemical. The drug interacts with some unique feature of the individual, not found in majority of subjects, and produces the uncharacteristic reaction. As such, the type of reaction is restricted to individuals with a particular genotype (*see* p. 76). In addition, certain bizarre drug effects due to peculiarities of an individual (for which no definite genotype has been described) are included among idiosyncratic reactions, e.g.:

- Barbiturates cause excitement and mental confusion in some individuals.
- Quinine/quinidine cause cramps, diarrhoea, purpura, asthma, angioedema of face and hypotension in some patients.
- Chloramphenicol produces nondose-related serious aplastic anaemia in rare individuals.

6. Drug allergy (hypersensitivity)

It is an immunologically mediated reaction producing stereotype symptoms which are unrelated to the pharmacodynamic profile of the drug. The symptoms may appear even with much smaller doses and have a different time course of onset and duration. This is also called *drug hypersensitivity*; but does not refer to increased response which is called supersensitivity. The target organs primarily affected in drug allergy are skin, airways, blood vessels, blood cells and gastrointestinal tract.

Allergic reactions occur only in a small proportion of the population exposed to the drug and cannot be produced in other individuals at any dose. Prior sensitization is needed and a latent period of at least 1–2 weeks is required after the first exposure. However, the sensitizing exposure may go unnoticed or may be environmental. The drug or its metabolite acts as an antigen (AG), or more commonly a *hapten* (incomplete antigen: drugs have small molecules which become antigenic only after binding with an endogenous protein) and induce production of antibody (AB)/sensitized lymphocytes. Presence of AB to a drug is not necessarily followed by allergy to it. Chemically related drugs often show cross sensitivity. A particular drug can produce different types of allergic reactions in different individuals, while widely different drugs can produce similar reaction. The course of drug allergy is variable; an individual previously sensitive to a drug may subsequently tolerate it without a reaction and *vice versa*.

Cardinal features of drug allergy

- Manifestations unrelated to the pharmacodynamic actions of the drug.
- Manifestations similar to food/protein allergy, allergic diseases.
- Severity of reaction poorly correlated with dose of the drug; even small dose may trigger severe reaction.
- Occur only in few recipients, cannot be produced in other individuals.
- Prior sensitization (known/unknown) is needed.
- Positive dechallenge (on withdrawal of drug) and rechallenge (even with small dose).

Mechanism and types of allergic reactions

A. Humoral

Type-I (anaphylactic) reactions Reaginic antibodies (IgE) are produced which get fixed to the mast cells and basophils. On exposure to the drug, AG: AB reaction takes place on the mast cell surface (*see* Fig. 11.2) releasing mediators like histamine, 5-HT, leukotrienes (especially LT-C4 and D4), prostaglandins, PAF, etc. resulting in urticaria, itching, angioedema, bronchospasm, rhinitis or anaphylactic shock. Anaphylaxis is usually heralded by paresthesia, flushing, swelling of lips, generalized itching,

wheezing, palpitation followed by syncope. The manifestations occur quickly (within minutes to few hours) after challenge and are called *immediate hypersensitivity*. Antihistaminic drugs are beneficial in some of these reactions.

Type-II (cytolytic) reactions Drug + component of a specific tissue cell act as AG. The resulting antibodies (IgG, IgM) bind to the target cells; on reexposure AG: AB reaction takes place on the surface of these cells, complement is activated and cytolysis occurs resulting in one or more of thrombocytopenia, agranulocytosis, aplastic anaemia, haemolysis, organ damage (liver, kidney, muscle), systemic lupus erythematosus.

Type-III (retarded, Arthus) reactions These are mediated by circulating antibodies (predominantly IgG, mopping AB). AG: AB complexes bind complement and precipitate on vascular endothelium and basement membrane in tissues, release chemotactic mediators and lytic enzymes giving rise to a destructive inflammatory response. Manifestations are rashes, serum sickness (fever, arthralgia, lymphadenopathy), polyarteritis nodosa, Stevens-Johnson syndrome (erythema multiforme, arthritis, nephritis, myocarditis, mental symptoms). The reaction develops in 3–4 days after exposure, and usually subsides in 1–2 weeks.

B. Cell mediated

Type-IV (delayed hypersensitivity) reactions These are mediated through production of sensitized T-lymphocytes carrying receptors for the AG. On contact with the AG these T cells produce *lymphokines* which attract granulocytes and generate an inflammatory response, causing contact dermatitis, certain types of rashes, fever, photosensitization. The reaction generally takes 2–3 days to develop.

Treatment of drug allergy

The offending drug must be immediately stopped. Most mild reactions (like skin rashes) subside by themselves and donot require specific treatment. Antihistamines (H_1) are beneficial in some type I reactions (itching, urticaria, rhinitis, swelling of lips, etc.) and some skin rashes (*see* p. 182). In case of anaphylactic shock or angioedema of larynx the resuscitation council of UK has recommended the following measures:

- Put the patient in reclining position, administer oxygen at high flow rate and perform cardiopulmonary resuscitation if required.
- Inject adrenaline 0.5 mg (0.5 ml of 1 in 1000 solution for adult, 0.3 ml for child 6-12 years and 0.15 ml for child upto 6 years) i.m.; repeat every 5–10 min in case patient does not improve or improvement is transient. This is the only life saving measure. Adrenaline should not be injected i.v. (can itself be fatal) unless shock is immediately life threatening. If adrenaline is to be injected i.v., it should be diluted to 1:10,000 or 1:100,000 and infused slowly with constant monitoring.
- Administer a H_1 antihistaminic (pheniramine 20–40 mg or chlorpheniramine 10–20 mg) i.m./slow i.v. It may have adjuvant value.
- Intravenous glucocorticoid (hydrocortisone sod. succinate 200 mg) should be added in severe/recurrent cases. It acts slowly, but is specially valuable for prolonged reactions and in asthmatics. It may be followed by oral prednisolone for 3 days.

Adrenaline followed by a short course of glucocorticoids is indicated for bronchospasm attending drug hypersensitivity. Glucocorticoids are the only drug effective in type II, type III and type IV reactions.

Drugs frequently causing allergic reactions

Penicillins	Aspirin
Cephalosporins	Indomethacin
Sulfonamides	Carbamazepine
Tetracyclines	Allopurinol
Quinolones	ACE inhibitors
Metronidazole	Methyldopa
Abacavir	Hydralazine
Antitubercular drugs	Local anaesthetics
Phenothiazines	

Skin tests (intradermal, patch) or intranasal tests may forewarn in case of Type I hypersensitivity, but not in case of other types. However, these tests are not entirely reliable—false positive and false negative results are not rare.

7. Photosensitivity

It is a cutaneous reaction resulting from drug induced sensitization of the skin to UV radiation. The reactions are of two types:

(a) Phototoxic Drug or its metabolite accumulates in the skin, absorbs light and undergoes a photochemical reaction followed by a photobiological reaction resulting in local tissue damage (sunburn-like), i.e. erythema, edema, vesicular eruption, blistering which have fast onset and shorter duration after exposure ends. This is followed by hyperpigmentation and desquamation. The lesions may be more severe with larger doses of the drug. The shorter wave lengths (290–320 nm, UV-B) are responsible. Drugs involved in acute phototoxic reactions are tetracyclines (especially demeclocycline) and tar products. Drugs causing chronic and low grade sensitization are nalidixic acid, fluoroquinolones, dapsone, sulfonamides, phenothiazines, thiazides, amiodarone. This type of reaction is more common than photoallergic reaction.

(b) Photoallergic Drug or its metabolite induces a cell mediated immune response which on exposure to light of longer wave lengths (320–400 nm, UV-A) produces a papular or eczematous contact dermatitis like picture that may persist long after exposure. Occasionally, antibodies may also mediate photoallergy and the reaction takes the form of immediate flare, itching and wheal on exposure to sun. Even small doses may trigger the reaction and lesions may extend beyond the exposed area. Drugs involved are sulfonamides, sulfonylureas, griseofulvin, chloroquine, chlorpromazine, carbamazepine.

Photosensitivity reactions can be prevented or minimized by avoidance of exposure to sun and effective use of topical sun screens (SPF 15–60; *see* Ch. 66). Local treatment of acute sun burn and blistering consists of soothing lotions (e.g. calamine lotion), wet dressings and mild topical steroids. Strong topical steroids are needed for photoallergy; severe cases may require systemic steroid therapy.

8. Drug dependence and drug addiction

Drugs capable of altering mood and feelings are liable to repetitive use to derive euphoria, recreation, withdrawal from reality, social adjustment, etc. Some subjects who take the drug repeatedly for personal gratification, progress in indulgence with the drug and start according higher priority to taking the drug than to other basic needs, often in the face of known risks to health. Many of these drugs also induce adaptive physiological changes which result in escalation of the dose needed to produce the same effect. Thus, '*tolerance*' develops and physiological equilibrium is disturbed when the drug is not present. Confusing terminology, *viz* 'dependence', 'physical dependence', 'psychological dependence', 'addiction', 'habituation', 'drug abuse' has been used over the past to describe the above phenomena. The terms as understood and applied currently are briefly explained below.

Drug dependence It is an altered physiological state produced by repeated administration of a drug which necessitates the continued presence of the drug to maintain physiological equilibrium. Discontinuation of the drug results in a characteristic *withdrawal (abstinence) syndrome*. This has been earlier termed '*physical dependence*', but is now simply called 'dependence'. Since the essence of the process is adaptation of the nervous system to function normally in the presence of the drug, it has been also called '*neuroadaptation*'.

Drugs producing dependence are—opioids, barbiturates and other depressants including alcohol and benzodiazepines. Stimulant drugs, e.g. amphetamines, cocaine produce minimal or no dependence.

Drug addiction A person is said to have developed 'drug addiction' when he/she

believes that optimal state of well being is achieved only through the actions of the drug. The subject feels emotionally distressed if the drug is not taken. It often starts as liking for the drug effects and progresses to compulsive drug use in some individuals who lose control and cannot stop taking the drug, even if they known it to be harmful. This was earlier termed '*psychological dependence*'. However, to avoid confusion, the widely understood term '*drug addiction*' is used now.

Drug addiction is a pattern of compulsive drug use characterized by overwhelming involvement with the use of a drug. Procuring the drug and using it takes precedence over other activities. Even after withdrawal most addicts tend to relapse. Dependence, though a strong impetus for continued drug use, is not an essential feature of addiction. Amphetamines, cocaine, cannabis, LSD are drugs which produce addiction but little/no dependence. Moreover, drugs like nalorphine produce dependence without imparting addiction in the sense that there is little drug seeking behaviour.

Reinforcement It is the ability of the drug to produce effects that the user enjoys and which make him/her wish to take it again or to induce *drug seeking behaviour*. Certain drugs (opioids, cocaine) are strong reinforcers, while others (benzodiazepines) are weak reinforcers. Faster the drug acts, more reinforcing it is. Thus, inhaled drugs and those injected i.v. are highly reinforcing–produce an intense 'high' in dependent individuals.

Drug habituation This term has been used to denote less intensive involvement with the drug, so that its withdrawal produces only mild discomfort. Dependence is absent. Consumption of tea, coffee, tobacco, social drinking are regarded habituating but not addicting. Thus, the difference between addiction and habituation is only quantitative. It is difficult to delineate when 'desire' turns into 'craving'. As such, it is better to avoid using the term 'habituation' as a distinct phenomenon.

Drug abuse This is another frequently used term which refers to use of a drug by self medication in a manner and amount that deviates from the approved medical and social patterns in a given culture at a given time. The term conveys social disapproval of the manner and purpose of drug use. For regulatory agencies, *drug abuse* refers to any use of an ilicit drug.

The two major patterns of drug abuse are:

a. *Continuous use:* The drug is taken regularly, the subject wishes to continuously remain under the influence of the drug, e.g. opioids, alcohol, sedatives.
b. *Occasional use:* The drug is taken off-and-on to obtain pleasure or high, recreation (as in rave parties) or enhancement of sexual experience, e.g. cocaine, amphetamines, psychedelics, binge drinking (a pattern of excessive alcohol drinking), cannabis, solvents (inhalation), etc.

9. Drug withdrawal reactions

Apart from drugs that are usually recognised as producing dependence, sudden interruption of therapy with certain other drugs also results in adverse consequences, mostly in the form of worsening of the clinical condition for which the drug was being used, e.g.:

- Acute adrenal insufficiency may be precipitated by abrupt cessation of corticosteroid therapy.
- Severe hypertension, restlessness and sympathetic overactivity may occur shortly after discontinuing clonidine.
- Worsening of angina pectoris, precipitation of myocardial infarction may result from stoppage of β blockers.
- Frequency of seizures may increase on sudden withdrawal of an antiepileptic.

These manifestations are also due to adaptive changes, and can be minimized by gradual withdrawal.

10. Teratogenicity

It refers to the capacity of a drug to cause foetal abnormalities when administered to the pregnant mother. The placenta does not constitute a strict barrier, and any drug can cross it to a greater or lesser extent. The embryo is one of the most

Human teratogenic drugs

Drug	*Abnormality*
Thalidomide	phocomelia, multiple defects of internal organs
Anticancer drugs (methotrexate)	cleft palate, hydrocephalus, multiple defects, foetal death
Androgens	virilization; limb, esophageal, cardiac defects
Progestins	virilization of female foetus
Stilboestrol	vaginal carcinoma in teenage female offspring
Tetracyclines	discoloured and deformed teeth, retarded bone growth
Warfarin	depressed nose; eye and hand defects, growth retardation
Phenytoin	hypoplastic phalanges, cleft lip/palate, microcephaly
Phenobarbitone	various malformations
Carbamazepine	neural tube defects, assorted abnormalities
Valproate sod.	spina bifida and other neural tube defects, heart and limb abnormalities
Alcohol	low IQ baby, growth retardation, foetal alcohol syndrome
ACE inhibitors	hypoplasia of organs, growth retardation, foetal loss
Lithium	foetal goiter, cardiac and other abnormalities
Antithyroid drugs	foetal goiter and hypothyroidism
Indomethacin/aspirin	premature closure of ductus arteriosus
Isotretinoin	craniofacial, heart and CNS defects, hydrocephalus

dynamic biological systems and in contrast to adults, drug effects are often irreversible. The thalidomide disaster (1958–61) resulting in thousands of babies born with *phocomelia* (seal like limbs) and other defects focused attention onto this type of adverse effect.

In 1959 and subsequent couple of years, the incidence of a rare birth defect *phocomelia* (hands and feet arising almost directly from shoulders and pelvis, similar to flippers of a seal) shot up sharply in Europe. Other birth defects also increased considerably. Soon it was noticed that all mothers with malformed babies had taken a new sedative—anti-morning sickness drug *thalidomide* (which was marketed in 1957) during early pregnancy. Epidemiological studies confirmed that intake of thalidomide in the first trimester of pregnancy was responsible for the birth defects, and the drug was immediately banned worldwide. It has now been marketed again for restricted use as adjuvant in cancer chemotherapy.

Drugs can affect the foetus at 3 stages—

(i) *Fertilization and implantation*—conception to 17 days—failure of pregnancy which often goes unnoticed.

(ii) *Organogenesis*—18 to 55 days of gestation—most vulnerable period, deformities are produced.

(iii) *Growth and development*—56 days onwards — developmental and functional abnormalities can occur, e.g. ACE inhibitors can cause hypoplasia of organs, especially of lungs and kidneys; NSAIDs may induce premature closure of ductus arteriosus; androgens and progestins cause masculanization of female foetus, antithyroid drugs and lithium cause foetal goiter.

The type of malformation depends on the drug as well as the stage at which exposure to the teratogen occurred. Foetal exposure depends on the blood level and duration for which the drug remains in maternal circulation. The teratogenic potential of a drug is to be considered against the background of congenital abnormalities occurring spontaneously, which is ~ 2% of all pregnancies. Majority of implicated drugs are low grade teratogens, i.e. increase the incidence of malformations only slightly, which may be very difficult to detect, confirm or refute. Nevertheless, some drugs have been clearly associated with causing foetal abnormalities in human beings.

These are listed in the box on p.100. However, only few mothers out of all those who receive these drugs during the vulnerable period will get a deformed baby, but the exact risk posed by a drug is difficult to estimate.

The US-FDA has graded the documentation of risk for causing birth defects into five categories *viz.* A, B, C, D and X, indicating a range from A (safe) to X (contraindicated). Because evidence on teratogenic potential of drugs keeps accumulating, the FDA grading has become out-dated in many cases, and its utility is being questioned. The FDA is likely to change this grading system soon.

It is, therefore, wise to avoid all drugs during pregnancy, unless compelling reasons exist for their use, regardless of the assigned pregnancy category, or presumed safety (also *see* Appendix-2).

Frequency of spontaneous as well as drug induced malformations, especially neural tube defects, may be reduced by folate therapy during pregnancy.

11. Mutagenicity and Carcinogenicity

It refers to capacity of a drug to cause genetic defects and cancer respectively. Usually oxidation of the drug results in the production of reactive intermediates which affect genes and may cause structural changes in the chromosomes. Covalent interaction with DNA can modify it to induce mutations, which may manifest as heritable defects in the next generation. If the modified DNA sequences code for factors that regulate cell proliferation/growth, i.e. are protooncogenes, or for proteins that inhibit transcription of protooncogenes, a tumour (cancer) may be produced. Even without interacting directly with DNA, certain chemicals can promote malignant change in genetically damaged cells, resulting in carcinogenesis. Chemical carcinogenesis generally takes several (10–40) years to develop. Drugs implicated in these adverse effects are—anticancer drugs, radioisotopes, estrogens, tobacco. Generally, drugs which show mutagenic or carcinogenic potential are not approved for marketing/are withdrawn, unless they are useful in life-threatening conditions.

12. Drug induced diseases

These are also called *iatrogenic* (physician induced) diseases, and are functional disturbances (disease) caused by drugs which persist even after the offending drug has been withdrawn and largely eliminated, e.g.:

Peptic ulcer by NSAIDs and corticosteroids.
Parkinsonism by phenothiazines and other antipsychotics.
Hepatitis by isoniazid.
DLE by hydralazine.

☞ PROBLEM DIRECTED STUDY

6.1 A 40-year-man weighing 60 kg suffering from chronic cough with expectoration and fever was diagnosed to have cavitary pulmonary tuberculosis. He was put on the standard 1st line antitubercular regimen consisting of isoniazid (H) + rifampin (R) + pyrazinamide (Z) + ethambutol (E). His condition improved, but in the 4th week he developed jaundice with enlarged tender liver and rise in serum bilirubin as well as serum transaminase levels. He was suspected to have developed antitubercular drug induced hepatitis.

(a) Should his antitubercular treatment be stopped or continued?

(b) How would you proceed to confirm and identify the causative drug, and then select the alternative regimen?

(see Appendix-1 for solution)

SECTION 2

DRUGS ACTING ON AUTONOMIC NERVOUS SYSTEM

Autonomic Nervous System: General Considerations

ORGANIZATION AND FUNCTION

The autonomic nervous system (ANS) functions largely below the level of consciousness and controls visceral functions. The major differences between the somatic and autonomic nervous systems are given in Table II.1.

Like the somatic nervous system, the ANS consists of afferents, centre and efferents.

Autonomic afferents Most visceral nerves are mixed nerves and carry nonmyelinated visceral afferent fibres as well. The cell bodies of these afferent fibres are located in the dorsal root ganglion of spinal nerves and in the sensory ganglia (e.g. nodose ganglion of vagus) of cranial nerves. They mediate visceral pain as well as cardiovascular, respiratory and other visceral reflexes.

Central autonomic connections There are no exclusively autonomic areas in the CNS; considerable intermixing and integration of somatic and autonomic innervation occurs. The highest seat regulating autonomic functions is in the hypothalamus—posterior and lateral nuclei are primarily sympathetic while anterior and medial nuclei are primarily parasympathetic. Many autonomic centres (pupillary, vagal, respiratory, etc.) are located in the mid-brain and the medulla in relation to the cranial nerves. The lateral column in the thoracic spinal cord contains cells which give rise to the sympathetic outflow.

Autonomic efferents The motor limb of the ANS is anatomically divided into sympathetic and parasympathetic. Many organs receive both

Table II.1: Differences between somatic and autonomic nervous system

	Somatic	*Autonomic*
1. Organ supplied	Skeletal muscles	All other organs
2. Distal most synapse	Within CNS	Outside CNS (in ganglia)
3. Nerve fibres	Myelinated	Pregang.—myelinated Postgang.—non-myelinated
4. Peripheral plexus formation	Absent	Present
5. Primary efferent transmitter	Acetylcholine	Acetylcholine, Noradrenaline
6. Effect of nerve section on organ supplied	Paralysis and atrophy	Activity maintained, no atrophy

sympathetic and parasympathetic innervation and the two subdivisions are functionally antagonistic in majority of these. The level of activity of innervated organ at a given moment is the algebraic sum of sympathetic and parasympathetic tone. However, refractory period of atrial fibres is decreased by sympathetic as well as parasympathetic influences. Most blood vessels, spleen, sweat glands and hair follicles receive only sympathetic, while ciliary muscle, bronchial smooth muscle, gastric and pancreatic glands receive only parasympathetic innervation. Thus, the two divisions of ANS are not merely check-and-balance physiological antagonists of each other.

Enteric nervous system

The enteric nervous system (ENS) located in the gut wall consists of a submucosal (Meissner's) and a myenteric (Auerbach's) plexus along with its afferent and efferent neurons whose fibres travel anterograde, retrograde as well as in a circular manner. It receives inputs from both sympathetic and parasympathetic divisions of ANS, but in addition functions independently to integrate bowel movements as well as regulate secretion and absorption (*see* Fig. 48.2). As such, it has also been labelled as a distinct *'enteric nervous system'*.

The general layout of ANS is depicted in Fig. II.1 and the important differences between its two subdivisions are given in Table II.2.

NEUROHUMORAL TRANSMISSION

Neurohumoral transmission implies that nerves transmit their message across synapses and neuroeffector junctions by the release of humoral (chemical) messengers.

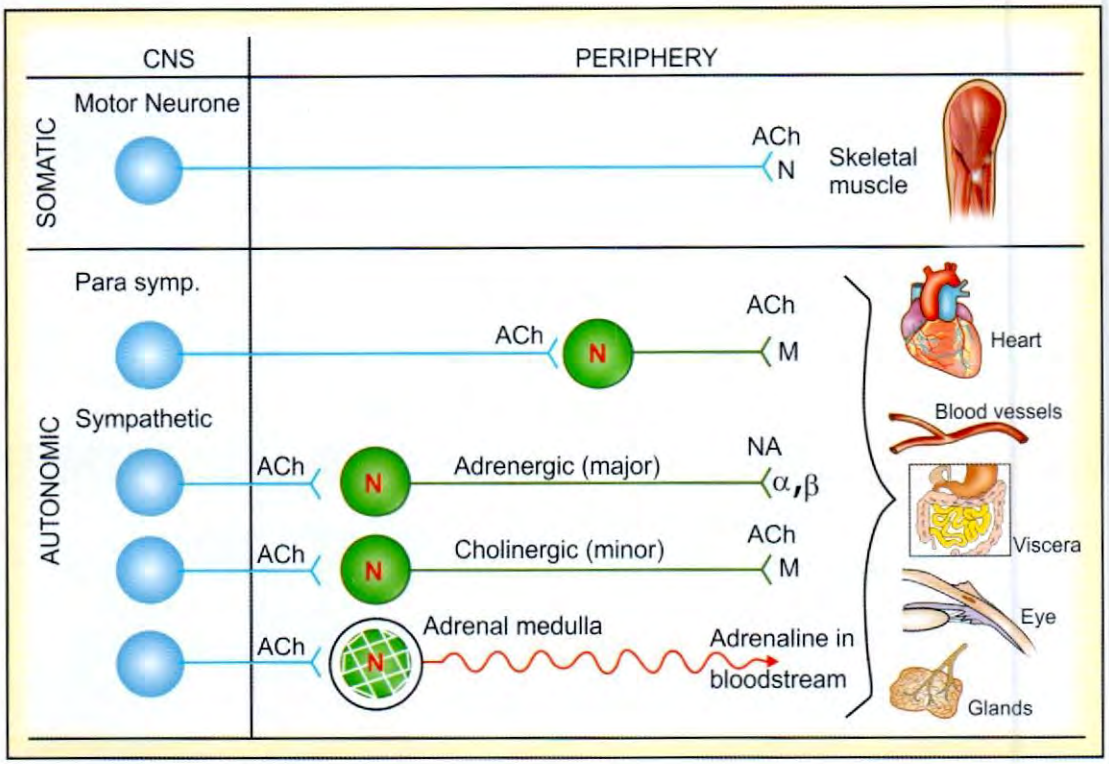


Fig. II.1: The general outlay of efferent autonomic nervous system. The transmitter released and the primary postjunctional receptor subtype is shown at each synapse/neuroeffector junction
ACh—Acetylcholine, NA—Noradrenaline, N—Nicotinic, M—Muscarinic, α—α adrenergic, β—β adrenergic

Table II.2: Differences between sympathetic and parasympathetic divisions of the autonomic nervous system

	Sympathetic	*Parasympathetic*
1. Origin	Dorso-lumbar (T_1 to L_2 or L_3)	Cranio-sacral (III, VII, IX, X; S_2–S_4)
2. Distribution	Wide	Limited to head, neck and trunk
3. Ganglia	Away from the organs supplied	On or close to the organ supplied
4. Postgang. fibre	Long	Short
5. Pre: post ganglionic fibre ratio	1: 20 to 1: 100	1: 1 to 1: 2 (except in enteric plexuses)
6. Neuroeffector transmitter	Major: NA Minor: ATP, NPY, DA, ACh	Major: ACh Minor: VIP, NO
7. Stability of transmitter	NA stable, diffuses for wider actions	ACh—rapidly destroyed locally
8. Important function	Tackling stress and emergency	Assimilation of food, conservation of energy

NA—Noradrenaline, ACh—Acetylcholine, ATP—Adenosine triphosphate, NPY—Neuropeptide Y, DA—Dopamine, VIP—Vasoactive intestinal peptide, NO—Nitric oxide

Junctional transmission was thought to be electrical (it does occur in some lower animals and probably in certain areas of mammalian brain) but observations at the turn of last century prompted Elliott (1905) to suggest that sympathetic nerves functioned by the release of an adrenaline-like substance, and Dixon (1907) to propose that vagus released a muscarine like chemical. Otto Loewi (1921) provided direct proof of humoral transmission by perfusing two frog hearts in series. Stimulation of vagus nerve of the first heart caused arrest of both. Thus, a chemical must have been released by vagal stimulation in the first heart which passed in the perfusate and arrested the second heart. This *vagusstoff* was found in 1926 to be acetylcholine, which earlier Dale (1914) had characterised as 'parasympathomimetic'. The sympathetic transmitter was eventually shown to be noradrenaline in 1946 by Von Euler. Many humoral transmitters (dopamine, 5-HT, GABA, glutamic acid, purines, peptides, etc.) are now known.

To be considered as a postjunctionally acting neurohumoral transmitter a substance must fulfill the following criteria:

(i) It should be present in the presynaptic neurone (usually along with enzymes synthesizing it).

(ii) It should be released in the medium following nerve stimulation.

(iii) Its application should produce responses identical to those produced by nerve stimulation.

(iv) Its effects should be antagonized or potentiated by other substances which similarly alter effects of nerve stimulation.

Steps in neurohumoral transmission

I. Impulse conduction The resting transmembrane potential (70 mV negative inside) is established by high K^+ permeability of axonal membrane and high axoplasmic concentration of this ion coupled with low Na^+ permeability and its active extrusion from the neurone. Stimulation or arrival of an electrical impulse causes a sudden increase in Na^+ conductance → depolarization and overshoot (reverse polarization: inside becoming 20 mV positive); K^+ ions then move out in the direction of their concentration gradient and repolarization is achieved. The ionic distribution is normalized during the refractory period by the activation of Na^+ K^+ pump. The action potential (AP) thus generated sets up local circuit currents which activate ionic channels at the next excitable part of the membrane (next node of Ranvier in myelinated fibre) and the AP is propagated without decrement.

Tetrodotoxin (from puffer fish) and saxitoxin (from certain shell-fish) selectively abolish

increase in Na^+ conductance in nerve fibres and thus block impulse conduction.

II. Transmitter release The transmitter (excitatory or inhibitory) is stored in prejunctional nerve endings within 'synaptic vesicles' (Fig. II.2). Nerve impulse promotes fusion of vesicular and axonal membranes through Ca^{2+} entry which fluidizes membranes. All contents of the vesicle (transmitter, enzymes and other proteins) are extruded by exocytosis (also *see* Fig. 2.6) in the junctional cleft.

While majority of the neurotransmitters are preformed, kept stored in synaptic vesicles and released on activation by exocytosis as outlined above, some mediators like NO, prostaglandins, endocannabinoids are synthesized on demand and reach their target by diffusion or by active transport.

The release process can be modulated by the transmitter itself and by other agents through activation of specific receptors located on the prejunctional membrane, e.g. noradrenaline (NA) release is inhibited by NA (α_2 receptor), dopamine, adenosine, prostaglandins and enkephalins while isoprenaline (β_2 receptor) and angiotensin (AT_1 receptor) increase NA release. Similarly, α_2 and muscarinic agonists inhibit acetylcholine (ACh) release at autonomic neuroeffector sites (but not in ganglia and skeletal muscles).

III. Transmitter action on postjunctional membrane The released transmitter combines with specific receptors on the postjunctional membrane and depending on its nature induces an excitatory postsynaptic potential (EPSP) or an inhibitory postsynaptic potential (IPSP).

EPSP Increase in permeability to cations → Na^+ or Ca^{2+} influx (through fast or slow channels) causes *depolarization* followed by K^+ efflux. These ionic movements are passive as the flow is down the concentration gradients.

IPSP Increase in permeability to anions, so that Cl^- ions move in (axonal Cl^- concentration is lower than its extracellular concentration) and tend to hyperpolarize the membrane → an IPSP is generated. Stabilization of the membrane or hyperpolarization can also result

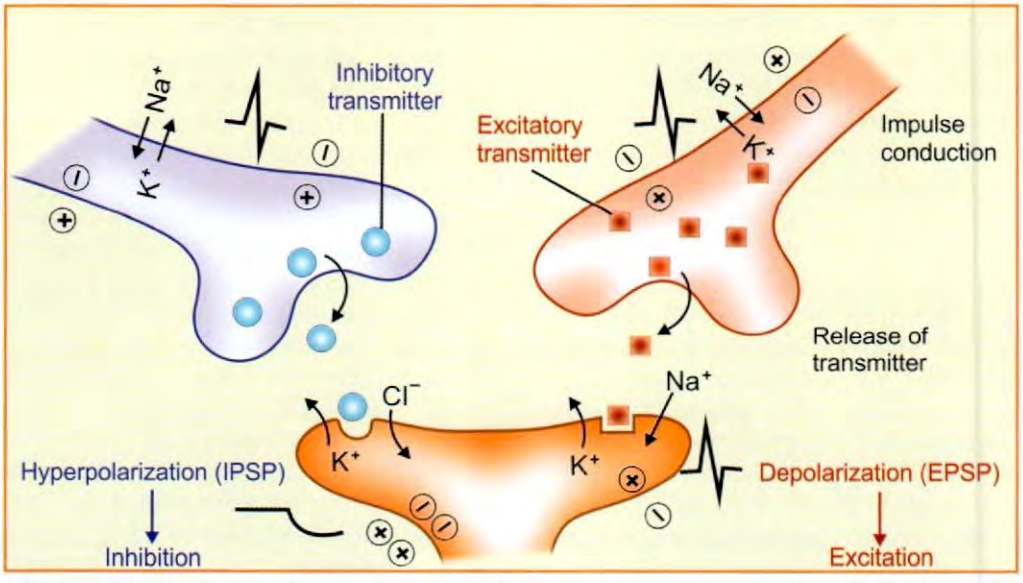


Fig. II.2: Diagrammatic representation of steps in excitatory and inhibitory neurohumoral transmission: EPSP—Excitatory postsynaptic potential; IPSP—Inhibitory postsynaptic potential

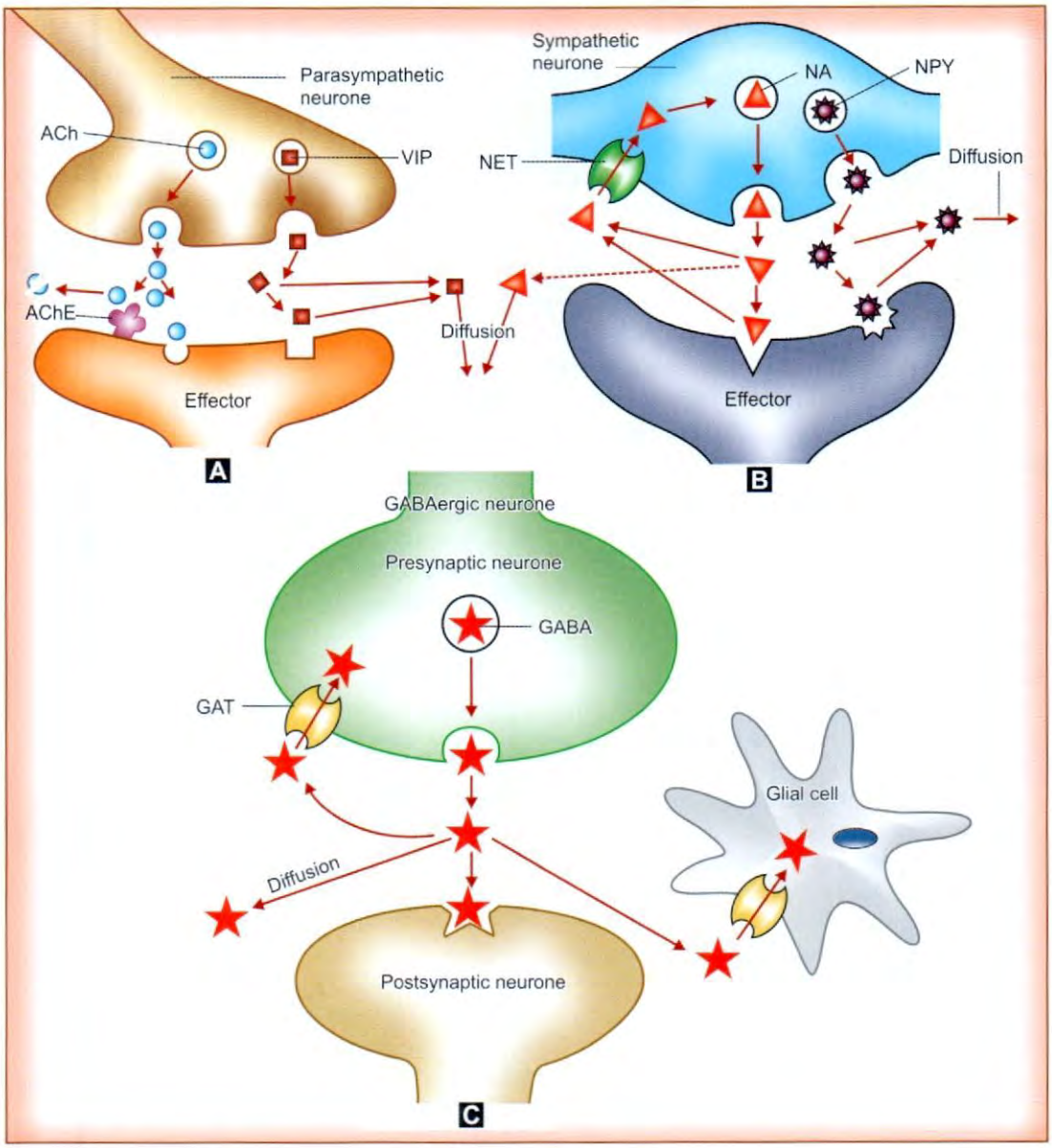


Fig. II.3: Mechanisms of termination of transmitter action

A. Parasympathetic neurone: The primary transmitter acetylcholine (ACh), which is an ester, is rapidly hydrolysed by a specific enzyme acetylcholinesterase (AChE) located strategically on the synaptic membrane. A common co-transmitter is vasoactive intestinal peptide (VIP), which on release diffuses slowly to be degraded by peptidases at distant sites. It may act on the same as well as neighbouring effectors.

B. Sympathetic neurone: The primary transmitter, an amine, noradrenaline (NA) is largely taken back into the neurone by membrane-bound norepinephrine transporter (NET) and recycled. A minor fraction diffuses away. One of the cotransmitters is neuropeptide Y (NPY), which on release meets the same fate as VIP.

C. Gabaergic neurone: The amino acid transmitter gamma-aminobutyric acid (GABA) released into the synaptic cleft is partly taken up into the neurone by GABA transporter (GAT), as well as into neighbouring glial cells. Some of it dissipates by diffusion.

from selective increase in permeability to K^+ ions, which move out carrying +ive charges.

In addition, a trophic influence on junctional morphology and functional status is exerted by the background basal release of the transmitter.

IV. Postjunctional activity A suprathreshold EPSP generates a propagated postjunctional AP which results in nerve impulse (in neurone), contraction (in muscle) or secretion (in gland). An IPSP stabilizes the postjunctional membrane and resists depolarizing stimuli.

V. Termination of transmitter action The various mechanisms of termination of transmitter action are depicted in Fig. II.3. Following its combination with the receptor, the transmitter is either locally degraded (e.g. ACh) or is mainly taken back into the prejunctional neurone by active reuptake and partly diffuses away (e.g. NA). Specific monoamine transporter proteins like norepinephrine transporter (NET), dopamine transporter (DAT), serotonin transporter (SERT) are expressed on the axonal membrane for this purpose. The rate of termination of transmitter action governs the rate at which responses can be transmitted across a junction (1 to 1000/sec).

Aminoacid transmitters (glutamate, GABA) are also partly taken up by active transport into neuronal and neighbouring glial cells, but no active reuptake of peptide neurotransmitters (VIP, NPY, enkephalins, etc.) occurs. They diffuse away and are broken down by peptidases at distant sites.

Cotransmission

It has become apparent that the classical 'one neurone—one transmitter' model is an over simplification. On stimulation, most peripheral and central neurones have been shown to release more than one active substance. In the ANS, besides the primary transmitters ACh and NA, neurones have been found to elaborate purines (ATP, adenosine), peptides (vasoactive intestinal peptide or VIP, neuropeptide-Y or NPY, substance P, enkephalins, somatostatin, etc.), nitric oxide (NO) and prostaglandins as cotransmitters. In most autonomic cholinergic neurones VIP is associated with ACh, while ATP is associated with both ACh and NA. The transmitter at some parasympathetic sites is NO, and these are called *nitrergic nerves*. Vascular adrenergic nerves contain NPY which causes long lasting vasoconstriction. The cotransmitter is stored in the same neurone but in distinct synaptic vesicles or locations (Fig. II.4). However, ATP is stored with NA in the same vesicle. On being released by nerve impulse the cotransmitter may serve to regulate the presynaptic release of the primary transmitter and/or postsynaptic sensitivity to it (neuromodulator role). The cotransmitter may also serve as an alternative transmitter in its own right and/or exert a trophic influence on the synaptic structures.

Nonadrenergic, noncholinergic (NANC) transmission has been demonstrated in the autonomic innervation of the gut, vas deferens,

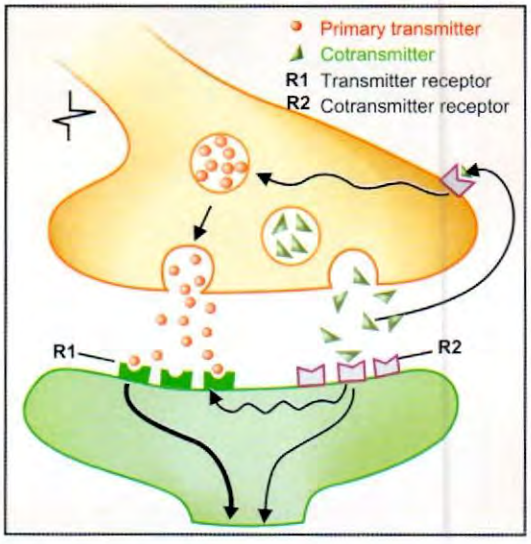


Fig. II.4: Cotransmission
The cotransmitter is stored in the prejunctional nerve terminal alongwith the primary transmitter, but in separate vesicles (in some cases in the same vesicle itself). Nerve impulse releases both the transmitters concurrently. Acting on its own receptors, the cotransmitter modifies responsiveness of the effector to the primary transmitter or substitutes for it. Cotransmitter may also act on prejunctional receptors and modulate release of the transmitters

urinary tract, salivary glands and certain blood vessels, where nerve stimulation is able to evoke limited responses even in the presence of total adrenergic and cholinergic blockade. For example, it has been shown that stimulation of sympathetic nerve to guinea pig vas deferens elicits a biphasic contractile response, the initial short-lasting phase of which is mediated by ATP (through P2 receptors) and the second longer lasting phase by NA (through α_1 receptors).

The time-course of action of the primary transmitter and the cotransmitter is usually different. The cotransmitter VIP of parasympathetic neurones produces a slow and long-lasting response, while another one (NO) has an intermediate time-course of action between VIP and ACh (fast acting). Similarly, in sympathetic neurones, the cotransmitter NPY is slower acting and ATP faster acting than NA. Moreover, cotransmitters like NO, VIP, NPY diffuse to a wider area, and can affect receptors at some distance from the site of release.

Many anomalous findings have been explained by the revelation of cotransmission.

Chapter 7 Cholinergic Transmission and Cholinergic Drugs

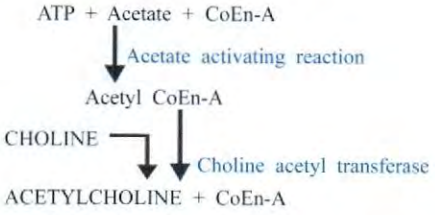
CHOLINERGIC TRANSMISSION

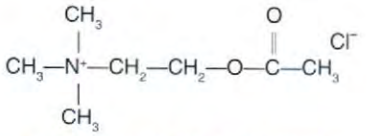
Acetylcholine (ACh) is a major neurohumoral transmitter at autonomic, somatic as well as central sites. These sites are listed in Table 7.1

Synthesis, storage and destruction of ACh

The cholinergic neuronal mechanisms are summarized in Fig. 7.1.

Acetylcholine is synthesized locally in the cholinergic nerve endings by the following pathway—





ACETYLCHOLINE CHLORIDE

Choline is actively taken up by the axonal membrane by a Na^+: choline cotransporter (Na^+ChT) and acetylated with the help of ATP and coenzyme-A by the enzyme *choline acetyl transferase* (ChAT) present in the axoplasm. *Hemicholinium* (HC3) blocks choline uptake (the rate limiting step in ACh synthesis) and depletes ACh. Most of the ACh is stored within small clear synaptic vesicles which align mainly near the synaptic membrane. Active transport of ACh into synaptic vesicles is effected by a vesicle associated transporter (VAT), which is blocked by *vesamicol*. The cholinergic axon also contains some large dense-core vesicles located relatively away from the synaptic membrane. These vesicles contain peptide cotransmitters, such as VIP.

Release of ACh from nerve terminals occurs in small quanta. The amount contained in individual vesicles is extruded in pulses by exocytosis. In response to a nerve AP synchronous release of multiple quanta triggers postjunctional events.

Two toxins interfere with cholinergic transmission by affecting release: *botulinum toxin* inhibits release, while *black widow spider toxin* induces massive release and depletion.

Botulinum toxin

Botulinum toxin A and B are highly potent exotoxins produced by *Clostridium botulinum* that are responsible for 'botulism' (a type of food poisoning). These neurotoxic proteins cause long-lasting loss of cholinergic transmission by interacting with axonal proteins involved in exocytotic release of ACh. Localized injection of minute quantity of botulinum toxin A (BOTOX) or its haemagglutinin complex (DYSPORT) can be used in the treatment of a number of spastic and other neurological conditions like blepharospasm, spastic cerebral palsy, strabismus, spasmodic torticollis, nystagmus, hemifacial spasm, post stroke spasticity, spasmodic dysphonia, axillary hyperhydrosis, etc. which are due to overactivity of cholinergic nerves. It is being employed popularly as beauty treatment for removal of age-related facial wrinkles. However, incorrect injection or overdose can be dangerous; ptosis, diplopia, facial swelling, dry mouth,

Table 7.1: Sites of cholinergic transmission and type of receptor involved

Site	*Type of receptor*	*Selective agonist*	*Selective antagonist*
1. a. All postganglionic parasymp. b. Few postganglionic symp. (sweat glands, some blood vessels)	Muscarinic	Muscarine	Atropine
2. a. Ganglia (both symp. and parasymp). b. Adrenal medulla	Nicotinic (N_N)	DMPP*	Hexamethonium
3. Skeletal muscles	Nicotinic (N_M)	PTMA**	d-tubocurarine
4. CNS (cortex, basal ganglia, spinal cord and other sites)	Muscarinic	Muscarine/ Oxotremorine	Atropine
	Nicotinic	Carbachol	d-tubocurarine

* DMPP—Dimethyl phenyl piperazinium
** PTMA—Phenyl trimethyl ammonium

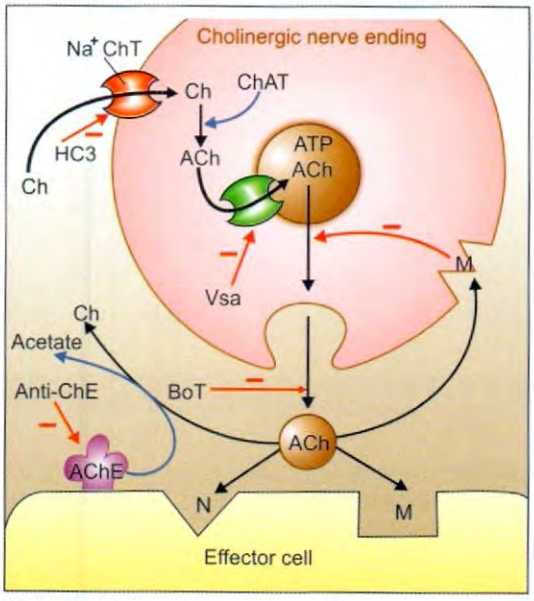


Fig. 7.1: Cholinergic neuronal mechanisms
Minus sign indicates inhibition, while bold arrow indicates active transport
Ch—Choline, ACh—Acetylcholine, ChAT—Choline acetyl transferase, AChE—Acetylcholinesterase, Anti-ChE—Anticholinesterase, M—Muscarinic receptor, N—Nicotinic receptor, HC3—Hemicholinium, BoT—Botulinum toxin, Vsa—Vesamicol, Na^+ChT—Na^+–Choline Cotransporter.

dysphagia, dysarthria, muscular weakness and even respiratory paralysis has occurred.

Cholinesterase Immediately after release, ACh is hydrolyzed by the enzyme cholinesterase and choline is recycled. A specific (*Acetylcholinesterase*—AChE or true cholinesterase) and a nonspecific (*Butyrylcholinesterase*—BuChE or pseudocholinesterase) type of enzyme occurs in the body; important differences between these two types of the enzyme are given in Table 7.2. While AChE is strategically located at all cholinergic sites and serves to inactivate ACh instantaneously, BuChE present in plasma and elsewhere probably serves to metabolize ingested esters.

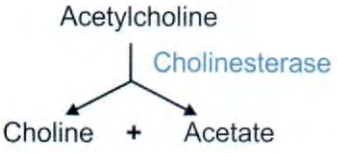


Table 7.2: Differences between the two types of cholinesterases

	Acetylcholinesterase (True)	*Butyrylcholinesterase (Pseudo)*
1. Distribution	All cholinergic sites, RBC, gray matter	Plasma, liver, intestine, white matter
2. Hydrolysis		
ACh	Very fast (in μs)	Slow
Methacholine	Slower than ACh	Not hydrolysed
Benzoylcholine	Not hydrolysed	Hydrolysed
Butyrylcholine	Not hydrolysed	Hydrolysed
3. Function	Termination of ACh action	Hydrolysis of ingested esters

Cholinoceptors

Two classes of receptors for ACh are recognised —*muscarinic* and *nicotinic*; the former is a G protein coupled receptor, while the latter is a ligand gated cation channel.

Muscarinic These receptors are selectively stimulated by muscarine and blocked by atropine. They are located primarily on autonomic effector cells in heart, blood vessels, eye, smooth muscles and glands of gastrointestinal, respiratory and urinary tracts, sweat glands, etc. and in the CNS. While autonomic ganglia primarily function through nicotinic (N_N) receptors, subsidiary muscarinic receptors are also present, which appear to play a modulatory role by inducing a long-lasting late EPSP.

Muscarinic autoreceptors are present prejunctionally on postganglionic cholinergic nerve endings. Activation of these receptors inhibits further ACh release. Similar ones have been demonstrated on adrenergic terminals: their activation inhibits NA release (may contribute to vasodilator action of injected ACh). All blood vessels have muscarinic receptors (though most of them lack cholinergic innervation) located on endothelial cells whose activation releases EDRF (nitric oxide) which diffuses to the smooth muscle to cause relaxation.

Subtypes of muscarinic receptor By pharma-cological as well as molecular cloning techniques, muscarinic receptors have been divided into 5 subtypes M_1, M_2, M_3, M_4 and M_5. The first 3 are the major subtypes (Table 7.3) that are present on effector cells as well as on prejunctional nerve endings, and are expressed both in peripheral organs as well as in the CNS. The M_4 and M_5 receptors are present mainly on nerve endings in certain areas of the brain and regulate the release of other neurotransmitters. Functionally, M_1, M_3 and M_5 fall in one class while M_2 and M_4 fall in another class. Muscarinic agonists have shown little subtype selectivity, but some relatively selective antagonists have been produced (pirenzepine for M_1, tripitramine for M_2 and darifenacin for M_3). Most organs have more

Table 7.3: Characteristics of important subtypes of muscarinic receptor

	M_1	M_2	M_3
1. Location and function subserved	*Autonomic ganglia:* Depolarization (late EPSP) *Gastric glands:* Hist. release, acid secretion *Enteric neurones* ↑ intestinal secretion *CNS:* Learning, memory, motor activity	*SA node:* Hyperpolarization, ↓ rate of impulse generation *AV node:* ↓ velocity of conduction *Atrium:* shortening of APD, ↓ contractility *Ventricle:* ↓ contractility (slight) (receptors sparse) *Cholinergic nerve endings:* ↓ ACh release *CNS:* tremor, analgesia *Visceral smooth muscle:* contraction	*Visceral and bronchial smooth muscle:* contraction *Iris:* constriction of pupil *Ciliary muscle:* contraction *Exocrine glands:* secretion *Vascular endothelium:* release of NO → vasodilatation
2. Nature	Gq-protein coupled	Gi/Go-protein coupled	Gq-protein coupled
3. Transducer mechanism	IP_3/DAG—↑ cytosolic Ca^{2+}, PLA_2↑—PG synthesis	K^+ channel opening, ↓ cAMP	IP_3/DAG—↑ cytosolic Ca^{2+} PLA_2↑—PG synthesis
4. Agonists*	MCN-343A, Oxotremorine	Methacholine	Bethanechol
5. Antagonists*	Pirenzepine, Telenzepine	Methoctramine, Tripitramine	Solifenacin, Darifenacin

*Relatively selective

— ACh activates and atropine blocks all 3 subtypes of muscarinic receptors.

— The CNS contains all subtypes of muscarinic receptors, but M_1 appear to predominate.

— Most smooth muscles and glands have both M_2 and M_3 subtypes; M_3 predominates.

than one subtype, but usually one subtype predominates in a given tissue.

M_1: The M_1 is primarily a neuronal receptor located on ganglion cells, enteric and central neurones, especially in cortex, hippocampus and corpus striatum. It plays a major role in mediating gastric secretion, relaxation of lower esophageal sphincter (LES) caused by vagal stimulation, intestinal secretion and in learning, memory, motor functions, etc.

M_2: Cardiac muscarinic receptors are predominantly M_2 and mediate vagal bradycardia. Autoreceptors on cholinergic nerve endings are also of M_2 subtype. Smooth muscles express some M_2 receptors as well which, like M_3, mediate contraction.

M_3: Visceral smooth muscle contraction and glandular secretions are elicited through M_3 receptors, which also mediate vasodilatation through EDRF release. Together the M_2 and M_3 receptors mediate most of the well-recognized muscarinic actions including contraction of LES.

The muscarinic receptors are G-protein coupled receptors having the characteristic 7 membrane traversing amino acid sequences. The M_1 and M_3 (also M_5) subtypes function through Gq protein (*see* Fig. 4.7) and activate membrane bound phospholipase C (PLc)—generating inositol trisphosphate (IP_3) and diacylglycerol (DAG) which in turn release Ca^{2+} intracellularly—cause depolarization, glandular secretion, raise smooth muscle tone and release NO (from endothelium). They also activate phospholipase A_2 resulting in enhanced synthesis and release of prostaglandins and leucotrienes in certain tissues. The M_2 (and M_4) receptor opens K^+ channels (through $\beta\gamma$ subunits of regulatory protein Gi) and inhibits adenylyl cyclase (through α subunit of Gi, as depicted in Fig. 4.6), resulting in hyperpolarization, reduced pacemaker activity, slowing of conduction and decreased force of contraction in the heart. The M_4 receptor has been implicated in facilitation/inhibition of transmitter release in certain areas of the brain, while M_5 has been found to dilate cerebral arterioles, facilitate dopamine release and mediate reward behaviour.

Nicotinic These receptors are selectively activated by nicotine and blocked by tubocurarine or hexamethonium. They are rosette-like pentameric structures (*see* Fig. 4.4) which enclose a ligand gated cation channel: their activation causes opening of the channel and rapid flow of cations resulting in depolarization and an action potential. On the basis of location and selective agonists and antagonists, two subtypes N_M and N_N (previously labelled N_1 and N_2) are recognized (Table 7.4).

N_M: These are present at skeletal muscle endplate: are selectively stimulated by phenyl trimethyl ammonium (PTMA) and blocked by tubocurarine. They mediate skeletal muscle contraction.

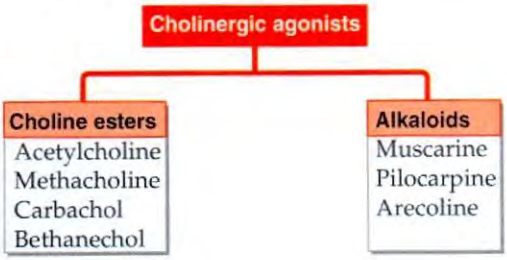
N_N: These are present on ganglionic cells (sympathetic as well as parasympathetic), adrenal medullary cells (embryologically derived from the same site as ganglionic cells), in spinal cord and certain areas of brain. They are selectively stimulated by dimethyl phenyl piperazinium (DMPP), blocked by hexamethonium, and constitute the primary pathway of transmission in ganglia.

Table 7.4: Characteristics of subtypes of nicotinic receptor

	N_M	N_N
1. Location and function subserved	*Neuromuscular junction:* depolarization of muscle end plate —contraction of skeletal muscle	*Autonomic ganglia:* depolarization —postganglionic impulse *Adrenal medulla:* catecholamine release *CNS:* site specific excitation or inhibition
2. Nature	Has intrinsic ion channel, pentamer of $\alpha 2\ \beta\ \varepsilon$ or γ and δ subunits, each subunit has 4 TM segments	Has intrinsic ion channel, pentamer of only α or α,β subunits, each subunit has 4 TM segments
3. Transducer mechanism	Opening of cation (Na^+, K^+) channels	Opening of cation (Na^+, K^+, Ca^{2+}) channels
4. Agonists	PTMA, Nicotine	DMPP, Nicotine
5. Antagonists	Tubocurarine, α-Bungarotoxin	Hexamethonium, Trimethaphan

CHOLINERGIC DRUGS (Cholinomimetic, Parasympathomimetic)

These are drugs which produce actions similar to that of ACh, either by directly interacting with cholinergic receptors (cholinergic agonists) or by increasing availability of ACh at these sites *(anticholinesterases)*.



ACTIONS (of ACh as Prototype)

Depending on the type of receptor through which it is mediated, the peripheral actions of ACh are classified as muscarinic or nicotinic. The central actions are not so classifiable and are described separately.

A. Muscarinic actions

1. Heart ACh hyperpolarizes the SA nodal cells and decreases their rate of diastolic depolarization. As a result, rate of impulse generation is reduced—*bradycardia* or even cardiac arrest may occur.

At the A-V node and His-Purkinje fibres refractory period (RP) is increased and *conduction is slowed*: P-R interval increases and partial to complete A-V block may be produced. The *force of atrial contraction is markedly reduced* and RP of atrial fibres is abbreviated. Due to nonuniform vagal innervation, the intensity of effect on RP and conduction of different atrial fibres varies—inducing inhomogeneity and predisposing to atrial fibrillation or flutter.

Ventricular contractility is also decreased but the effect is not marked. The cardiac muscarinic receptors are of the M_2 subtype.

2. Blood vessels All blood vessels are dilated, though only few (skin of face, neck, salivary glands) receive cholinergic innervation. Fall in BP and flushing, especially in the blush area occurs. Muscarinic (M_3) receptors are present on vascular endothelial cells: vasodilatation is primarily mediated through the release of an *endothelium dependent relaxing factor* (EDRF) which is nitric oxide (NO). The PLc-IP_3/DAG pathway activates endothelial NO synthase through the Ca^+-Calmodulin mechanism. When the endothelium is damaged by disease, ACh can diffuse to the vascular smooth muscle and cause vasoconstriction *via* M_3 receptors located on their plasma membrane.

Stimulation of cholinergic nerves to the penis causes erection by releasing NO and dilating cavernosal vessels through M_3 receptors. However, this response is minimal with injected cholinomimetic drugs.

3. Smooth muscle Smooth muscle in most organs is contracted (mainly through M_3 receptors). Tone and peristalsis in the gastrointestinal tract is increased and sphincters relax → abdominal cramps and evacuation of bowel.

Peristalsis in ureter is increased. The detrusor muscle contracts while the bladder trigone and sphincter relaxes → voiding of bladder.

Bronchial muscles constrict, asthmatics are highly sensitive → bronchospasm, dyspnoea, precipitation of an attack of bronchial asthma.

4. Glands Secretion from all parasympathetically innervated glands is increased *via* M_3 and some M_2 receptors: sweating, salivation, lacrimation, increased tracheobronchial and gastric secretion. The effect on pancreatic and intestinal glands is not marked. Secretion of milk and bile is not affected.

5. Eye Contraction of circular muscle of iris resulting in miosis.

Contraction of ciliary muscle causing spasm of accommodation, increased aqueous outflow facility, reduction in intraocular tension (especially in glaucomatous patients).

B. Nicotinic actions

1. Autonomic ganglia Both sympathetic and parasympathetic ganglia are stimulated. This

effect is manifested at higher doses. High dose of ACh given after atropine causes tachycardia and rise in BP due to stimulation of sympathetic ganglia and release of catecholamines.

2. Skeletal muscles Iontophoretic application of ACh to muscle endplate causes contraction of the fibre. Intraarterial injection of high dose can cause twitching and fasciculations, but i.v. injection is generally without any effect (due to rapid hydrolysis of ACh).

C. CNS actions

ACh injected i.v. does not penetrate blood-brain barrier and no central effects are seen. However, direct injection into the brain produces arousal response followed by depression. Cholinergic drugs which enter brain produce complex behavioral and neurological effects.

The important features of other choline esters are summarised in Table 7.5.

Interactions Anticholinesterases potentiate ACh markedly, methacholine to less extent and have only additive action with carbachol or bethanechol, depending upon the role of ChE in the termination of action of the particular choline ester. Atropine and its congeners competitively antagonize muscarinic actions.

Adrenaline is a physiological antagonist.

Uses Choline esters are rarely, if ever, used clinically. ACh is not used because of evanescent and nonselective action.

Bethanechol It has been used in postoperative/postpartum nonobstructive urinary retention, neurogenic bladder to promote urination. It can afford symptomatic relief in congenital megacolon and gastroesophageal reflux, but is rarely used for these. Side effects are prominent: belching, colic, involuntary urination/defecation, flushing, sweating, fall in BP, bronchospasm.

Dose: 10–40 mg oral, 2.5–5 mg s.c.;
UROTONIN, BETHACOL 25 mg tab.

CHOLINOMIMETIC ALKALOIDS

Pilocarpine It is obtained from the leaves of *Pilocarpus microphyllus* and other species. It has prominent muscarinic actions and also stimulates ganglia.

Pilocarpine causes marked sweating, salivation and increase in other secretions. The cardiovascular effects are complex. Small doses generally cause fall in BP (muscarinic), but higher doses elicit rise in BP and tachycardia which is probably due to ganglionic stimulation (through ganglionic muscarinic receptors). Applied to the eye, it penetrates cornea and promptly causes miosis, ciliary muscle contraction and fall in intraocular tension lasting 4–8 hours.

Pilocarpine is used only in the eye as 0.5–4% drops. It is a third-line drug in open angle glaucoma. An initial stinging sensation in the eye and painful spasm of accommodation are frequent side effects. Other uses as a miotic are—to counteract mydriatics after they have been used for testing refraction and to prevent/break adhesions of iris with lens or cornea by alternating it with mydriatics.

Though it can be used as a sialogogue, no oral preparation is available.

PILOCAR 1%, 2%, 4% eye drops, CARPINE 0.5% eye drops, PILODROPS 2% eye drops.

Muscarine It occurs in poisonous mushrooms *Amanita muscaria* and *Inocybe* species and has only muscarinic actions. It is not used therapeutically but is of toxicological importance.

Mushroom poisoning Depending on the toxic principle present in the particular species, at least 3 types of mushroom poisoning is known.

Table 7.5: Properties of choline esters

Choline ester	Hydrolysis by		Actions		Selective action on
	ACh E	BuChE	Musc.	Nico.	
Acetylcholine	+++	++	++	+	Non-selective
Methacholine	+	–	++	±	CVS
Carbachol	–	–	+	++	g.i.t., bladder
Bethanechol	–	–	+	–	g.i.t., bladder

Muscarine type (Early mushroom poisoning) due to *Inocybe* and related species. Symptoms characteristic of muscarinic actions appear within an hour of eating the mushroom, and are promptly reversed by atropine.

Hallucinogenic type It is due to muscimol and other isoxazole compounds which are present in *A. muscaria* and related mushrooms in much larger quantities than is muscarine. These compounds activate amino acid receptors, and block muscarinic receptors in the brain; have hallucinogenic property. Manifestations of poisoning are primarily central. There is no specific treatment and atropine is contraindicated. Another hallucinogenic mushroom is *Psilocybe mexicana* whose active principle psilocybine is a tryptaminergic (5-HT related) compound.

Phalloidin type (Late mushroom poisoning) It is due to peptide toxins found in *A. phalloides, Galerina* and related species. These inhibit RNA and protein synthesis. The symptoms start after many hours and are due to damage to the gastrointestinal mucosa, liver and kidney. Treatment consists of supportive measures. Thioctic acid may have some antidotal effect.

Arecoline It is found in betel nut *Areca catechu* and has muscarinic as well as nicotinic actions, including those on skeletal muscle endplate. It also has prominent CNS effect: has been tried in dementia as an enhancer of cognitive functions, but not found useful—has no therapeutic use.

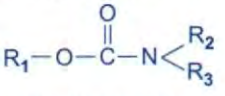
ANTICHOLINESTERASES

Anticholinesterases (anti-ChEs) are agents which inhibit ChE, protect ACh from hydrolysis—produce cholinergic effects *in vivo* and potentiate ACh both *in vivo* and *in vitro*. Quaternary ammonium anti-ChEs like neostigmine have additional direct action on nicotinic cholinoceptors.

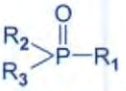
CHEMISTRY

Anti-ChEs are mostly esters of carbamic acid or derivatives of phosphoric acid. Some other anti-ChEs like edrophonium, tacrine, donepezil and galantamine have carbamate like action but are chemically non-carbamates.

The generic formula of carbamates and organophosphates is shown below:

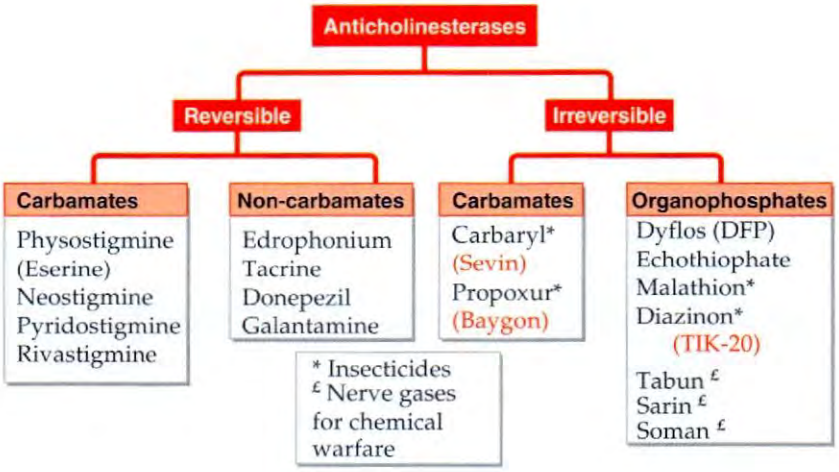


CARBAMATES



ORGANOPHOSPHATES

The R_1 in carbamates may have a nonpolar tertiary amino N, e.g. in physostigmine, rendering the compound lipid soluble. In others, e.g. neostigmine, R_1 has a quaternary N^+—rendering it lipid insoluble. All organophosphates are highly lipid soluble except echothiophate which is water soluble.



MECHANISM OF ACTION

The anti-ChEs react with the enzyme essentially in the same way as ACh. The carbamates and phosphates respectively carbamylate and phosphorylate the esteratic site of the enzyme.

The mammalian AChE has been cloned and details of its structure as well as mode of interaction with ACh and various anti-ChEs has been worked out.

The active region of AChE forms a gorge which contains an *anionic site* (near glutamate 334) and an *esteratic site* formed by serine 203, and histidine 447 (Fig. 7.2A). Hydrolysis of ACh involves electrostatic attraction of positively charged N^+ of ACh to the anionic site (Fig. 7.2B) and nucleophilic attack by serine-OH which is activated by the adjacent histidine leading to acetylation of serine (Fig. 7.2C). The acetylated enzyme reacts with water to produce acetic acid and choline (Fig. 7.2D).

Whereas the acetylated enzyme reacts with water extremely rapidly and the esteratic site is freed in a fraction of a millisecond, the carbamylated enzyme (reversible inhibitors) reacts slowly (Fig. 7.2E, F) and the phosphorylated enzyme (irreversible inhibitors) reacts extremely slowly or not at all (Fig. 7.2G). It is noteworthy that edrophonium and tacrine attach only to the anionic site and do not form covalent bonds with the enzyme, while organophosphates attach only to the esteratic site forming strong covalent bonds. Reactivation of edrophonium-inhibited enzyme occurs in < 10 min, because the interaction is by formation of weak hydrogen bonds, and does not involve hydrolysis of the inhibitor, but only its diffusion; therefore action is brief. The half-life of reactivation of carbamylated enzyme (1/2 to 6 hours) is less than that of synthesis of fresh enzyme protein, while that of phosphorylated enzyme (in days) is more than the regeneration time. The phosphorylated enzyme may also undergo 'aging' by the loss of one of the alkyl groups and become totally resistant to hydrolysis. Thus, apparently reversible and irreversible enzyme inhibition is obtained, though the basic pattern of inhibitor-enzyme interaction remains the same.

PHARMACOLOGICAL ACTIONS

The actions of anti-ChEs are due to amplification of endogenous ACh. As such they are qualitatively similar to those of directly acting cholinoceptor stimulants. However, relative intensity of action on muscarinic, ganglionic, skeletal muscle and CNS sites varies among the different agents.

Lipid-soluble agents (physostigmine and organophosphates) have more marked muscarinic and CNS effects; stimulate ganglia but action on skeletal muscles is less prominent.

Lipid-insoluble agents (neostigmine and other quaternary ammonium compounds) produce more marked effect on the skeletal muscles (they have direct action on muscle endplate N_M receptors as well), stimulate ganglia, but muscarinic effects are less prominent. They do not penetrate CNS and have no central effects.

Ganglia Local hydrolysis of ACh is less important in ganglia: inactivation occurs partly by diffusion and hydrolysis in plasma. Anti-ChEs stimulate ganglia primarily through muscarinic receptors present there. High doses cause persistent depolarization of the ganglionic nicotinic receptors and blockade of transmission.

CVS Cardiovascular effects of anti-ChEs are complex. Whereas muscarinic action would produce bradycardia and hypotension (fall in BP is mainly due to bradycardia), ganglionic stimulation would tend to increase heart rate and BP. Action on medullary centres (stimulation followed by depression) further complicates the picture, so does ganglionic blockade with high doses. Thus, the overall effects are often unpredictable and depend on the agent and its dose. Bradycardia and a small rise in BP are common with moderate doses of many anti-ChEs.

Skeletal muscles After treatment with anti-ChEs, the ACh released by a single nerve impulse is not immediately destroyed—rebinds to the same receptor, diffuses to act on neighbouring receptors and causes retrograde activation of prejunctional fibres. The resulting repetitive firing produces twitching and fasciculations. Force of contraction in partially curarized and myasthenic muscles is increased, but muscle twitching is not prominent. Higher doses cause

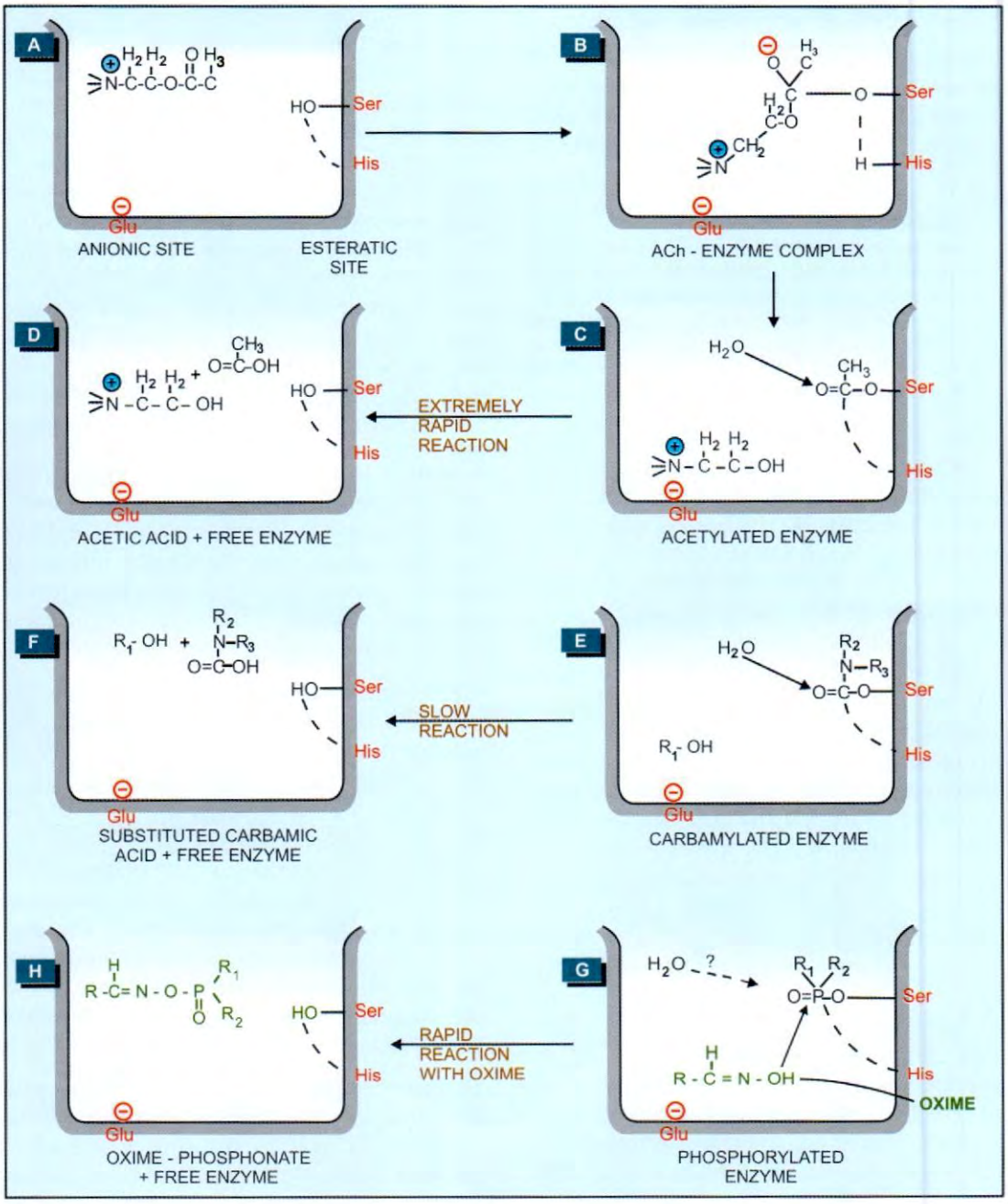


Fig. 7.2: Schematic representation of reaction of acetylcholine (A–D), or carbamate anticholinesterase (E, F), or organophosphate anticholinesterase (G) with cholinesterase enzyme; and reactivation of phosphorylated enzyme by oxime (G, H)
Ser—Serine; His—Histidine; Glu—Glutamic acid.

persistent depolarization of endplates resulting in blockade of neuromuscular transmission giving rise to weakness and paralysis. Direct action of neostigmine and its congeners at the muscle endplates results in augmentation of these features.

CNS Lipophilic anti-ChEs which penetrate into brain produce a generalised alerting response. Cognitive function may be improved in Alzheimer's disease. However, higher doses produce excitement, mental confusion, disorientation, tremors and convulsions followed by coma.

Other effects These result from stimulation of smooth muscles and glands of the gastrointestinal, respiratory, urinary tracts and in the eye as described for ACh: *viz.* enhanced g.i. motility and secretion, bronchoconstriction and increased airway secretion, voiding of bladder due to detrusor muscle contraction with trigone and sphincter relaxation, miosis and ciliary muscle contraction → lowering of intraocular tension in glaucoma.

PHARMACOKINETICS

Physostigmine It is rapidly absorbed from g.i.t. and parenteral sites. Applied to the eye, it penetrates cornea freely. It crosses blood-brain barrier and is disposed after hydrolysis by ChE.

Neostigmine and congeners These are poorly absorbed orally; oral dose is 20–30 times higher than parenteral dose. They do not effectively penetrate cornea or cross blood-brain barrier. They are partially hydrolysed and partially excreted unchanged in urine.

Organophosphates These are absorbed from all sites including intact skin and lungs. They are hydrolysed as well as oxidised in the body and little is excreted unchanged.

INDIVIDUAL COMPOUNDS

The important features of physostigmine and neostigmine are presented in Table 7.6.

Physostigmine eye drops are usually prepared freshly by ophthalmology departments.
BI-MIOTIC 0.25% eye drops with 2% pilocarpine nitrate.

Neostigmine PROSTIGMIN, MYOSTIGMIN, TILSTIGMIN 15 mg tab, 0.5 mg/ml in 1 ml and 5 ml inj.

Pyridostigmine Resembles neostigmine in all respects but is dose to dose less potent and longer acting, less frequent dosing is required in myasthenia gravis.
DISTINON, MYESTIN 60 mg tab; 1–3 tab TDS.
Ambenonium is another longacting congener used in myasthenia.

Edrophonium Resembles neostigmine in action, has a brief duration (10–30 min), suitable only as a diagnostic agent for myasthenia gravis.

Dose: 2–10 mg i.v.

Tacrine It is a lipophilic acridine compound which interacts with ChE in a manner analogous to edrophonium. It crosses blood-brain barrier and has a longer duration of action. By increasing brain ACh levels it was found to produce some symptomatic improvement in Alzheimer's disease, but has gone into disuse due to hepatotoxicity (*see* Ch. 35).

Rivastigmine This lipophilic relatively cerebroselective ChE inhibitor has been introduced for Alzheimer's disease (AD), *see* Ch. 35.

Donepezil Another centrally acting anti-AChE that has produced cognitive and behavioural improvement in AD. It is long-acting and suitable for once daily administration (*see* Ch. 35).

Galantamine This natural alkaloid inhibitor of cerebral AChE has in addition weak agonistic action on nicotinic receptors. It is being used to afford symptomatic relief in AD (*see* Ch. 35).

Dyflos It is Diisopropyl-fluoro-phosphate (DFP), a very potent and long-acting anti-ChE. It is now obsolete as a miotic.

Echothiophate It is an organophosphate with quaternary structure. It is water soluble; and was used as a long acting miotic.

Precautions Anti-ChEs are contraindicated in sick sinus, A-V conduction defects and hypotensive states. They are to be used cautiously in peptic ulcer, hypertension, asthma, COPD and seizure patients.

USES

1. As miotic

(a) In glaucoma: Miotics increase the tone of ciliary muscle (attached to scleral spur) as well as that of sphincter pupillae which pull on and somehow improve alignment of the trabeculae

Table 7.6: Comparative features of physostigmine and neostigmine

	Physostigmine	*Neostigmine*
1. Source	Natural alkaloid from *Physostigma venenosum* (Calabar bean)	Synthetic
2. Chemistry	Tertiary amine derivative	Quaternary ammonium compound
3. Oral absorption	Good	Poor
4. CNS actions	Present	Absent
5. Applied to eye	Penetrates cornea	Poor penetration
6. Direct action on N_M cholinoceptors	Absent	Present
7. Prominent effect on	Autonomic effectors	Skeletal muscles
8. Important use	Miotic (glaucoma)	Myasthenia gravis
9. Dose	0.1–1.0% eye drops	0.5–2.5 mg i.m./s.c. 15–30 mg orally
10. Duration of action	Systemic 4–6 hrs In eye 6 to 24 hrs	3–4 hrs.

so that outflow facility is increased. As a result i.o.t. falls in open angle glaucoma.

Pilocarpine is the preferred miotic. The action is rapid and short lasting (4–6 hr); 6–8 hourly instillation is required and even then i.o.t. may fluctuate inbetween. Diminution of vision, especially in dim light (due to constricted pupil), spasm of accommodation and brow pain are frequent side effects. Systemic effects—nausea, diarrhoea, sweating and bronchospasm may occur with higher concentration eye drops.

Physostigmine (0.1%) is used only to supplement pilocarpine. Miotics are now 3rd choice drugs, used only as add on therapy in advanced cases. However, they are effective in aphakic glaucoma. Pilocarpine (along with other drugs) is used in angle closure glaucoma as well.

(b) To reverse the effect of mydriatics after refraction testing.

(c) To prevent formation of adhesions between iris and lens or iris and cornea, and even to break those which have formed due to iritis, corneal ulcer, etc.—a miotic is alternated with a mydriatic.

2. Myasthenia gravis

Myasthenia gravis is an autoimmune disorder affecting about 1 in 10,000 population, due to development of antibodies directed to the nicotinic receptors (NR) at the muscle endplate. The number of free N_M cholinoceptors may be reduced to 1/3 of normal or less (Fig. 7.3) and structural damage to the neuromuscular junction. This results in weakness and easy fatigability on repeated activity, with recovery after rest. The eyelid, external ocular, facial and pharyngeal muscles are generally involved first. Later, limb and respiratory muscles get affected. Neostigmine and its congeners are the first line drugs used to restore muscle strength. They improve muscle contraction by allowing ACh released from prejunctional endings to accumulate and act on the receptors over a larger area, as well as by directly depolarizing the endplate.

Treatment is usually started with *neostigmine* 15 mg orally 6 hourly; dose and frequency is then adjusted to obtain optimum relief from weakness. However, the dosage requirement may fluctuate from time to time and there are often unpredictable periods of remission and exacerbation. Pyridostigmine is an alternative which needs less frequent dosing. If intolerable muscarinic side effects are produced, atropine can be added to block them. These drugs have no effect on the basic disorder which often progresses; ultimately it may not be possible

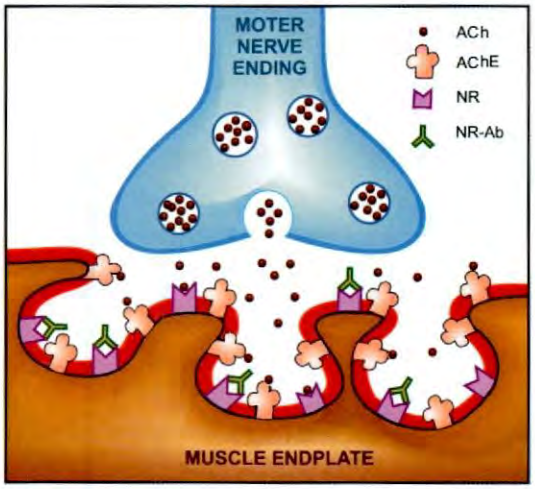


Fig. 7.3: Neuromuscular junction of myasthenic muscle
In myasthenia gravis the population of nicotinic receptors (NR) available at muscle endplate for binding acetylcholine (ACh) is markedly reduced due to their obliteration by nicotinic receptor antibodies (NR-Ab). Acetylcholinesterase (AChE) molecules located strategically at the muscle endplate rapidly hydrolyse ACh. Anticholinesterases inhibit AChE, allowing the same ACh molecules to repeatedly interact with the available NRs; frequency of ACh-NR interaction is increased

to restore muscle strength adequately with anti-ChEs alone.

Thymectomy is now generally advised for patients with generalised weakness, particularly for those with a thymoma and for younger patients. It is effective in majority of the cases. Thymectomy produces gradual improvement, and even complete remission has been obtained. Thymus may contain modified muscle cells with NRs on their surface, which may be the source of the antigen for production of anti-NR antibodies in myasthenic patients.

Corticosteroids afford improvement in myasthenia gravis by their immunosuppressant action. They inhibit production of antibodies to NR, and may increase synthesis of new NRs. However, they are generally reserved for patients who do not respond adequately to anti-ChEs and have failed after thymectomy or are unsuitable for it. Prednisolone 30–60 mg/day induces remission in about 80% of advanced cases. After tapering the dose, 10 mg daily or on alternate days can be used for maintenance therapy. However, long term use of corticosteroids has problems of its own (*see* Ch. 20).

Immunosuppressants like azathioprine and cyclosporine are also beneficial in advanced cases. Both inhibit NR-antibody synthesis by affecting T-cells. Azathioprine is generally used first but has a slow onset of affect; may take months to induce a remission. However, it is good for maintaining remission.

Removal of antibodies by *plasmapheresis* (plasma exchange) is another approach. It may produce dramatic but often short-lived improvement in myasthenic crisis.

Myasthenic crisis is characterized by acute weakness of respiratory muscles. It is managed by tracheal intubation and mechanical ventilation. Generally, i.v. methylprednisolone pulse therapy is given while anti-ChEs are withheld for 2–3 days followed by their gradual reintroduction. Most patients can be weaned off the ventilator in 1–3 weeks. Plasmapheresis hastens recovery.

Overtreatment with anti-ChEs If the dose of the antiChE is not adjusted according to the fluctuating requirement, relative overdose may occur from time-to-time. Overdose also produces weakness by causing persistent depolarization of muscle endplate, and is called *cholinergic weakness.* Late cases with high anti-ChE dose requirements often alternately experience myasthenic and cholinergic weakness and these may assume crisis proportions.

The two types of weakness require opposite treatments. They can be differentiated by *edrophonium test*—

Inject edrophonium (2 mg. i.v.)
- improvement→myasthenic crisis
- no improvement or worsening→cholinergic crisis

Diagnostic tests for myasthenia gravis

(a) ***Ameliorative test:*** Initially edrophonium 2 mg is injected i.v. as a test dose. If nothing untoward happens, the remaining 8 mg is injected after 30–60 sec. Reversal of weakness

and short-lasting improvement in the strength of affected muscles occurs only in myasthenia gravis and not in other muscular dystrophies.

In case edrophonium is not available, the test can be performed with 1.5 mg i.v. neostigmine. Atropine pretreatment may be given to block the muscarinic effects of neostigmine.

(b) *Provocative test:* myasthenics are highly sensitive to d-tubocurarine; 0.5 mg i.v. causes marked weakness in them but is ineffective in non-myasthenics. This test is hazardous.

(c) Demonstration of anti-NR antibodies in plasma or muscle biopsy specimen is a more reliable test.

3. Postoperative paralytic ileus/urinary retention This may be relieved by 0.5–1 mg s.c. neostigmine, provided no organic obstruction is present; but is seldom employed.

4. Postoperative decurarization Neostigmine 0.5–2.0 mg (30–50 µg/kg) i.v., preceded by atropine or glycopyrrolate 10 µg/kg to block muscarinic effects, rapidly reverses muscle paralysis induced by competitive neuromuscular blockers.

5. Cobra bite Cobra venom has a curare like neurotoxin. Though specific antivenom serum is the primary treatment, neostigmine + atropine prevent respiratory paralysis.

6. Belladonna poisoning Physostigmine 0.5–2 mg i.v. repeated as required is the specific antidote for poisoning with belladonna or other anticholinergics. It penetrates blood-brain barrier and antagonizes both central and peripheral actions. However, physostigmine often itself induces hypotension, arrhythmias and undesirable central effects. It is therefore employed only as a last resort. Neostigmine does not block the central effect, but is less risky.

7. Other drug overdosages Tricyclic antidepressants, phenothiazines and many antihistaminics have additional anticholinergic property. Overdose symptoms and coma produced by these drugs are partly antagonized by physostigmine. However, it may worsen the fall in BP and arrhythmias; use therefore is risky. Physostigmine also appears to have a modest nonspecific arousal effect in CNS depression produced by diazepam or general anaesthetics, but use for this purpose is rarely warranted.

8. Alzheimer's disease (AD) Characterized by progressive dementia, AD is a neurodegenerative disorder, primarily affecting cholinergic neurones in the brain. Various measures to augment cholinergic transmission in the brain have been tried. The relatively cerebroselective anti-ChEs, *rivastigmine, donepezil* and *galantamine* are now commonly used. For details *see* Ch. 35.

ANTICHOLINESTERASE POISONING

Anticholinesterases are easily available and extensively used as agricultural and household insecticides; accidental as well as suicidal and homicidal poisoning is common.

Local muscarinic manifestations at the site of exposure (skin, eye, g.i.t.) occur immediately and are followed by complex systemic effects due to muscarinic, nicotinic and central actions. They are—

- Irritation of eye, lacrimation, salivation, sweating, copious tracheo-bronchial secretions, miosis, blurring of vision, bronchospasm, breathlessness, colic, involuntary defecation and urination.
- Fall in BP, bradycardia or tachycardia, cardiac arrhythmias, vascular collapse.
- Muscular fasciculations, weakness, respiratory paralysis (central as well as peripheral).
- Irritability, disorientation, unsteadiness, tremor, ataxia, convulsions, coma and death.
- Death is generally due to respiratory failure.

Treatment

1. Termination of further exposure to the poison—fresh air, wash the skin and mucous membranes with soap and water, gastric lavage according to need.
2. Maintain patent airway, positive pressure respiration if it is failing.
3. Supportive measures—maintain BP, hydration, control of convulsions with judicious use of diazepam.
4. Specific antidotes—

(a) *Atropine* It is highly effective in counteracting the muscarinic symptoms, but higher doses are required to antagonize the central effects. It does not reverse peripheral muscular paralysis which is a nicotinic action. All cases of anti-ChE (carbamate or organophosphate) poisoning must be promptly given atropine

2 mg i.v. repeated every 10 min till dryness of mouth or other signs of atropinization appear (upto 200 mg has been administered in a day). Continued treatment with maintenance doses may be required for 1–2 weeks.

(b) *Cholinesterase reactivators* Oximes are used to restore neuromuscular transmission only in case of organophosphate anti-ChE poisoning. The phosphorylated ChE reacts very slowly or not at all with water. However, if more reactive OH groups in the form of oximes (generic formula R–CH = N–OH) are provided, reactivation occurs more than a million times faster (*see* Fig. 7.2G and H).

Pralidoxime (2-PAM) has a positively charged quaternary nitrogen: attaches to the anionic site of the enzyme which remains unoccupied in the presence of organophosphate inhibitors. Its oxime end reacts with the phosphorus atom attached to the esteratic site: the oxime-phosphonate so formed diffuses away leaving the reactivated ChE. Pralidoxime is ineffective as an antidote to carbamate anti-ChEs (physostigmine, neostigmine, carbaryl, propoxur) in which case the anionic site of the enzyme is not free to provide attachment to it. It is rather contraindicated in carbamate poisoning, because not only it does not reactivate carbamylated enzyme, it has weak anti-ChE activity of its own.

Pralidoxime (NEOPAM, PAM-A INJ. 500 mg/20 ml infusion, LYPHE 1 g/vial for inj.) is injected i.v. slowly in a dose of 1–2 g (children 20–40 mg/kg). Another regimen is 30 mg/kg i.v. loading dose, followed by 8–10 mg/kg/hour continuous infusion till recovery. Pralidoxime causes more marked reactivation of skeletal muscle ChE than at autonomic sites and not at all in the CNS, because it does not penetrate into brain. Treatment should be started as early as possible (within few hours), before the phosphorylated enzyme has undergone 'aging' and become resistant to hydrolysis. Doses may be repeated according to need (max. 12 g in first 24 hrs. Lower doses according to symptoms are continued for 1–2 weeks). The role of oximes in organophosphate poisoning is only adjunctive to that of atropine, which remains the primary antidote. Moreover, the clinical benefit of oxime therapy is highly variable depending upon the compound involved (different organophosphates 'age' at different rates), the amount of poison that has entered the body, time lapse before therapy is started and dose of the oxime.

Other oximes are obidoxime (more potent than pralidoxime) and diacetyl-monoxime (DAM), which is lipophilic.

Chronic organophosphate poisoning Repeated exposure to certain fluorine containing and triaryl organophosphates results in polyneuritis and demyelination after a latent period of days to weeks. Sensory disturbances occur first followed by muscle weakness, tenderness and depressed tendon reflexes—lower motor neurone paralysis. In the second phase, spasticity and upper motor neurone paralysis gradually supervenes. Recovery may take years. The mechanism of this toxicity is not known, but it is not due to inhibition of ChE; there is no specific treatment.

☞ PROBLEM DIRECTED STUDY

7.1 A man aged 45 years presented with gradual onset complaints of double vision, drooping eyelids, difficulty in chewing food and weakness of limbs which is accentuated by exercise. The symptoms fluctuate in intensity over time. A provisional diagnosis of myasthenia gravis is made.

(a) Can a pharmacological test be performed to confirm/refute the diagnosis?

(b) In case the diagnosis is confirmed, can this disease be cured by medication?

(c) Is there a surgical solution for this illness?

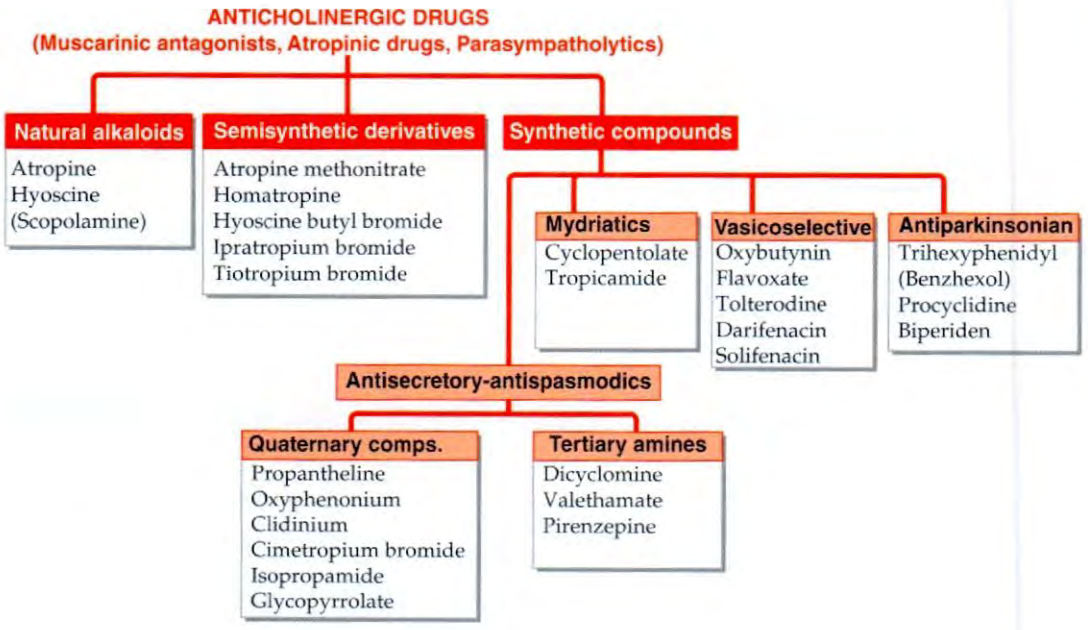
(see Appendix-1 for solution)

Chapter 8 Anticholinergic Drugs and Drugs Acting on Autonomic Ganglia

ANTICHOLINERGIC DRUGS (Muscarinic receptor antagonists, Atropinic, Parasympatholytic)

Conventionally, the term 'anticholinergic drugs' is restricted to those which block actions of ACh on autonomic effectors and in the CNS exerted through muscarinic receptors. Though nicotinic receptor antagonists also block certain actions of ACh, they are generally referred to as 'ganglion blockers' and 'neuromuscular blockers'.

Atropine, the prototype drug of this class, is highly selective for muscarinic receptors, but some of its synthetic substitutes do possess significant nicotinic blocking property in addition. The selective action of atropine can easily be demonstrated on a piece of guinea pig ileum where ACh induced contractions are blocked without affecting those evoked by histamine, 5-HT or other spasmogens. The selectivity is, however, lost at very high doses. All anticholinergics are competitive antagonists.



In addition, many other classes of drugs, i.e. TCAs, phenothiazines, antihistamines and disopyramide possess significant antimuscarinic actions.

The atropinic natural alkaloids are found in plants of the solanaceae family. The levo-isomers are much more active than the dextroisomers. Atropine is racemic while scopolamine is *l*-hyoscine.

PHARMACOLOGICAL ACTIONS
(Atropine as prototype)

The actions of atropine can be largely predicted from knowledge of parasympathetic responses. Prominent effects are seen in organs which normally receive strong parasympathetic tone. Atropine blocks all subtypes of muscarinic receptors.

1. CNS Atropine has an overall CNS stimulant action. However, these effects are not appreciable at low doses which produce only peripheral effects because of restricted entry into the brain. Hyoscine produces central effects (depressant) even at low doses.

- Atropine stimulates many medullary centres —vagal, respiratory, vasomotor.
- It depresses vestibular excitation and has antimotion sickness property. The site of this action is not clear—probably there is a cholinergic link in the vestibular pathway, or it may be exerted at the cortical level.
- By blocking the relative cholinergic overactivity in basal ganglia, it suppresses tremor and rigidity of parkinsonism.
- High doses cause cortical excitation, restlessness, disorientation, hallucinations and delirium followed by respiratory depression and coma.

Majority of the central actions are due to blockade of muscarinic receptors in the brain, but some actions may have a different basis.

2. CVS

Heart The most prominent effect of atropine is tachycardia. It is due to blockade of M_2 receptors on the SA node through which vagal tone decreases HR. Higher the existing vagal tone— more marked is the tachycardia (maximum in young adults, less in children and elderly). On i.m./s.c. injection transient initial bradycardia often occurs. Earlier believed to be due to stimulation of vagal centre, it is now thought to be caused by blockade of muscarinic autoreceptors (M_1) on vagal nerve endings, thereby augmenting ACh release. This is suggested by the finding that selective M_1 antagonist pirenzepine is equipotent to atropine in causing bradycardia. Moreover, atropine substitutes which do not cross blood-brain barrier also produce initial bradycardia. Atropine abbreviates refractory period of A-V node and facilitates A-V conduction, especially if it has been depressed by high vagal tone. P-R interval is shortened.

BP Since cholinergic impulses are not involved in the maintenance of vascular tone, atropine does not have any consistent or marked effect on BP. Tachycardia and vasomotor centre stimulation tend to raise BP, while histamine release and direct vasodilator action (at high doses) tend to lower BP.

Atropine blocks vasodepressor action of cholinergic agonists.

3. Eye The autonomic control of iris muscles and the action of mydriatics as well as miotics is illustrated in Fig. 8.1. Topical instillation of atropine causes mydriasis, abolition of light reflex and cycloplegia lasting 7–10 days. This results in photophobia and blurring of near vision. The ciliary muscles recover somewhat earlier than sphincter pupillae. The intraocular tension tends to rise, especially in narrow angle glaucoma. However, conventional systemic doses of atropine produce minor ocular effects.

4. Smooth muscles All visceral smooth muscles that receive parasympathetic motor innervation are relaxed by atropine (M_3 blockade). Tone and amplitude of contractions of stomach and intestine are reduced; the passage of chyme is slowed—constipation may occur, spasm may be relieved. However, peristalsis is only incompletely suppressed because it is

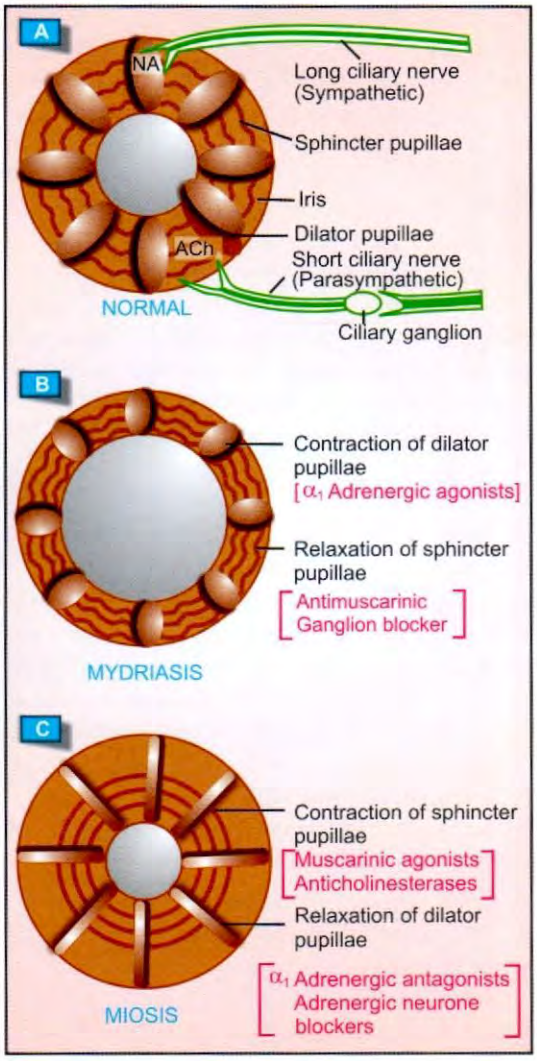


Fig. 8.1: Autonomic control of pupil (A); and site of action of mydriatics (B) and miotics (C)

primarily regulated by local reflexes in the enteric plexus, and other neurotransmitters (5-HT, enkephalin, etc.) are involved. Enhanced motility due to injected cholinergic drugs is more completely antagonised than that due to vagal stimulation, because intramural neurones which are activated by vagus utilize a number of noncholinergic transmitters as well.

Atropine causes bronchodilatation and reduces airway resistance, especially in COPD and asthma patients. Inflammatory mediators like histamine, PGs, leucotrienes and kinins which participate in asthma increase vagal activity in addition to their direct stimulant action on bronchial muscle and glands. Atropine attenuates their action by antagonizing the reflex vagal component.

Atropine has relaxant action on ureter and urinary bladder; urinary retention can occur in older males with prostatic hypertrophy. However, this relaxant action can be beneficial for increasing bladder capacity and controlling detrusor hyperreflexia in neurogenic bladder/enuresis. Relaxation of biliary tract is less marked and effect on uterus is minimal.

5. Glands Atropine markedly decreases sweat, salivary, tracheobronchial and lacrimal secretion (M_3 blockade). Skin and eyes become dry, talking and swallowing may be difficult.

Atropine decreases secretion of acid, pepsin and mucus in the stomach, but the primary action is on volume of secretion so that pH of gastric contents may not be elevated unless diluted by food. Since bicarbonate secretion is also reduced, rise in pH of fasting gastric juice is only modest. Relatively higher doses are needed and atropine is less efficacious than H_2 blockers in reducing acid secretion. Intestinal and pancreatic secretions are not significantly reduced. Bile production is not under cholinergic control, so not affected.

6. Body temperature Rise in body temperature occurs at higher doses. It is due to both inhibition of sweating as well as stimulation of temperature regulating centre in the hypothalamus. Children are highly susceptible to atropine fever.

7. Local anaesthetic Atropine has a mild anaesthetic action on the cornea.

Atropine has been found to enhance ACh (also NA) release from certain postganglionic parasympathetic and sympathetic nerve endings, and thus produce paradoxical responses. This is due to blockade of release inhibitory muscarinic autoreceptors present on these nerve terminals.

The sensitivity of different organs and tissues to atropine varies and can be graded as—

Saliva, sweat, bronchial secretion > eye, bronchial muscle, heart > smooth muscle of intestine, bladder > gastric glands and smooth muscle.

The above differences probably reflect the relative dependence of the function on cholinergic tone *vis a vis* other influences, and variation in synaptic gaps in different organs. The pattern of relative activity is nearly the same for other atropine substitutes except *pirenzepine* which inhibits gastric secretion at doses that have little effect on other secretions, heart and eye. This is probably because atropine equally blocks M_1, M_2 and M_3 receptors whereas pirenzepine is a selective M_1 antagonist.

Atropine more effectively blocks responses to exogenously administered cholinergic drugs than those to parasympathetic nerve activity. This may be due to release of ACh very close to the receptors by nerves and involvement of cotransmitters (*see* p. 108).

Hyoscine This natural anticholinergic alkaloid differs from atropine in many respects; these differences are presented in Table 8.1.

PHARMACOKINETICS

Atropine and hyoscine are rapidly absorbed from g.i.t. Applied to eyes they freely penetrate cornea. Passage across blood-brain barrier is somewhat restricted. About 50% of atropine is metabolized in liver and rest is excreted unchanged in urine. It has a t½ of 3–4 hours. Hyoscine is more completely metabolized and has better blood-brain barrier penetration.

Atropine sulfate: 0.6–2 mg i.m., i.v. (children 10 µg/kg), 1–2% topically in eye.

ATROPINE SULPHATE: 0.6 mg/ml inj., 1% eye drop/ointment; ATROSULPH 1% eye drop, 5% eye oint.

Hyoscine hydrobromide: 0.3–0.5 mg oral, i.m.; also as transdermal patch.

Combinations of atropine with analgesics and antipyretics are banned in India.

ATROPINE SUBSTITUTES

Many semisynthetic derivatives of belladonna alkaloids and a large number of synthetic compounds have been introduced with the aim of producing more selective action on certain functions. Most of these differ only marginally from the natural alkaloids, but some appear promising.

Quaternary compounds

These drugs have certain common features—

- Incomplete oral absorption (10–30%).
- Poor penetration in brain and eye; central and ocular effects are not seen after parenteral/oral administration.
- Elimination is generally slower; majority are longer acting than atropine.
- Have higher nicotinic blocking property. Some degree of ganglionic blockade may occur at clinical doses producing postural hypotension and impotence as additional side effects.
- At high doses some degree of neuromuscular blockade may also occur.

CHAPTER 8

Table 8.1: Comparative features of atropine and hyoscine

	Atropine	*Hyoscine*
1. Chief source	*Atropa belladonna, Datura stramonium*	*Hyoscyamys niger*
2. Alkaloidal ester of tropic acid with	Tropine (base)	Scopine (base)
3. CNS effect low dose high dose	Excitatory Excitation (mild) Excitation (strong), halucination	Depressant (amnesia, fatigue, drowsiness, N-REM sleep) Excitation, halucination
4. Anticholinergic property	More potent on heart, bronchial muscle and intestines	More potent on eye and secretory glands
5. Duration of action	Longer	Shorter
6. Anti-motion sickness	+ +	+ + +

Drugs in this category are—

1. *Hyoscine butyl bromide* 20–40 mg oral, i.m., s.c., i.v.; less potent and longer acting than atropine; used for esophageal and gastrointestinal spastic conditions.

BUSCOPAN 10 mg tab., 20 mg/ml amp.

2. *Atropine methonitrate* 2.5–10 mg oral, i.m.; for abdominal colics and hyperacidity.

MYDRINDON 1 mg (adult), 0.1 mg (child) tab; in SPASMOLYSIN 0.32 mg tab;

3. *Ipratropium bromide* 40–80 µg by inhalation; it acts selectively on bronchial muscle without altering volume or consistency of respiratory secretions. Another desirable feature is that in contrast to atropine, it does not depress mucociliary clearance by bronchial epithelium. It has a gradual onset and late peak (at 40–60 min) of bronchodilator effect in comparison to inhaled sympathomimetics. Thus, it is more suitable for regular prophylactic use rather than for rapid symptomatic relief during an attack. Action lasts 4–6 hours. It acts on receptors located mainly in the larger central airways (contrast sympathomimetics whose primary site of action is peripheral bronchioles, *see* Fig. 16.2). The parasympathetic tone is the major reversible factor in chronic obstructive pulmonary disease (COPD). Therefore, ipratropium is more effective in COPD than in bronchial asthma. Transient local side effects like dryness of mouth, scratching sensation in trachea, cough, bad taste and nervousness are reported in 20–30% patients, but systemic effects are rare because of poor absorption from the lungs and g.i.t. (major fraction of any inhaled drug is swallowed).

IPRAVENT 20 µg and 40 µg/puff metered dose inhaler, 2 puffs 3–4 times daily; 250 µg/ml respirator soln., 0.4–2 ml nebulized in conjunction with a β_2 agonist 2–4 times daily. Also used to control rhinorrhoea in perennial rhinitis and common cold; IPRANASE-AQ 0.084% nasal spray (42 µg per actuation), 1–2 sprays in each nostril 3–4 times a day.

4. *Tiotropium bromide* A newer congener of ipratropium bromide which binds very tightly to bronchial M_1/M_3 muscarinic receptors producing long lasting bronchodilatation. Binding to M_2 receptors is less tight, confering relative M_1/M_3 selectivity (less likely to enhance ACh release from vagal nerve endings in lungs due to M_2 receptor blockade). Like ipratropium, it is not absorbed from respiratory and g.i. mucosa and has exhibited high bronchial selectivity of action.

TIOVA 18 µg rotacaps; 1 rotacap by inhalation OD.

5. *Propantheline* 15–30 mg oral; it was a popular anticholinergic drug used for peptic ulcer and gastritis. It has some ganglion blocking activity as well and is claimed to reduce gastric secretion at doses which produce only mild side effects. Gastric emptying is delayed and action lasts for 6–8 hours. Use has declined due to availability of H_2 blockers and proton pump inhibitors.

PROBANTHINE 15 mg tab.

6. *Oxyphenonium* 5–10 mg (children 3–5 mg) oral; similar to propantheline, recommended for peptic ulcer and gastrointestinal hypermotility.

ANTRENYL 5, 10 mg tab.

7. *Clidinium* 2.5–5 mg oral; This antisecretory-antispasmodic has been used in combination with benzodiazepines for nervous dyspepsia, gastritis, irritable bowel syndrome (IBS), colic, peptic ulcer, etc.

In SPASRIL, ARWIN 2.5 mg tab with chlordiazepoxide 5 mg. NORMAXIN, CIBIS 2.5 mg with dicyclomine 10 mg and chlordiazepoxide 5 mg.

8. *Cimetropium bromide* A quaternary ammonium anticholinergic-antispasmodic drug, especially promoted for IBS. About 50% patients of IBS get 30–70% relief in abdominal pain and loose motion. Dryness of mouth is the commonest side effect.

Dose: 50 mg 2–3 times a day. IBSCIM 50 mg tab.

9. *Isopropamide* 5 mg oral; indicated in hyperacidity, nervous dyspepsia, IBS and other gastrointestinal problems, specially when associated with emotional/mental disorders.

In STELABID, GASTABID 5 mg tab. with trifluoperazine 1 mg.

10. *Glycopyrrolate* 0.2–0.4 mg i.m. (4–5 µg/kg), potent and rapidly acting antimuscarinic lacking central effects. It is almost exclusively

used for preanaesthetic medication and during anaesthesia. GLYCO-P 0.2 mg/ml amp., 1 mg in 5 ml vial, PYROLATE 0.2 mg/ml, 1 ml amp, 10 ml vial.

An inhalational powder formulation has been approved for 50 µg once daily inhalation for symptomatic relief in chronic obstructive pulmonary disease (COPD).

Tertiary amines

1. *Dicyclomine* 20 mg oral/i.m., children 5–10 mg; has direct smooth muscle relaxant action in addition to weak and somewhat M_1 selective anticholinergic action. It exerts antispasmodic action at doses which produce few atropinic side effects. However, infants have exhibited atropinic toxicity symptoms and it is not recommended below 6 months of age. It also has antiemetic property: has been used in morning sickness and motion sickness. Dysmenorrhoea and irritable bowel are other indications.
CYCLOSPAS-D, 20 mg with dimethicone 40 mg tab; CYCLOPAM INJ. 10 mg/ml in 2 ml, 10 ml, 30 ml amp/vial, also 20 mg tab with paracetamol 500 mg; in COLIMEX, COLIRID 20 mg with paracetamol 500 mg tab, 10 mg/ml drops with dimethicone.

2. *Valethamate:* The primary indication of this anticholinergic-smooth muscle relaxant is to hasten dilatation of cervix when the same is delayed during labour, and as visceral antispasmodic, for urinary, biliary, intestinal colic.
Dose: 8 mg i.m., 10 mg oral repeated as required.
VALAMATE 8 mg in 1 ml inj, EPIDOSIN 8 mg inj., 10 mg tab.

3. *Pirenzepine* It selectively blocks M_1 muscarinic receptors (*see* p. 112) and inhibits gastric secretion without producing typical atropinic side effects (these are due to blockade of M_2 and M_3 receptors). The more likely site of action of pirenzepine in stomach is intramural plexuses and ganglionic cells rather than the parietal cells themselves. It was indicated in peptic ulcer, but has been overshadowed by H_2 blockers and proton pump inhibitors.

Vasicoselective anticholinergics

1. *Oxybutynin* This antimuscarinic has high affinity for receptors in urinary bladder and salivary glands alongwith additional smooth muscle relaxant and local anaesthetic properties. It is relatively selective for M_3 and M_1 subtypes with less action on the M_2 subtype. Because of vasicoselective action, it is used for detrusor instability resulting in urinary frequency and urge incontinence. Beneficial effects have been demonstrated in post-prostatectomy vasical spasm, neurogenic bladder, spina bifida and nocturnal enuresis. Anticholinergic side effects are common after oral dosing, but intravesical instillation increases bladder capacity with few side effects. Oxybutynin is metabolized by CYP3A4; its dose should be reduced in patients being treated with inhibitors of this isoenzyme.
Dose: 5 mg BD/TDS oral; children above 5 yr 2.5 mg BD.
OXYBUTIN, CYSTRAN, OXYSPAS 2.5 mg and 5 mg tabs.

2. *Tolterodine:* This relatively M_3 selective muscarinic antagonist has preferential action on urinary bladder; less likely to cause dryness of mouth and other anticholinergic side effects. It is indicated in overactive bladder with urinary frequency and urgency. Since it is metabolized by CYP3A4, dose should be halved in patients receiving CYP3A4 inhibitors (erythromycin, ketoconazole, etc.)
Dose: 1–2 mg BD or 2–4 mg OD of sustained/extended release tab. oral. ROLITEN, TOLTER 1, 2 mg tabs, TORQ 2, 4 mg SR tab.

3. *Flavoxate* It has properties similar to oxybutynin and is indicated in urinary frequency, urgency and dysuria associated with lower urinary tract infection.
URISPAS, FLAVATE, FLAVOSPAS 200 mg tab, 1 tab TDS.

4. *Darifenacin* Another relatively M_3 selective antimuscarinic with preferential action on bladder muscles; indicated in urinary incontinence, urgency and frequency. The biological t½ is 13–19 hours and the extended release tablet works for 24 hours.
Dose: 7.5–15 mg OD
DARILONG, ESIGARD 7.5 mg, 15 mg ER tabs.

5. *Solifenacin* It is similar to darifenacin; no clinically significant difference between the two has been observed in clinical trials on patients with overactive bladder.
Dose: 5–10 mg OD
BISPEC, SOLICEPT 5, 10 mg tabs.

Drotaverine It is a non-anticholinergic smooth muscle antispasmodic which acts by inhibiting

phosphodiesterase-4 (PDE-4) selective for smooth muscle. Elevation of intracellular cAMP/cGMP attends smooth muscle relaxation. Changes in membrane ionic fluxes and membrane potential have also been shown. It has been used orally as well as parenterally in intestinal, biliary and renal colics, IBS, uterine spasms, etc. without anticholinergic side effects. Adverse effects reported are headache, dizziness, constipation and flushing. Fall in BP can occur on i.v. injection.

Dose: 40–80 mg TDS; DROTIN, DOTARIN, DOVERIN 40, 80 mg tabs, 40 mg/2 ml inj.

Mydriatics

Atropine is a potent mydriatic but its slow and long-lasting action is undesirable for refraction testing. Though the pupil dilates in 30–40 min, cycloplegia takes 1–3 hours, and the subject is visually handicapped for about a week. Atropine substitutes attempt to overcome these difficulties. However, atropine itself is used in iridocyclitis, keratitis, etc.

1. *Homatropine* It is 10 times less potent than atropine. Instilled in the eye, it acts in 45–60 min, mydriasis lasts 1–3 days while accommodation recovers in 1–2 days. It often produces unsatisfactory cycloplegia in children who have high ciliary muscle tone.

HOMATROPINE EYE, HOMIDE 1%, 2% eye drops.

2. *Cyclopentolate* It is potent and rapidly acting; mydriasis and cycloplegia occur in 30–60 min and last about a day. It is preferred for cycloplegic refraction, but children may show transient behavioural abnormalities due to absorption of the drug after passage into the nasolacrimal duct. It is also used in iritis and uveitis.

CYCLOMID EYE 0.5%, 1%; CYCLOGYL, CYCLOPENT 1% eye drops.

3. *Tropicamide* It has the quickest (20–40 min) and briefest (3–6 hours) action, but is a relatively unreliable cycloplegic. However, it is satisfactory for refraction testing in adults and as a short acting mydriatic for fundoscopy. The mydriatic action can be augmented by combining with phenylephrine.

OPTIMIDE, TROPICAMET, TROMIDE 0.5%, 1.0% eye drops. TROPAC-P, TROPICAMET PLUS 0.8% with phenylephrine 5% eye drops.

Antiparkinsonian drugs (*see* Ch. 31)

USES

1. As antisecretory

• *Preanaesthetic medication* When irritant general anaesthetics (ether) were used, prior administration of anticholinergics (atropine, hyoscine, glycopyrrolate) was imperative to check increased salivary and tracheobronchial secretions. However, with current use of nonirritating anaesthetics (halothane, etc.) the requirement has decreased, though atropine may still be employed because halothane sensitizes the heart to NA mediated ventricular arrhythmias which are specially prone to occur during vagal slowing. Atropinic drugs also prevent laryngospasm, not by an action on laryngeal muscles, which are skeletal muscles, but by reducing respiratory secretions that reflexly predispose to laryngospasm. Vasovagal attack during anaesthesia can also be prevented.

• *Pulmonary embolism* Atropine befefits by reducing pulmonary secretions evoked reflexly by embolism.

• To check excessive sweating or salivation, e.g. in parkinsonism. Use of anticholinergics in peptic ulcer is obsolete.

2. As antispasmodic

1. Intestinal and renal colic, abdominal cramps: symptomatic relief is afforded if there is no mechanical obstruction. However, in renal colic parenteral opioids and NSAIDs provide greater pain relief than atropine. Atropine is less effective in biliary colic and is not able to completely counteract biliary spasm due to opiates (nitrates are more effective).
2. Nervous, functional and drug induced diarrhoea may be controlled to some extent, but anticholinergics are not useful in infective diarrhoea.

3. Spastic constipation, IBS: modest symptomatic relief in abdominal discomfort and irregular bowel evacuation may be obtained. Amitriptyline and other TCAs may befefit non-responders.
4. Pylorospasm, gastric hypermotility, gastritis, nervous dyspepsia may be partially suppressed.
5. To relieve urinary frequency and urgency, enuresis in children. Vasicoselective M_3 antimuscarinics like oxybutynin, tolterodine, flavoxate and darifenacin have demonstrated good efficacy. They may also increase bladder capacity, but dry mouth and other anticholinergic effects are dose limiting.
6. Dysmenorrhoea: Anticholinergics are not very effective; NSAIDs are superior.

3. Bronchial asthma, asthmatic bronchitis, COPD

Reflex vagal activity is an important factor in causing bronchoconstriction and increased secretion in chronic bronchitis and COPD, but to a lesser extent in bronchial asthma. Orally administered atropinic drugs are bronchodilators, but less effective than adrenergic drugs; not clinically used. They dry up secretion in the respiratory tract, may lead to its inspissation and plugging of bronchioles resulting in alveolar collapse and predisposition to infection. The mucociliary clearance is also impaired. Inhaled ipratropium bromide has been found specially effective in asthmatic bronchitis and COPD, though less so in bronchial asthma. Given by aerosol, it neither decreases respiratory secretions nor impairs mucociliary clearance, and there are few systemic side effects. Thus, it has a place in the management of COPD. Its time course of action makes it more suitable for regular prophylactic use rather than for control of acute attacks. The additive bronchodilator action with adrenergic drugs is utilised to afford relief in acute exacerbation of asthma/COPD by administering a combination of nebulised ipratropium and β_2 agonist through a mask.

Tiotropium bromide is an equally effective and longer acting alternative to ipratropium bromide, good for once daily maintenance therapy. After regular use, it has been found to reduce episodes of COPD exacerbations.

4. As mydriatic and cycloplegic

(i) *Diagnostic* For testing error of refraction, both mydriasis and cycloplegia are needed. Tropicamide having briefer action has now largely replaced homatropine for this purpose. Phenylephrine is often combined with tropicamide for faster and stronger mydriatic action. These drugs do not cause sufficient cycloplegia in children: more potent agents like atropine or hyoscine have to be used. Atropine ointment (1%) applied 24 hours and 2 hours before is often preferred for children below 5 years. Cyclopentolate drops are a more rapidly acting alternative to atropine.

To facilitate fundoscopy only mydriasis is needed; a short acting antimuscarinic may be used, but phenylephrine is preferred, especially in the elderly, for fear of precipitating or aggravating glaucoma.

(ii) *Therapeutic* Because of its long lasting mydriatic-cycloplegic and local anodyne (pain relieving) action on cornea, atropine is very valuable in the treatment of iritis, iridocyclitis, choroiditis, keratitis and corneal ulcer. It gives rest to the intraocular muscles and cuts down their painful spasm. Atropinic drugs alternated with a miotic prevent adhesions between iris and lens or iris and cornea and may even break them if already formed.

5. As cardiac vagolytic

Atropine is useful in counteracting sinus bradycardia and partial heart block in selected patients where increased vagal tone is responsible, e.g. in some cases of myocardial infarction and in digitalis toxicity. However, cardiac arrhythmias or ischaemia may be precipitated in some cases.

6. For central action

• *Parkinsonism* (*see* Ch. 31) Central anticholinergics are less effective than levodopa. They

are used in mild cases, in drug-induced extrapyramidal syndromes and as adjuvant to levodopa.

• *Motion sickness* Hyoscine is the most effective drug for motion sickness. It is particularly valuable in highly susceptible individuals and for vigorous motions. The drug should be given prophylactically (0.2 mg oral), because administration after symptoms have setin is less effective; action lasts 4–6 hours. A transdermal preparation applied behind the pinna 4 hours before journey has been shown to protect for 3 days. Side effects with low oral doses and transdermal medication are few, but dry mouth and sedation can occur: driving is risky. Dicyclomine is another anticholinergic used for motion sickness. These drugs are not effective in other types of vomiting.

• Scopolamine had earned a reputation as a 'lie detector' during world war II: its amnesic and depressant action was believed to put the subject 'off guard' in the face of sustained interrogation and sleep deprivation, so that he came out with the truth.

7. To antagonise muscarinic effects of drugs and poisons

Atropine is the specific antidote for anti ChE and early mushroom poisoning (*see* Ch. 7). Atropine or glycopyrrolate is also given to block muscarinic actions of neostigmine used for myasthenia gravis, decurarization or cobra envenomation.

SIDE EFFECTS AND TOXICITY

Side effects are quite common with the use of atropine and its congeners. These are due to facets of its action other than for which it is being used. They cause inconvenience but are rarely serious.

Belladonna poisoning may occur due to drug overdose or consumption of seeds and berries of belladonna/datura plant. Children are highly susceptible. Manifestations are due to exaggerated pharmacological actions.

Dry mouth, difficulty in swallowing and talking.

Dry, flushed and hot skin (especially over face and neck), fever, difficulty in micturition, decreased bowel sounds. A scarlet rash may appear.

Dilated pupil, photophobia, blurring of near vision, palpitation.

Excitement, psychotic behaviour, ataxia, delirium, dreadful visual hallucinations.

Hypotension, weak and rapid pulse, cardiovascular collapse with respiratory depression. Convulsions and coma occur only in severe poisoning.

Diagnosis Methacholine 5 mg or neostigmine 1 mg s.c. fails to induce typical muscarinic effects.

Treatment If the poison has been ingested, gastric lavage should be done with tannic acid ($KMnO_4$ is ineffective in oxidizing atropine). The patient should be kept in a dark quiet room. Cold sponging or ice bags are applied to reduce body temperature. Physostigmine 1–3 mg s.c. or i.v. antagonises both central and peripheral effects, but has been found to produce hypotension and arrhythmias in some cases. As such, it is generally not recommended. Neostigmine does not antagonise the central effects. Therefore, most cases are just treated symptomatically.

Other general measures (maintenance of blood volume, assisted respiration, diazepam to control convulsions) should be taken as appropriate.

Contraindications Atropinic drugs are absolutely contraindicated in individuals with a narrow iridocorneal angle—may precipitate acute congestive glaucoma. However, marked rise in intraocular tension is rare in patients with wide angle glaucoma.

Caution is advocated in elderly males with prostatic hypertrophy—urinary retention can occur.

Interactions

1. Absorption of most drugs is slowed because atropine delays gastric emptying. This results in slower absorption and greater peripheral degradation of levodopa—less of it reaches the brain. This does not occur when a peripheral decarboxylase inhibitor is combined.

   On the other hand, extent of digoxin and tetracycline absorption may be increased due to longer transit time in the g.i.t.

2. Antacids interfere with absorption of anticholinergics.
3. Antihistaminics, tricyclic antidepressants, phenothiazines, disopyramide, pethidine have anticholinergic property—additive side effects occur with atropinic drugs.
4. MAO inhibitors interfere with metabolism of anticholinergic antiparkinsonian drugs—delirium may occur.

DRUGS ACTING ON AUTONOMIC GANGLIA

Acetylcholine is the primary excitatory neurotransmitter in both sympathetic and parasympathetic ganglia. Drugs which inhibit synthesis (hemicholinium) or release (botulinum toxin, procaine) of ACh can interfere with ganglionic transmission, but drugs which act on cholinergic receptors in the ganglia are more selective.

In addition to the dominant nicotinic N_N receptors, which mediate the primary rapid depolarization of ganglionic cells, there are modulatory muscarinic M_1, M_2, adrenergic, dopaminergic, amino acid and peptidergic receptors which bring about secondary, slowly developing but longer lasting changes in membrane potential, both positive and negative, that modulate the primary response. Separate catecholamine (NA, DA) and amino acid transmitter containing cells are present in ganglia, but peptide cotransmitters are released from the preganglionic cholinergic terminals themselves. Thus, autonomic ganglion is not merely a one transmitter—one cell junction, but a complex system capable of local adjustments in the level of excitability.

GANGLIONIC STIMULANTS

Selective nicotinic agonists	Nonselective/muscarinic agonists
Nicotine (small dose) Lobeline Dimethyl phenyl piperazinium (DMPP) Tetramethyl ammonium Varenicline	Acetylcholine Carbachol Pilocarpine Anticholinesterases MCN 343-A

Nicotine

It is the principal alkaloid in tobacco (*Nicotiana tabacum*). It acts as an agonist on both N_N and N_M subtypes of nicotinic cholinergic receptors (NRs). Sympathetic as well as parasympathetic ganglia are stimulated, but larger doses cause persistent depolarization and ganglionic blockade. Nicotine is important in the context of smoking and tobacco chewing. The only clinical indication of nicotine is short-term replacement therapy in tobacco abstinent subjects. There is no therapeutic application of ganglionic stimulants, because no useful purpose can be served by stimulating both sympathetic and parasympathetic ganglia concurrently.

Treatment of smoking cessation/ quitting tobacco chewing

Majority of smokers (and tobacco chewers) wish to quit smoking/chewing, but fail to do so because of nicotine dependence. The most important measure to help smokers quit is counselling and motivation. This may be supplemented by pharmacotherapy. The goals of such pharmacotherapy are:

- To reduce the craving for the satisfying (reward) effects of nicotine.
- To suppress the physical withdrawal symptoms of nicotine which manifest as restlessness, irritability, anxiety, aggression, inability to concentrate, depressed mood and unhappiness.

Heavy smokers may even develop tremors.

The drugs currently utilized for the above goals are:

- Nicotine replacement
- Partial agonists of α4β2 NRs (Varenicline)
- Antidepressants (Bupropion)

Nicotine transdermal This patch formulation of nicotine is applied once daily on the hip/abdomen/chest/upper arm as an aid to smoking cessation. It ameliorates the symptoms of nicotine withdrawal, but only partially suppresses the craving, because the intermittent peak nicotine blood levels that occur during smoking are not reproduced by the patch.

NICOTINELL-TTS 10, 20, 30 cm^2 patches releasing 7, 14, 21 mg nicotine per 24 hr respectively. in those smoking > 20 cigarettes every day-start with 30 cm^2 patch, shift to smaller patches every 5–8 days, treat for 3–4 weeks (max. 12 weeks).

Nicotine chewing gum Developed as an alternative to nicotine transdermal, this formulation is found more satisfying by some dependent subjects. The number of gum pieces chewed daily can be adjusted according to the need felt.

NULIFE 1, 2, 4 mg chewing gum; for those smoking >20 cigarettes/day—start with 4 mg gum chewed and retained in mouth for 30 min when urge to smoke is felt. After a few days change over to 2 mg gum and then to 1 mg gum. Not more than 15 pieces are to be allowed in a day. Treatment can be started at lower doses for less heavy smokers.

A nasal spray delivering 0.5 mg per activation, and an inhaler with nicotine cartridge are also available in some countries.

Side effects of nicotine replacement therapy are headache, dyspepsia, abdominal cramps, loose motions, insomnia, flu-like symptoms and local irritation. Vasospastic angina may be precipitated. Cardiac arrhythmias and ischaemic heart disease are the contraindications.

Varenicline This α4β2 subtype NR selective partial agonist has been marketed as oral tablets in many countries (UK, USA, Europe, etc), and recently in India, to help smoking cessation. Evidence has shown that the reward (reinforcing) action of nicotine is exerted through the α4β2 subtype of neuronal NRs which are mainly localized in nucleus accumbens and other mesolimbic areas. Activation of these NRs by nicotine induces DA release which produces feelings of satisfaction/reward and has reinforcing effect. Since varenicline is a partial agonist at these receptors, it provides some level of nicotine substitution, but blocks the reward effect of smoking. Clinically it has been found to reduce craving as well as nicotine withdrawal symptoms in those who stop smoking. Abstinence rates at one year of cessation are comparable to those of nicotine replacement and of bupropion. However, utility of varenicline is limited by its side effects, which are mood changes, irrational behaviour, appetite and taste disturbances, sleep disorder and agitation. Warning has been issued that it may promote suicidal thoughts.

Dose: Initially 0.25 mg BD; gradually increase upto 1 mg BD according to need, for not more than 12 weeks; then taper off.

CHAMPIX 0.5, 1.0 mg tabs.

Bupropion This atypical antidepressant inhibits reuptake of DA and NA, and has been marketed as a sustained release tablet specifically for smoking cessation. Clinical efficacy has been rated equivalent to nicotine replacement, and it has produced fewer side effects (*see* Ch. 33).

GANGLION BLOCKING AGENTS

The competitive ganglion blockers were used in the 1950s for hypertension and peptic ulcer, but have been totally replaced now because they produce a number of intolerable side

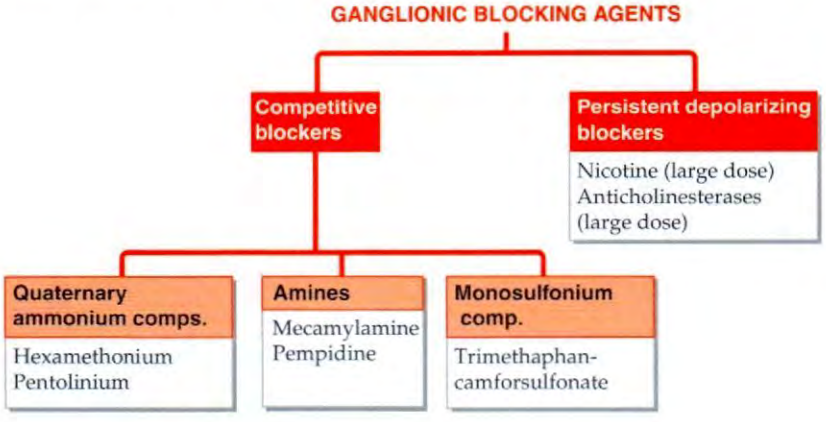


Table 8.2: Relative autonomic tone and effects of ganglionic blockade on organ function

Organ	*Dominant tone*	*Effect of ganglionic blockade (Side effect)*
1. Heart	Para-symp.	Tachycardia (palpitation)
2. Blood vessels	Symp.	Vasodilatation, abolition of reflexes (postural and exercise hypotension, syncope)
3. Iris	Para-symp.	Mydriasis (photophobia)
4. Ciliary muscle	Para-symp.	Cycloplegia (blurring of near vision)
5. Intestines	Para-symp.	Decreased motility (distension, constipation)
6. Bladder	Para-symp.	Decreased tone (difficulty in micturition)
7. Male sexual function	Para-symp. Symp.	Inhibition of erection Inhibition of ejaculation } (impotence)
8. Salivary glands	Para-symp.	Inhibition of salivation (dryness of mouth, difficulty in swallowing and talking)
9. Sweat glands	Symp. (cholinergic)	Inhibition of sweating (anhydrosis)

effects (*see* Table 8.2). In fact, these side effects help in understanding the relative roles of sympathetic and parasympathetic divisions in regulating the various organ functions. None of the ganglion blockers is commercially marketed now as a medicine, and these drugs have no clinical relevance.

Trimethaphan It is an ultrashort acting ganglion blocker, which was infused i.v. to produce controlled hypotension and to lower BP in hypertensive emergency due to aortic dissection.

Mecamylamine Either alone or in combination with nicotine patch, mecamylamine was tried for smoking cessation. It appears to block the reward effect of nicotine and improve abstinence rate compared to placebo.

☞ PROBLEM DIRECTED STUDY

8.1 An elderly male aged 74 years was brought to the hospital since he had not passed urine for the past 24 hours and had severe pain in lower abdomen. On examination there was a bulge in the pubic region due to full urinary bladder. On catheterization, he passed 1.5L urine and the pain was relieved.

He gave the history of having difficulty in passing urine, poor stream, frequent urge to urinate and post-void dribbling for the last 3 years. Over the past few days he had been experiencing episodes of vertigo for which he was prescribed a medicine that he was taking for 2 days. Examination of the prescription revealed that he was taking tab. Dimenhydrinate 50 mg 3 times daily.

(a) Could there be any relationship between the anti-vertigo medication and the episode of acute urinary retention?

(see Appendix-1 for solution)

Chapter 9 Adrenergic Transmission and Adrenergic Drugs

ADRENERGIC TRANSMISSION

Adrenergic (more precisely 'Noradrenergic') transmission is restricted to the sympathetic division of the ANS. There are three closely related endogenous catecholamines (CAs) which act as signal molecules.

Noradrenaline (NA) It acts as transmitter at postganglionic sympathetic sites (except at sweat glands, and some vasodilator fibres) and in certain areas of brain. Small quantities are secreted by the adrenal medulla.

Adrenaline (Adr) It is secreted by adrenal medulla as the major hormone. It may also have a transmitter role in the brain, but not at peripheral sympathetic nerve terminals.

Dopamine (DA) It is a major transmitter in basal ganglia, limbic system, CTZ, anterior pituitary, etc. and in a limited manner in the periphery (renal blood vessels, etc.) as well.

1. Synthesis of CAs Catecholamines are synthesized from the amino acid phenylalanine as depicted in Fig. 9.1. Tyrosine hydroxylase is a specific and the rate limiting enzyme. Its inhibition by α-methyl-p-tyrosine (metyrosine) results in depletion of CAs. This inhibitor can be used in pheochromocytoma before surgery and in inoperable cases to block synthesis of CAs. All other enzymes of CA synthesis are rather nonspecific and can act on closely related substrates, e.g. dopa decarboxylase can form 5-HT from 5-hydroxytryptophan and α methyl DA from α methyl dopa. Synthesis of NA occurs in all adrenergic neurones, while that of Adr occurs only in the adrenal medullary cells. It requires high concentration of glucocorticoids reaching there through the intraadrenal portal circulation for induction of the methylating enzyme.

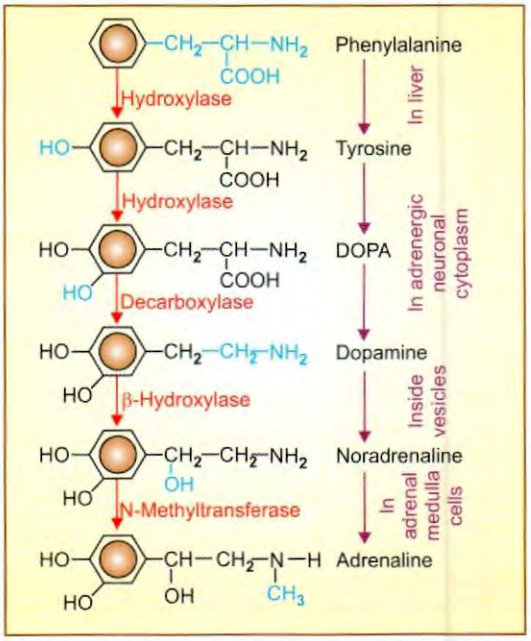


Fig. 9.1: Steps in the synthesis of catecholamines

2. Storage of CAs NA is stored in synaptic vesicles or 'granules' within the adrenergic nerve terminal (Fig. 9.4). The vesicular membrane actively takes up DA from the cytoplasm and the final step of synthesis of NA takes place inside the vesicle which contains dopamine β-hydroxylase. NA is then stored as a complex with ATP (in a ratio of 4 : 1) which is adsorbed on a protein *chromogranin*. In the adrenal medulla the NA thus formed within the chromaffin granules diffuses out into the cytoplasm, is methylated and

Adr so formed is again taken up by a separate set of granules. The cytoplasmic pool of CAs is kept low by the enzyme monoamine oxidase (MAO) present on the outer surface of mitochondria.

3. Release of CAs The nerve impulse coupled release of CA takes place by *exocytosis* (*see* p. 106) and all the vesicular contents (NA or Adr, ATP, dopamine β hydroxylase, chromogranin) are poured out. In case of vesicles which in addition contain peptides like enkephalin or neuropeptide Y (NPY), these cotransmitters are simultaneously released. The release is modulated by presynaptic receptors, of which α_2 inhibitory control is dominant.

The autoreceptors of other cotransmitters (Y_2 receptor of NPY and P1 receptor of ATP) also inhibit transmitter release. In addition, numerous heteroreceptors are expressed on the adrenergic neurone which either inhibit (dopaminergic, serotonergic, muscarinic and PGE_2 receptors) or enhance (β_2 adrenergic, angiotensin AT_1 and nicotinic receptors) NA release.

Indirectly acting sympathomimetic amines (tyramine, amphetamine, etc.) also induce release of NA, but they do so by displacing NA from the nerve ending binding sites and by exchange diffusion utilizing norepinephrine transporter (NET) the carrier of uptake-1 (described below) as depicted in Fig. 9.5. This process is not exocytotic and does not require Ca^{2+}.

4. Reuptake of CAs There is a very efficient mechanism by which NA released from the nerve terminal is recaptured. This occurs in 2 steps—

Axonal uptake An active amine pump (NET) is present at the neuronal membrane (*see* Fig. 9.4) which transports NA by a Na^+ coupled mechanism. It takes up NA at a higher rate than Adr and had been labelled *uptake-1*. The indirectly acting sympathomimetic amines like tyramine/amphetamine but not isoprenaline, also utilize this pump for entering the neurone. This uptake is the most important mechanism for terminating the postjunctional action of NA. From 75% to 90% of released NA is retaken back into the neurone. This pump is inhibited by cocaine, desipramine and few other drugs.

Vesicular uptake The membrane of intracellular vesicles has another amine pump the 'vesicular monoamine transporter' (VMAT-2), which transports CA from the cytoplasm to the interior of the storage vesicle. The VMAT-2 transports monoamines by exchanging with H^+ ions. The vesicular NA is constantly leaking out into the axoplasm and is recaptured by this mechanism. This carrier also takes up DA formed in the axoplasm for further synthesis to NA. Thus, it is very important in maintaining the NA content of the neurone. This uptake is inhibited by reserpine, resulting in depletion of CAs.

Extraneuronal uptake of CAs (uptake-2) is carried out by extraneuronal amine transporter (ENT or OCT3) and other organic cation transporters OCT1 and OCT2 into cells of other tissues. In contrast to NET this uptake transports Adr at a higher rate than NA, is not Na^+ dependent and is not inhibited by cocaine, but inhibited by corticosterone. It may capture circulating Adr, but is quantitatively minor and not of physiological or pharmacological importance.

5. Metabolism of CAs The pathways of metabolism of CAs are depicted in Fig. 9.2. Part of the NA leaking out from vesicles into cytoplasm as well as that taken up by axonal transport is first attacked by MAO, while that which diffuses into circulation is first acted upon by catechol-o-methyl transferase (COMT) in liver and other tissues. In both cases, the alternative enzyme can subsequently act to produce vanillylmandelic acid (VMA). Other intermediate step enzymes involved are aldehyde reductase (AR), aldehyde dehydrogenase (AD) and alcohol dehydrogenase (ADH). The major metabolites excreted in urine are VMA and 3-methoxy-4-hydroxy phenyl glycol (a reduced product) along with some metanephrine, normetanephrine and 3,4 dihydroxy mandelic acid (DOMA). These metabolites are mostly conjugated with glucuronic acid or sulfate before excretion in urine. Only 25–50 μg of NA and 2–5 μg of Adr are excreted in the free form in 24 hours. However, metabolism does not play an important role in terminating the action of neuronally released CAs.

6. Adrenergic receptors Adrenergic receptors are membrane bound G-protein coupled receptors which function primarily by increasing or decreasing the intracellular production

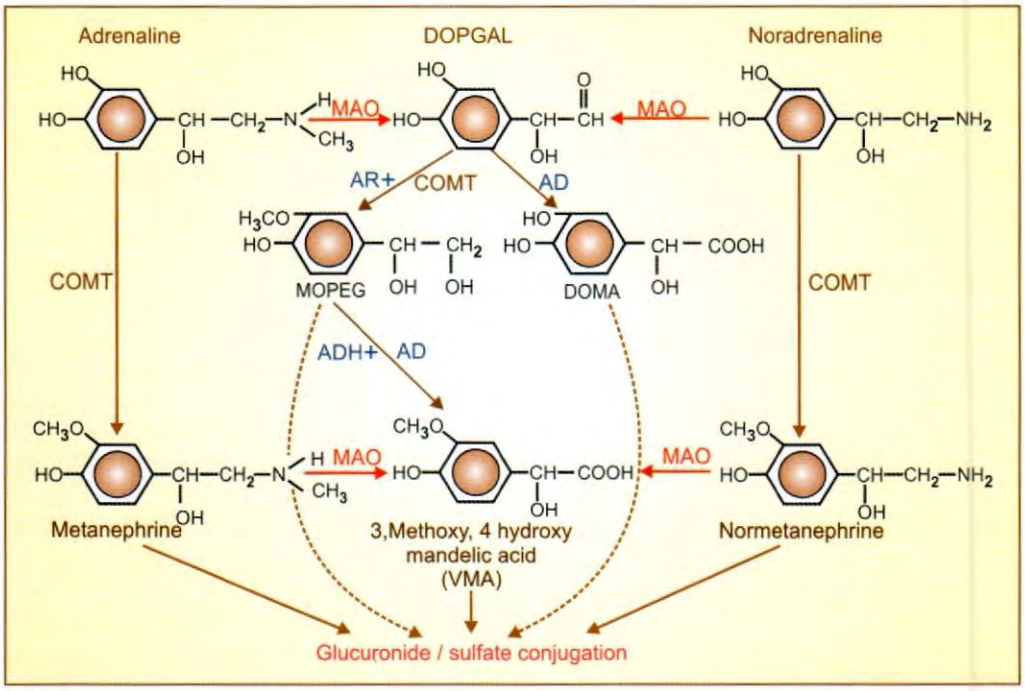


Fig. 9.2: Metabolism of catecholamines
MAO—Monoamine oxidase; COMT—Catechol-O-methyl transferase; AR—Aldehyde reductase; AD—Aldehyde dehydrogenase; ADH—Alcohol dehydrogenase; DOMA—3,4 dihydroxy mandelic acid; MOPEG—3-methoxy, 4-hydroxy phenyl glycol; VMA—vanillyl mandelic acid

of second messengers cAMP or IP_3/DAG. In some cases the activated G-protein itself operates K^+ channels or Ca^{2+} channels, or increases prostaglandin production.

Ahlquist (1948), on the basis of two distinct rank order of potencies of adrenergic agonists (Fig. 9.3), classified adrenergic receptors into two types α and β. This classification was confirmed later by the discovery of selective α and β adrenergic antagonists. Important features of α and β receptors are given in Table 9.1.

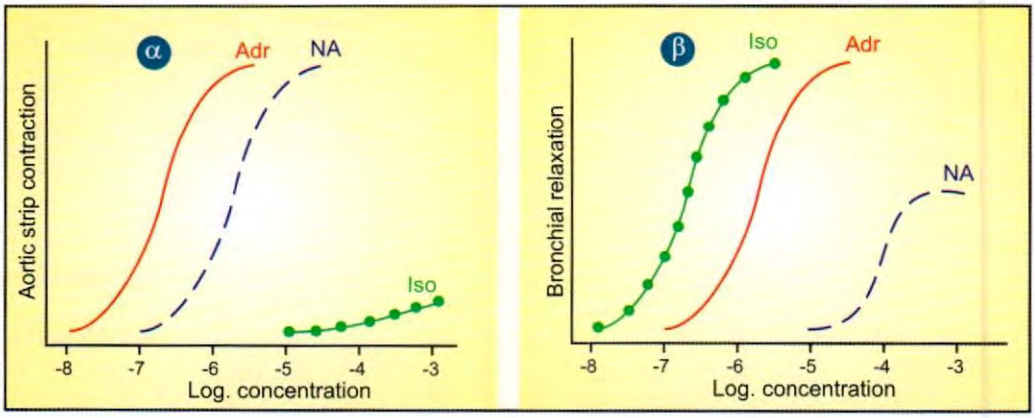


Fig. 9.3: Dose-response curves of 3 catecholamines adrenaline (Adr), noradrenaline (NA) and isoprenaline (Iso) on isolated aortic strip and isolated bronchial smooth muscle illustrating two distinct rank orders of potencies respectively for α and β adrenergic receptors

Table 9.1: Differences between α and β adrenergic receptors

	α	β
1. Rank order of potency of agonists	*Adr > NA > Iso	Iso > Adr > NA
2. Antagonist	Phentolamine	Propranolol
3. Coupling protein	Gq/Gi/Go	Gs
4. Effector pathway	IP_3/DAG↑, cAMP ↓, K^+ channel ↑	cAMP↑, Ca^{2+} channel ↑

* Though inherently NA is equipotent to Adr on □ receptors, in test systems with intact neuronal reuptake, it appears less potent due to faster reuptake.

On the basis of relative organ specificity of selective agonists and antagonists, the β receptors were further subdivided into β_1 and β_2 subtypes. Later, β_3 (atypical β) receptors were described which are more sensitive to NA than to Adr, and have very low affinity for the classical β blockers. The β_3 receptors are located on adipocytes, mediate lipolysis and induce thermogenesis. Selective β_3 agonists have been investigated as antiobesity drugs. Another location of β_3 receptors is on detrusor muscle of urinary bladder; activation causing relaxation. A relatively β_3 selective agonist *mirabegron* has been recently found useful in the symptomatic treatment of overactive bladder by relaxing the detrusor muscle.

Table 9.2: Differences between β_1, β_2 and β_3 receptors

	β_1	β_2	β_3
1. Location	Heart, JG cells in kidney	Bronchi, blood vessels, uterus, liver, g.i.t., urinary tract, eye	Adipose tissue, Detrusor muscle of bladder
2. Selective agonist	Dobutamine	Salbutamol, terbutalin	Mirabegron
3. Selective antagonist	Metoprolol, Atenolol	ICI 118551 α-methyl propranolol	CGP 20712A (also β_1) ICI 118551 (also β_2)
4 Relative potency of NA and Adr	Adr ≥ NA	Adr >> NA	NA > Adr

In the mid 1970s the α receptors were demonstrated to be present prejunctionally as well. To differentiate these release inhibitory prejunctional α receptors, a subdivision into α_1 and α_2 was suggested. However, the present classification into α_1 and α_2 is based on pharmacological criteria (selectivity of agonists and antagonists) and not on anatomical location. Thus, α_2 receptors are located prejunctionally as well as postjunctionally in certain tissues. The vascular smooth muscle cells express both α_1 and α_2 receptors, and NA causes vasoconstriction by activating both subtypes. Molecular cloning has further identified 3 subtypes of α_1 (α_{1A}, α_{1B}, α_{1D}) and 3 subtypes of α_2 (α_{2A}, α_{2B}, α_{2C}) receptors.

Though tissue distribution of subtypes of α_1 and α_2 receptors has been mapped, there is lot of overlap. Sufficiently subtype selective agonists or antagonists have also not yet been developed to pharmacologically exploit the molecular heterogeneity of subtypes of α_1 and α_2 receptors.

The adrenergic neuronal mechanisms and action of drugs which modify them are depicted in Fig. 9.4. A summary of drugs acting through adrenergic neuronal mechanisms is presented in Table 9.4

Table 9.3: Differences between α_1 and α_2 receptors

	α_1	α_2
Location	Postjunctional on effector organs	Prejunctional on nerve ending (α_{2A}), also postjunctional in brain, pancreatic β cells and extrajunctional in certain blood vessels, platelets
Function subserved	GU Smooth muscle–contraction Vasoconstriction Gland—secretion Gut—relaxation	Inhibition of transmitter release Vasoconstriction Decreased central sympathetic flow Decreased insulin release Platelet aggregation
Selective agonist	Phenylephrine	Clonidine
Selective antagonist	Prazosin	Yohimbine, Rauwolscine
Coupling protein	Gq	Gi/Go
Effector pathway	IP_3/DAG ↑ Phospholipase A_2 ↑—PG release	cAMP ↓ K^+ channel ↑ Ca^{2+} channel ↓ or ↑ IP_3/DAG ↑

GU: Genitourinary

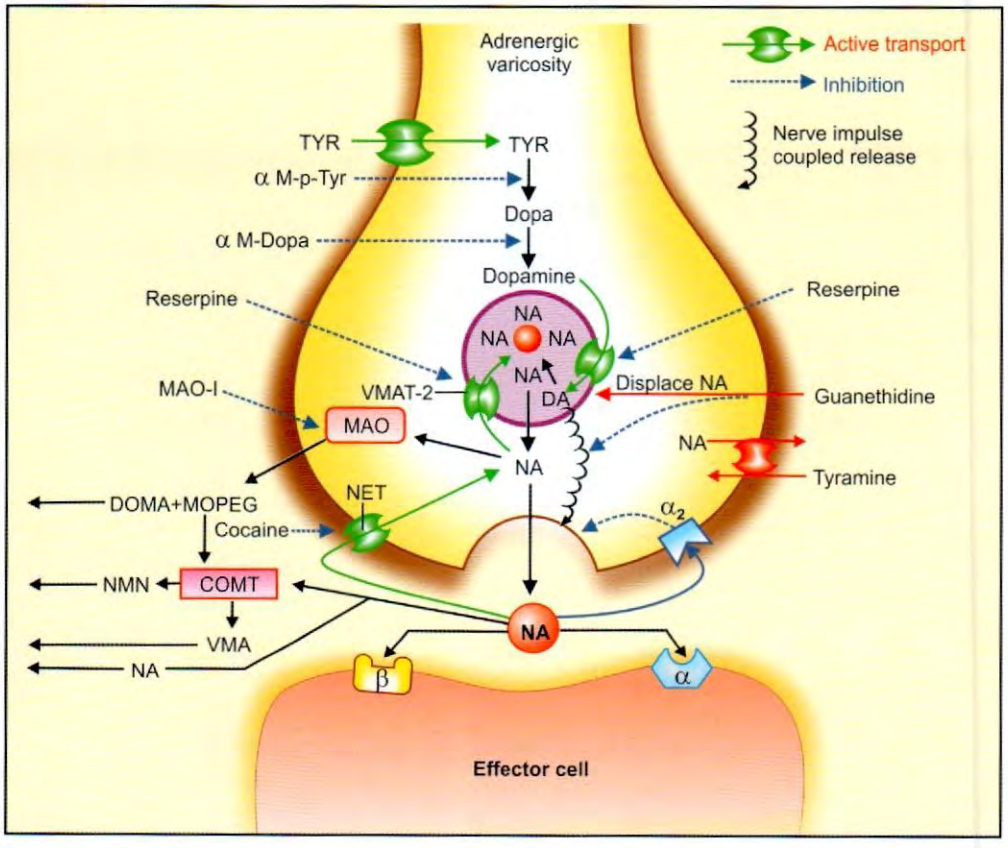


Fig. 9.4: Schematic representation of adrenergic neurotransmission and its modification by drugs
TYR—tyrosine; α M-p-Tyr—α methyl-p-tyrosine; α M-Dopa—α methyl dopa; MAO—monoamine oxidase; MAOI—monoamine oxidase inhibitor; COMT—catechol-o-methyl transferase; NMN—nor-metanephrine; VMA—vanillyl mandelic acid; NET—Norepinephrine transporter; VMAT-2—Vesicular monoamine transporter; DOMA—3,4 dihydroxy mandelic acid; MOPEG—3-Methoxy,4-hydroxy phenyl glycol.

Table 9.4: Summary of drug action through modification of adrenergic transmission

Step/site	*Action*	*Drug*	*Response*
1. Synthesis of NA	Inhibition Utilisation of same synthetic pathway	α-methyl-p-tyrosine α-methyl dopa	Depletion of NA Replacement of NA by α-methyl NA (false transmitter)
2. Axonal reuptake	Blockade	Cocaine, desipramine, guanethidine	Potentiation of NA (endo-and exogenous), inhibition of tyramine action
3. Vesicular reuptake	Blockade	Reserpine	Depletion of NA (degraded by MAO)
4. Nerve impulse coupled release of NA	Inhibition	Guanethidine, bretylium	Loss of adrenergic transmission
5. Neuronal NA pool	Exchange diffusion	Tyramine, amphetamine	Indirect sympathomimetic
6. Metabolism	MAO-inhibition MAO-A inhibition MAO-B inhibition COMT inhibition	Nialamide, tranylcypromine Moclobemide Selegiline Tolcapone, entacapone	Potentiation of NA (slight), —of tyramine (marked) Potentiation (slight) of NA and tyramine Potentiation of DA in brain Potentiation of NA and DA (slight)
7. Receptors	Mimicking Blockade	Phenylephrine Clonidine Isoprenaline Dobutamine Salbutamol Phentolamine Prazosin Yohimbine Propranolol Metoprolol	α_1 sympathomimetic α_2–inhibition of NA release, ↓ sympathetic outflow $\beta_1 + \beta_2$ —sympathomimetic β_1—sympathomimetic: cardiac stimulation β_2—sympathomimetic: bronchodilatation $\alpha_1 + \alpha_2$—blockade α_1—blockade α_2—blockade $\beta_1 + \beta_2$—blockade β_1—blockade

ADRENERGIC DRUGS (Sympathomimetics)

These are drugs with actions similar to that of Adr or that of sympathetic stimulation. They can be divided into:

Direct sympathomimetics These are drugs which act directly as agonists on α or β or both α and β adrenoceptors, e.g. Adr, NA, isoprenaline (Iso), phenylephrine, methoxamine, xylometazoline, salbutamol and many others.

Indirect sympathomimetics These drugs act on adrenergic neurone to release NA, which then acts on the adrenoceptors, e.g. tyramine, amphetamine.

Mixed action sympathomimetics These drugs act directly as well as indirectly—ephedrine, mephentermine.

ACTIONS

The peripheral actions of Adr in most tissues have been clearly differentiated into those

Table 9.5: Adrenergic responses mediated through α and β receptors

α actions	β actions
1. Constriction of arterioles and veins → rise in BP ($\alpha_1 + \alpha_2$)	Dilatation of arterioles and veins → fall in BP (β_2)
2. Heart—little action	Cardiac stimulation (β_1), ↑ rate, force and conduction velocity
3. —	Bronchodilatation (β_2)
4. Contraction of radial muscles of iris → mydriasis (α_1), decreased aqueous secretion	No effect on iris, slight relaxation of ciliary muscle, Enhanced aqueous secretion
5. Intestinal relaxation, contraction of sphincters	Intestinal relaxation (β_2)
6. Bladder trigone, prostate—contraction (α_1)	Detrusor—relaxation (β_2, β_3)
7. Uterus—contraction (α_1)	Relaxation (β_2)
8. Splenic capsule—contraction (α_1)	Relaxation (β_2) (slight)
9. Neuromuscular transmission facilitated, ↑ ACh release	Active state—prolonged in fast contracting muscle, abbreviated in slow contracting muscle; tremors (β_2)
10. Insulin secretion inhibited (α_2) (dominant)	Augmented insulin (mild) and glucagon secretion (β_2)
11. —	Liver—glycogenolysis (β_2) → hyperglycaemia Muscle—glycogenolysis (β_2) → hyperlactacidaemia Fat—lipolysis ($\beta_1 + \beta_2 + \beta_3$) → increased blood FFA, calorigenesis
12. —	Renin release from kidney (β_1)
13. Male sex organs—ejaculation (α_1)	—
14. Salivary gland—K^+ and water secretion (α_1)	Ptylin secretion
15. —	ADH secretion from posterior pituitary (β_1)
16. Adrenergic nerve—inhibits NA release terminals	Facilitates NA release (mild action)

mediated by α or β receptors depending on the predominant receptor type present in a given tissue. These are tabulated in Table 9.5. The receptor subtype, wherever defined, has been mentioned in parenthesis. The actions of a particular sympathomimetic amine depend on its relative activity at different types of adrenergic receptors.

Adr : $\alpha_1 + \alpha_2 + \beta_1 + \beta_2$ and weak β_3 action
NA : $\alpha_1 + \alpha_2 + \beta_1 + \beta_3$ but no β_2 action
Iso : $\beta_1 + \beta_2 + \beta_3$ but no α action

Important actions of Adr, NA and isoprenaline are compared in Table 9.6.

The overall actions are—

1. Heart Adr increases heart rate by enhancing the pacemaker activity of SA node. The slope of slow diastolic depolarization of cells in the SA node is increased. Adr also activates latent pacemakers in A-V node and Purkinje fibres. As a result arrhythmias can occur with high doses that raise BP markedly. Raised BP reflexly depresses the SA node and unmasks the latent pacemakers. Certain anaesthetics (chloroform, halothane) sensitize the heart to arrhythmic action of Adr. Idioventricular rate is increased in patients with complete heart block.

Force of cardiac contraction is increased. Development of tension as well as rate of relaxation is accelerated. Thus, systole is shortened more than diastole. Cardiac output and oxygen consumption of the heart are markedly enhanced.

Conduction velocity through A-V node, bundle of His, atrial and ventricular fibres is increased; partial A-V block may be overcome. Refractory period (RP) of all types of cardiac

Table 9.6: Comparative effects of intravenous infusion of adrenaline, noradrenaline and isoprenaline

	Adr	*NA*	*Iso*
1. Heart rate	↑	↓	↑↑
2. Cardiac output	↑↑	–	↑↑
3. BP—Systolic	↑↑	↑↑	↑
Diastolic	↓↑	↑↑	↓↓
Mean	↑	↑↑	↓
4. Blood flow			
Skin and mm	↓	↓	–
Sk. muscle	↑↑	–, ↓	↑
Kidney	↓	↓	–
Liver	↑↑	–	↑
Coronary	↑	↑	↑
5. Bronchial muscle	↓↓	–	↓↓
6. Intestinal muscle	↓↓	↓	↓
7. Blood sugar	↑↑	–, ↑	↑

cells is abbreviated. All cardiac actions are predominantly β_1 receptor mediated.

When BP rises markedly, reflex bradycardia occurs due to stimulation of vagus. Noradrenaline injected i.v. usually elicits bradycardia by this mechanism.

2. Blood vessels Both vasoconstriction (α) and vasodilatation (β_2) can occur depending on the drug, its dose and the vascular bed. Constriction predominates in cutaneous, mucous membrane and renal beds. Vasoconstriction occurs through both α_1 and α_2 receptors. However, location of α_2 (extrajunctional) receptors is such that they are activated only by circulating CAs, whereas α_1 (junctional) receptors primarily mediate responses to neuronally released NA. Vasodilatation predominates in skeletal muscles, liver and coronaries. The direct effect on cerebral vessels is not prominent—blood flow through this bed parallels change in BP.

The action of adrenergic drugs is most marked on arterioles and precapillary sphincters; larger arteries and veins are affected at higher doses.

3. BP The effect depends on the amine, its dose and rate of administration.

- NA causes rise in systolic, diastolic and mean BP; it does not cause vasodilatation (no β_2 action), peripheral resistance increases consistently due to α action.
- Isoprenaline causes rise in systolic but marked fall in diastolic BP (β_1—cardiac stimulation, β_2— vasodilatation). The mean BP generally falls.
- Adr given by slow i.v. infusion or s.c. injection causes rise in systolic but fall in diastolic BP; peripheral resistance decreases because vascular β_2 receptors are more sensitive than α receptors. Mean BP generally rises. Pulse pressure is increased.
- Rapid i.v. injection of Adr (in animals) produces a marked increase in both systolic as well as diastolic BP (at high concentration α response predominates and vasoconstriction occurs even in skeletal muscles). The BP returns to normal within a few minutes and a secondary fall in mean BP follows. The mechanism is—rapid uptake and dissipation of Adr → concentration around the receptor is reduced → low concentrations are not able to act on α receptors but continue to act on β_2 receptors.

When an α blocker has been given, only fall in BP is seen which was first described by Dale, and is called *vasomotor reversal of Dale.*

4. Respiration Adr and isoprenaline, but not NA are potent bronchodilators (β_2). This

action is more marked when the bronchi are constricted. Adr given by aerosol additionally decongests bronchial mucosa by α action. Adr can directly stimulate respiratory centre (RC) but this action is seldom manifest at clinically used doses. Rapid i.v. injection (in animals) causes transient apnoea due to reflex inhibition of RC. Toxic doses of Adr cause pulmonary edema by shifting blood from systemic to pulmonary circuit.

5. Eye Mydriasis occurs due to contraction of radial muscles of iris (α_1), but this is minimal after topical application, because Adr penetrates cornea poorly. The intraocular tension tends to fall, especially in wide angle glaucoma.

Adr has complex effects on aqueous humor dynamics (*see* p. 168).

Action of adrenaline on aqueous humor dynamics

Receptor		*Agonist action*
α_1	:	Vasoconstriction of ciliary vessels → reduced aqueous formation
α_2	:	Reduced secretory activity of ciliary epithelium
?α	:	Augmentation of uveo-scleral outflow
β_2	:	Enhanced secretory activity of ciliary epithelium Facilitation of trabecular outflow

Overall, aqueous formation is reduced and outflow is facilitated.

6. GIT In isolated preparations of gut, activation of both α and β receptors produces relaxation. In intact animals and man peristalsis is reduced and sphincters are constricted, but the effects are brief and of no clinical import.

7. Bladder, prostate, vas deferens Detrusor is relaxed (β_2, β_3) and trigone is constricted (α_1): both actions tend to oppose bladder voiding. The tone of prostatic muscle is increased by activation of α_1 receptors. Rhythmic contractions of vas deferens and seminal vesicles which participate in ejaculation are also mediated through α_1 receptors.

8. Uterus Adr can both contract and relax uterine muscle, respectively through α and β receptors. The overall effect varies with species, hormonal and gestational status. Human uterus is relaxed by Adr at term of pregnancy, but at other times, its concentrations are enhanced.

9. Splenic capsule Contracts (α) and more RBCs are poured in circulation. This action is not evident in man.

10. Skeletal muscle Neuromuscular transmission is facilitated. In contrast to action on autonomic nerve endings, α receptor activation on motor nerve endings augments ACh release, probably because it is of the α_1 subtype. The direct effect on muscle fibres is exerted through β_2 receptors and differs according to the type of fibre. The active state is abbreviated and less tension is developed in the slow contracting red fibres. There is incomplete fusion of individual responses. This along with enhanced firing of muscle spindles is responsible for the tremors produced by β_2 agonists. The action on rapidly contracting white fibres is to prolong the active state and increase the tension developed.

11. CNS Adr, in clinically used doses, does not produce any marked CNS effects because of poor penetration in brain, but restlessness, apprehension and tremor may occur. Activation of α_2 receptors in the brainstem (by selective α_2 agonists like clonidine) results in decreased sympathetic outflow → fall in BP and bradycardia.

12. Metabolic Adr causes glycogenolysis → hyperglycaemia, hyperlactacidaemia (β_2), as well as lipolysis → rise in plasma free fatty acid (FFA) and calorigenesis (β_2 + β_3). These are due to direct action on liver, muscle and adipose tissue cells. In addition metabolic effects result from reduction of insulin (α_2) and augmentation of glucagon (β_2) secretion.

Transient hyperkalaemia followed by hypokalaemia occurs due to initial release of K^+ from liver, and later its enhanced uptake into skeletal muscles as well as in liver.

Biochemical pathways of adrenergic responses

β actions The β actions are mediated through cAMP (*see* Fig. 4.6). Adr activates membrane bound enzyme *adenylyl cyclase* through a regulatory protein Gs → ATP is broken down to cAMP at the inner face. This in turn phosphorylates a number of intracellular

cAMP-dependent protein kinases and initiates a series of reactions:

(i) In *liver* and *muscle*, glycogen phosphorylase is activated causing glycogenolysis while glycogen synthase is inhibited. Both actions result in hyperglycaemia and hyperlactacidemia. Neoglucogenesis in liver adds to the hyperglycaemic response.

K^+ is first released from liver causing short-lasting hyperkalaemia. This is followed by more prolonged hypokalaemia due to K^+ uptake in muscle and later in liver as well.

(ii) In *adipose tissue*, triglyceride lipase is activated → increased plasma free fatty acids. Increased O_2 consumption and heat production result primarily by action on brown adipose tissue, which has predominant β_3 receptors.

(iii) In *heart*, proteins like troponin and phospholamban are phosphorylated. The former results in increased interaction with Ca^{2+} at the myofilaments → increased force of contraction; the latter causes sequestration of Ca^{2+} by sarcoplasmic reticulum → more rapid relaxation. The activated protein Gs, in addition, interacts directly with the Ca^{2+} channels in the membrane promoting influx of Ca^{2+} which reinforces the positive inotropic action exerted through cAMP.

(iv) In the *gut* and *bronchial muscle*, relaxation (accompanied with hyperpolarization) is induced, but the intermediate steps have not been clearly delineated.

(v) In *pancreatic islets* activation of β_2 receptors on α cells increases glucagon secretion, and that on β cells increases insulin secretion, both by raising intracellular cAMP. However, augmentation of insulin secretion is weak.

G-protein independent β receptor signaling and biased β receptor agonists

Continuous high rate activation causes desensitization of the β adrenergic receptors. An important mechanism of this desensitization is their interaction with an intracellular protein β-arrestin (β-arr) which prevents binding to Gs (*see* p.62). It has now been realized that the β-arr-β receptor complex, though incapable of generating G-protein mediated actions, can transduce qualitatively different responses through G-protein independent pathways. For example, normally excessive cardiac β_1 receptor activation produces cardiotoxic effects by increasing cardiac work load which play a role in the progression of CHF. However, activation of G-protein independent β_1 signaling has cardioprotective effect.

Attempts are now being made to produce β_1 agonists which will trigger only the β-arr mediated G-protein independent cardioprotective effects, and not the usual G-protein mediated cardiotoxic effects. Such agonists are being labeled '*Biased β receptor agonists*'.

α actions The pathways of α actions are varied and less well defined.

(i) In *smooth muscles* (including vascular) that are contracted through α_1 receptors, the activated Gq-protein increases IP_3/DAG production → mobilization of Ca^{2+} from intracellular organelle → activation of calmodulin dependent myosin light chain kinase → phosphorylation of myosin → contraction. The vasoconstrictor α_2 receptors probably enhance Ca^{2+} influx without utilizing IP_3.

(ii) The *prejunctional* α_2 receptor activates Gi-protein which then inhibits neuronal Ca^{2+} channels and also limits the intracellular availability of Ca^{2+} by decreasing cAMP production. Transmitter (NA) release is consequently diminished. Hyperpolarization through activation of G-protein gated K^+ channels may also occur.

(iii) In the *gut*, α_2 receptor activation hyperpolarizes the cholinergic neurone → decreased release of ACh → reduced tone; whereas α_1 receptors located directly on the smooth muscle cell increase K^+ efflux (by activating Ca^{2+} dependent K^+ channels) leading to hyperpolarization → relaxation.

(iv) In *pancreatic β cells*, stimulation of α_2 receptors reduces the formation of cAMP → decreased insulin release.

Administration and preparations

CAs are absorbed from the intestine but are rapidly degraded by MAO and COMT present in the intestinal wall and liver. They are thus orally inactive.

1. *Adrenaline (Epinephrine)* For systemic action, 0.2–0.5 mg s.c., i.m., action lasts ½ to 2 hrs. ADRENALINE 1 mg/ml inj; ADRENA 4 mg (of Adr. bitartrate=2mg Adr. base)/2 ml inj.

As local vasoconstrictor, 1 in 200,000 to 1 in 80,000 added to lidocaine;

in XYLOCAINE with ADRENALINE: lidocaine 21.3 mg + adrenaline 0.005 mg/ml inj; 30 ml vial. Lidocaine 2% with adrenaline 1:80,000 in 1.5 ml cartridge for dental anaesthesia.

2. *Noradrenaline (Norepinephrine, levarterenol)* It is administered only by slow i.v. infusion (2–4 μg/min). Local tissue necrosis occurs if the solution extravasates. Do not mix with $NaHCO_3$ in the same bottle, because rapid oxidation occurs at alkaline pH. The action of NA starts declining within 5 min of discontinuing infusion. Currently, NA is used as a pressor agent (along with volume replacement) only when strong vasoconstriction is required.

ADRENOR, NORAD, VASCUE, NORDRIN 2 mg (base)/2 ml amp.

3. *Isoprenaline (Isoproterenol)* 20 mg sublingual, 1–2 mg i.m., 5–10 μg/min i.v. infusion; action lasts 1–3 hrs. It is occasionally used to maintain idioventricular rate till pacemaker is implanted. For bronchial asthma, it has been superseded by selective β_2 agonists.

ISOPRIN, ISOSOL 4 mg/2 ml inj, NEOEPININE 20 mg sublingual tablets.

Adverse effects and contraindications

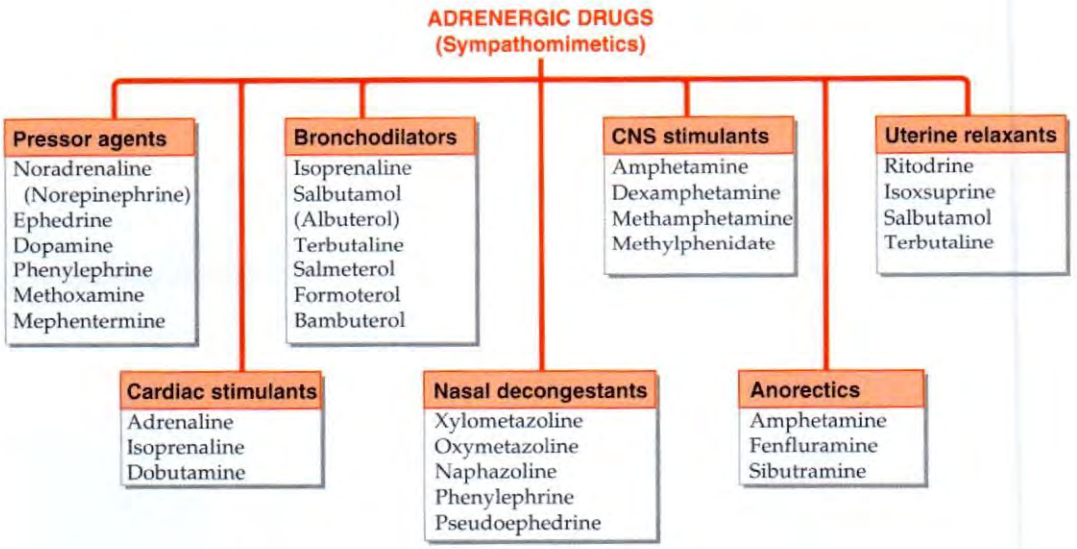
- Transient restlessness, headache, palpitation, anxiety, tremor and pallor may occur after s.c./i.m. injection of Adr.
- Marked rise in BP leading to cerebral haemorrhage, ventricular tachycardia/fibrillation, angina, myocardial infarction are the hazards of large doses or inadvertent i.v. injection of Adr.
- Adr is contraindicated in hypertensive, hyperthyroid and angina patients.
- Adr should not be given during anaesthesia with halothane (risk of arrhythmias) and to patients receiving β blockers (marked rise in BP can occur due to unopposed α action).

Salient features of important adrenergic drugs are described below.

Dopamine (DA) It is a dopaminergic (D1 and D2) as well as weaker adrenergic β_1 (but not β_2) + very weak α receptor agonist. The D1 receptors in renal and mesenteric blood vessels are the most sensitive: i.v. infusion of low dose of DA dilates these vessels (by raising intracellular cAMP). This increases g.f.r. In addition DA exerts natriuretic effect by D1 receptors on proximal tubular cells. Moderately higher doses produce a positive inotropic (direct β_1 and D1 action + that due to NA release), but little chronotropic effect on heart. Vasoconstriction (α_1 action) occurs only when large doses are infused. At doses normally employed, it raises cardiac output and systolic BP with little effect on diastolic BP. Effect on nonvascular α and β receptors is practically absent. Dopamine does not penetrate blood-brain barrier—no CNS effects.

Dopamine is used in patients of cardiogenic or septic shock and acute heart failure wherein it increases BP and urine outflow. It is administered by i.v. infusion (0.2–1 mg/min) which is regulated by monitoring BP and rate of urine formation.

DOPAMINE, INTROPIN, DOPACARD 200 mg in 5 ml amp; to be diluted and infused i.v.



SECTION 2

Dobutamine A derivative of DA, but not a D1 or D2 receptor agonist. Dobutamine acts mainly on β adrenergic receptors, and is a weak α agonist. The only prominent action of clinically employed doses (2–8 μg/kg/min i.v. infusion) is increased force of cardiac contraction and output, without significant change in peripheral resistance and BP. Compared to isoprenaline, increase in heart rate is less marked. As such, it is considered to be a relatively selective β_1 agonist. Dobutamine is used as an inotropic agent in pump failure accompanying myocardial infarction, cardiac surgery, and for short term management of severe congestive heart failure. It is less arrhythmogenic than Adr.

CRDIJECT 50 mg/4 ml and 250 mg per 20 ml amp, DOBUTREX, DOBUSTAT 250 mg vial.

Ephedrine It is a sympathomimetic alkaloid obtained from *Ephedra vulgaris* which mainly acts indirectly, but has some direct action as well on α and β receptors. Repeated injections produce tachyphylaxis, primarily because the neuronal pool of NA available for displacement is small. It is resistant to MAO, therefore, effective orally, but is about 100 times less potent than Adr, and longer acting (4–6 hours). Ephedrine crosses to brain and causes stimulation, but central: peripheral activity ratio is lower than that of amphetamine.

Ephedrine can be used for a variety of conditions, but lacks selectivity, and efficacy is low. Use is now restricted to that in mild chronic bronchial asthma and for hypotension during spinal anaesthesia, or occasionally for postural hypotension; 15–60 mg TDS.

EPHEDRINE HCl 15, 30 mg tab; SULFIDRIN 50 mg in 1 ml inj, in ENDRINE 0.75% nasal drops.

Amphetamines These are synthetic compounds having a pharmacological profile similar to ephedrine; orally active with relatively long duration (4–6 hours). They exert potent CNS stimulant and weaker peripheral cardiovascular actions. Maximal selectivity is exhibited by dextroamphetamine and methamphetamine, which in the usual doses produce few peripheral effects.

The central actions of amphetamines are largely mediated by release of NA from adrenergic

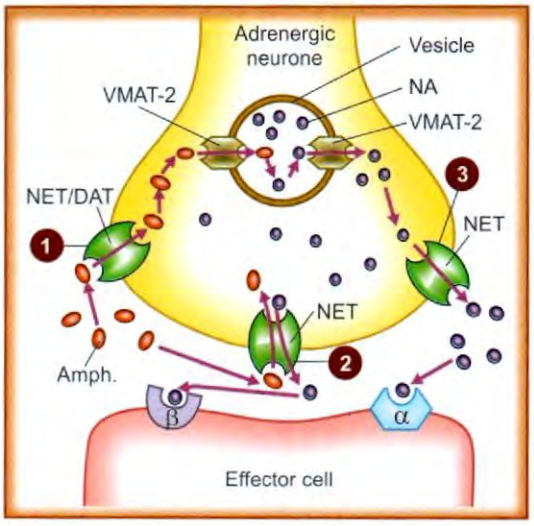


Fig. 9.5: Illustration of the mechanisms of noradrenaline release by amphetamine
Amphetamine (Amph) enters the adrenergic neurone by utilizing the neuronal norepinephrine transporter (NET) or dopamine transporter (DAT)-(1), and then the storage vesicles through vesicular monoamine transporter (VMAT2). It then displaces the stored noradrenaline (NA) into the neuronal cytoplasm, most of which is released into the synaptic cleft by exchange diffusion-(2) with extracellular Amph., or by reverse transport-(3), both utilizing NET. Note that this release is not exocytotic and does not require Ca^{2+}

neurones in the brain. This occurs mainly by *exchange diffusion* and *reverse transport* involving transporters like NET, DAT and VMAT2 as depicted in Fig. 9.5. However, the effects on locomotor activity, perception and the psychotic phenomena seen at high doses are probably due to DA and 5-HT release by processes similar to that for NA release. In addition, amphetamine inhibits neuronal reuptake of DA.

The central effects include alertness, increased concentration and attention span, postponement of sleep, euphoria, talkativeness, increased work capacity. Fatigue is allayed. Athletic performance is improved temporarily followed by deterioration. It is one of the drugs included in the 'dope test' for athletes. The reticular activating system is stimulated resulting in wakefulness and postponement of sleep deprivation induced physical disability. But this is short-lived and may be accompanied by anxiety,

restlessness, tremor, dysphoria and agitation. Use before examinations to keep awake can be counter-productive and needs to be discouraged.

Amphetamines stimulate respiratory centre, specially if it has been depressed. Hunger is suppressed as a result of inhibition of hypothalamic feeding centre. They also have weak anticonvulsant, analgesic and antiemetic actions: potentiate antiepileptics, analgesics and antimotion-sickness drugs. Peripheral effects on heart and BP are not significant at the usual doses (which cause only slight rise in BP), but tone of vesical sphincter is definitely increased.

Amphetamines are drugs of abuse. Abusers are generally teenagers seeking thrill or kick which is obtained on rapid i.v. injection. High doses produce euphoria, restlessness, insomnia, aggression, panic, marked excitement which may progress to mental confusion, delirium, hallucinations and an acute psychotic state. Peripheral component of toxicity includes rise in BP, palpitation, arrhythmias, vomiting, abdominal cramps and vascular collapse. Death is usually preceded by convulsions and coma.

Repeated use is more likely to produce long lasting behavioural abnormalities; psychosis may be precipitated. Though drug seeking behaviour is induced, withdrawal symptoms and dependence are not prominent.

Tolerance to central actions and toxic effects of amphetamine develops, and is both pharmacokinetic as well as pharmacodynamic. Starvation due to suppression of appetite produces acidic urine; amphetamine is ionized more at acidic pH and is excreted more rapidly.

Treatment of amphetamine toxicity includes administration of chlorpromazine which controls both central as well as peripheral α adrenergic effects.

Amphetamine: 5–15 mg oral; Dexamphetamine: 5–10 mg (children 2.5–5 mg) oral.

Methamphetamine: 5–10 mg oral.

Phenylephrine It is a selective α_1 agonist, with negligible β action. It raises BP by causing vasoconstriction. Because it has little cardiac action, reflex bradycardia is prominent. Topically it is used as a nasal decongestant and in the eye for producing mydriasis when cycloplegia is not required. Phenylephrine tends to reduce intraocular tension by constricting ciliary body blood vessels. Because it is orally active with longer duration of action (4–6 hours), it is also a constituent of orally administered nasal decongestant preparations. However, its FDCs with paracetamol and caffeine or with chlorpheniramine, paracetamol and dextromethorphan are banned in India. Central effects are not seen with usual clinical doses.

Dose: 2–5 mg i.m., 0.1–0.5 mg slow i.v. inj, 30–60 μg/min i.v. infusion; 5–10 mg oral; 0.25–0.5% nasal instillation; 5–10% topically in eye;

FRENIN 10 mg in 1 ml inj; DECOLD PLUS 5 mg with paracetamol 400 mg + chlorpheniramine 2 mg + caffeine 15 mg tab., SINAREST 10 mg with chlorpheniramine 2 mg, paracetamol 500 mg, caffeine 30 mg tab, FENOX 0.25% with nephazoline 0.025% nasal drops, DROSYN 10% eye drops, in DROSYN-T, TROPAC-P 5% with tropicamide 0.8% eye drops, in PHENIL eye drop 0.12% with chlorpheniramine 0.2% eye drops.

Methoxamine Another selective α_1 agonist with no β actions (has weak β blocking action). Resembles phenylephrine very closely. Occasionally used as a pressor agent.

Dose: 10–20 mg i.m.; 3–5 mg slow i.v. inj.

VASOXINE 20 mg/ml inj.

Mephentermine It produces both cardiac stimulation and vasoconstriction by directly activating α and β adrenergic receptors as well as by releasing NA. Cardiac output, systolic and diastolic BP are increased. The direct positive chronotropic effect on heart is generally counter balanced by vagal stimulation due to rise in mean BP.

Mephentermine is not a substrate for either MAO or COMT. Therefore it is active orally with longer duration of action (2–6 hr). It crosses blood-brain barrier to some extent—may produce excitatory effects at higher doses. It is used to prevent and treat hypotension due to spinal anaesthesia and surgical procedures, shock in myocardial infarction and other hypotensive states.

Dose: 10–20 mg oral/i.m., also by slow i.v. infusion.

MEPHENTINE 10 mg tab, 15 mg in 1 ml amp, 30 mg/ml in 10 ml vial, TERMIN 30 mg/ml in 10 ml vial.

SELECTIVE β_2 STIMULANTS

These include, salbutamol, terbutaline, salmeterol, formoterol and ritodrine. They cause bronchodilatation, vasodilatation and uterine relaxation, without producing significant cardiac stimulation. However, β_2 selectivity is only relative. Salbutamol has β_2:β_1 action ratio of about 10. They are primarily used in bronchial asthma (for description *see* Ch. 16). Other uses are:

- As uterine relaxant to delay premature labour. Ritodrine is sometimes used as the preferred drug (*see* Ch. 23);
- In familial hyperkalaemic periodic paralysis—β_2 agonists benefit by enhancing K^+ uptake into muscles, thereby lowering plasma K^+ levels.

The most important side effect of selective β_2 agonists is muscle tremor, while tachycardia and arrhythmias are less likely.

Isoxsuprine It is an orally effective long-acting β receptor stimulant which has direct smooth muscle relaxant property as well. It has been used as uterine relaxant for threatened abortion and dysmenorrhoea, but efficacy is poor. Though indicated in peripheral vascular diseases, actual benefits are disappointing.
Side effects: nausea, tachycardia, flushing, hypotension, dizziness, tremor.

Dose: 5–10 mg oral or i.m. 4–6 hourly,

DUVADILAN 10 mg tab, 40 mg SR cap, 10 mg/2 ml inj.

NASAL DECONGESTANTS

These are α agonists which on topical application as dilute solution (0.05–0.1%) produce vasoconstriction in the nasal mucosa which primarily expresses α receptors. The imidazoline compounds—naphazoline, xylometazoline and oxymetazoline are relatively selective α_2 agonist (like clonidine). They have a longer duration of action (12 hours) than ephedrine. After-congestion in nasal mucosa is claimed to be less than that with ephedrine or phenylephrine. They may cause initial stinging sensation (specially naphazoline). Regular use of these agents for long periods should be avoided because mucosal ciliary function is impaired: atrophic rhinitis and anosmia can develop due to persistent vasoconstriction. These drugs can be absorbed from the nose and produce systemic effects, mainly CNS depression and rise in BP. Nasal decongestants should be used cautiously in hypertensives and in those receiving MAO inhibitors.

Xylometazoline: 0.05–0.1% topical in nose; OTRIVIN 0.05% (pediatric), 0.1% (adult) nasal drops and nasal spray, OTRINOZ 0.025%, 0.05% and 0.1% nasal drops.

Oxymetazoline: 0.025–0.05% topical in nose; NASIVION, SINAREST 0.025% (pediatric), 0.05% nasal drops, RHINOJET 0.05% nasal spray.

Naphazoline: 0.1% topical in nose; PRIVINE 0.1% nasal drops.

Pseudophedrine An enantiomer of ephedrine which causes vasoconstriction, especially in mucosae and skin, but has fewer CNS and cardiac effect, and is a poor bronchodilator. Combined with antihistaminics, mucolytics, antitussives and analgesics in FDCs, it is believed to afford symptomatic relief in common cold, allergic rhinitis, blocked eustachian tubes and upper respiratory tract infections. Its FDC with cetirizine and paracetamol has been recently banned in India. Because of diversion of pseudoephedrine to manufacture methamphetamine for illicit trade as a drug of abuse, its marketing has been restricted globally.

ANORECTIC AGENTS

Though amphetamines suppress appetite, their use as anorectic agents is precluded by their adverse central effects. A number of related drugs were developed which inhibit feeding centre (like amphetamine) but have little/no CNS stimulant action or abuse liability. All of them act by releasing (reverse transport) or by inhibiting the reuptake of NA/DA or 5-HT, thus enhancing monoaminergic transmission in the brain. Accordingly they may be grouped into:

Noradrenergic agents: Phentermine, phenylpropanolamine (PPA), diethylpropion, mazindol.

Serotonergic agents: Fenfluramine, dexfenfluramine.

Noradrenergic + serotonergic agent: Sibutramine.

Fenfluramine and dexfenfluramine were extensively used by slimming centres, though tolerance to the anorectic action developed in 2–3 months. In the late 1990s echocardiographic abnormalities, valvular defects, pulmonary hypertension and sudden deaths were related to their use, and these drugs are now banned in most countries.

Sibutramine and R-Sibutramine Introduced subsequently, these drugs caused weight loss in obese people and were routinely used by slimming centres. Several side effects were noted; serious adverse reactions, including cardiovascular events and death were reported to the US-FDA and drug committees in Europe leading to ban on their

use. After its own assessment, India has also banned these drugs from March 2011.

Thus, currently no sympathomimetic anorectic drug is approved for use.

THERAPEUTIC USES

1. Vascular uses

- *Shock/acute hypotension* Shock may be due to haemorrhage, volume depletion (severe diarrhoea, vomiting, burn, etc.), cardiogenic (myocardial infarction, arrhythmias, etc.), anaphylactic, neurogenic (in trauma, drug overdose, etc.) or septic (gram negative bacteraemia, severe infection). It is a medical emergency. Urgent measures are directed to restoring and maintaining blood pressure and perfusion of vital organs. Volume replacement and treatment of the underlying cause are the primary modalities. However, rapid volume replacement may worsen cardiogenic shock and precipitate pulmonary edema. Continuously monitored i.v. infusion of sympathomimetic pressor agents like mephentermine, phenylephrine or noradrenaline is often used as an expedient measure to elevate very low BP and maintain cerebral circulation. The risk in the use of vasoconstrictor is that while raising BP they may also reduce perfusion of kidney and other vital organs.

  Use of inotropic sympathomimetic drugs in cardiogenic shock is tricky, because they may increase cardiac workload. Dopamine increases cardiac contractility without causing significant tachycardia. It also improves renal blood flow and may help to raise BP. Dobutamine has relatively more selective inotropic effect. Adrenaline 0.5 mg injected i.m. promptly is the drug of choice in anaphylactic shock (*see* p. 97). It not only raises BP, but also counteracts bronchospasm and laryngeal edema that may accompany. Because of this profile of action as well as rapidity of onset, Adr is the only life saving measure.

  Acute hypotension attending spinal/epidural anaesthesia, drug overdose and neurogenic shock is due to loss of sympathetic vasoconstrictor tone. It is treated by fluid infusion, elevation of legs, oxygen inhalation and monitored i.v. infusion of a sympathomimetic like mephentermine or ephedrine, which cause vasoconstriction as well as counteract bradycardia.
- *Persistent/postural hypotension* The most important cause of persistent low BP and postural hypotension is autonomic neuropathy which is common in diabetics, elderly people or may be idiopathic. Oral sympathomimetics like ephedrine or mephentermine may be used, but are not entirely satisfactory, because they cannot mimic the reflex vasoconstriction that normally operates to compensate for change of posture. Adequate hydration, electrolyte balance and use of elastic stockings may be helpful. Oral fludrocortisone may benefit in case of chronic adrenal insufficiency. Hypotension due to medications like α_1 blockers (used for urinary obstruction in prostatic hypertrophy), antihypertensive drugs, tricyclic antidepressants, neuroleptics, etc. should be treated by withholding/changing the drug or adjusting its dose.
- *Along with local anaesthetics* Adr 1 in 200,000 to 1 in 80,000 for infiltration, nerve block and spinal anaesthesia. Duration of anaesthesia is prolonged and systemic toxicity of the local anaesthetic is reduced. Local bleeding is minimised (*see* Ch. 26).
- *Control of local bleeding* From skin and mucous membranes, e.g. epistaxis, surgery/trauma related bleeding: compresses of Adr 1 in 10,000 or phenylephrine 1% soaked in cotton can control arteriolar and capillary bleeding. Noradrenaline 8 mg in 100–200 ml saline put in stomach through a tube can control bleeding from gastric erosions and stress ulcers.
- *Nasal decongestant* In colds, rhinitis, sinusitis, blocked nose or eustachian tube—one of the α-agonists is used as nasal drops. Shrinkage of mucosa provides relief, but after-congestion when action wears off, and

atrophy of mucosa on prolonged use are still a problem. The imidazolines should be used in lower concentrations in infants and young children, because children are more sensitive to central effects of these drugs. Nasal decongestants should be used very cautiously in hypertensive patients and in elderly males.

Pseudoephedrine and phenylephrine have been used orally as decongestants, but effective doses will constrict other blood vessels as well and cause rise in BP. Many oral FDCs containing these decongestants have been recently banned in India. However, oral vasoconstrictors do not produce after-congestion.

(v) *Peripheral vascular diseases* (like Buerger's disease, Raynaud's phenomena, diabetic vascular insufficiency, gangrene, frost bite, ischaemic ulcers, night leg cramps, cerebral vascular inadequacy) Vasodilators including isoxsuprine have been used, but are far from satisfactory, because in most cases the capacity of the affected vessels to dilate is severely limited, and ischaemia itself is a potent vasodilator.

2. Cardiac uses

- *Cardiac arrest* Adrenaline may be used to stimulate the heart in case of cardiac arrest due to drowning, electrocution, Stokes-Adams syndrome and other causes. Intravenous administration is justified in this setting with external cardiac massage. For i.v. injection, the 1 in 1000 solution of Adr should be diluted 10 times and slowly injected into jugular vein (or another central vein) and flushed with 20 ml saline to reach the heart in the absence of circulation.
- *Partial or complete A-V block* Isoprenaline may be used as temporary measure to maintain sufficient ventricular rate.
- *Congestive heart failure (CHF)* Adrenergic inotropic drugs are not useful in the routine treatment of CHF. However, controlled short term i.v. infusion of DA/dobutamine can tide over acute cardiac decompensation during myocardial infarction, cardiac surgery and in resistant CHF (*see* Ch. 38).
- *Dobutamine stress test* In patients unable to perform physical exercise (elderly patients or those with osteoarthritis of knee/hip) cardiac stress testing to expose ischaemic areas of the myocardium is accomplished by inducing cardiac stress pharmacologically with dobutamine. Dobutamine is infused i.v. at increasing rate to elicit peak cardiac workload, and ischaemic areas are mapped echocardiographically.

3. Bronchial asthma and COPD Adrenergic β_2 stimulants are the primary drugs for relief of reversible airway obstruction (*see* Ch. 16).

4. Allergic disorders Adr is a physiological antagonist of histamine which is an important mediator of many acute hypersensitivity reactions. It affords quick relief in urticaria, angioedema and is life saving in laryngeal edema or anaphylaxis (*see* p. 97). The vasoconstrictor, cardiac stimulant and bronchodilator actions of Adr contribute to its salutary effects. It is ineffective in delayed, retarded and other types of allergies.

5. Ocular uses Phenylephrine (5–10%) dilates the pupil, and is used to facilitate fundus examination, since cycloplegia is not required for this purpose. Lower concentrations (0.1–0.2%) are utilized to decongest conjunctiva in allergic conjunctivitis. Adrenergic drugs also lower intraocular pressure. The ester prodrug of Adr, *dipivefrine* is occasionally used as adjunctive medication in open angle glaucoma. *Apraclonidine* and *brimonidine* are selective α_2 adrenoceptor agonists used as second line add on drugs for glaucoma to supplement ocular PG analogues/β blockers (*see* p. 168).

6. Central uses

(i) *Attention deficit hyperkinetic disorder (ADHD):* It is also called minimal brain dysfunction, and is usually detected in childhood. The sufferer is considered a 'hyperkinetic child' (*see* Ch. 35 also). Amphetamines have an apparently paradoxical effect to calm down hyperkinetic children. This disorder is recognized as a mild grade of mental retardation or a reduction in the ability to concentrate, i.e. the span of time for which attention can be focused on a subject is abbreviated. Amphetamines by increasing attention span

improve behaviour and performance in studies. The child becomes more amenable. However, growth retardation may occur due to reduction in appetite. The risk-benefit ratio of such therapy disfavours use of amphetamine.

Methylphenidate, an amphetamine-like drug which produces milder side effects and less growth retardation, and *atomoxetine* (*see* Ch. 35) a NA reuptake blocker with better tolerability profile, are now preferred for ADHD. However, only severe cases of ADHD, or those who do not improve with psychological intervention alone should be treated with CNS stimulant drugs. Tricyclic antidepressants are also beneficial.

(ii) *Narcolepsy* Narcolepsy is sleep occurring in fits. It is adequately controlled by amphetamines. Development of tolerance, abuse and behavioural abnormalities are the calculated risks of such therapy. *Modafinil*, a newer psychostimulant with fewer behavioral adverse effects and lower dependence inducing potential, is being preferred now (*see* Ch. 35). Imipramine-like drugs are also useful in some patients, and are safer.

7. Uterine relaxant Isoxsuprine has been used in threatened abortion and dysmenorrhoea, but efficacy is doubtful. Selective β_2 stimulants, especially ritodrine, infused i.v. has been successfully used to postpone labour but maternal morbidity and mortality may be increased due to its cardiac and metabolic actions and incidents of pulmonary edema. If at all used, calcium channel blockers are now preferred over sympathomimetics to postpone labour (*see* Ch. 23).

8. Insulin hypoglycaemia By its hyperglycaemic action, Adr. can rapidly reverse insulin hypoglycaemia, but it should be used only as an expedient measure, while i.v./oral glucose should be given as soon as possible. Glucagon, if available, is a preferable emergency measure, because Adr. has strong cardiovascular effects as well.

SECTION 2

☞ PROBLEM DIRECTED STUDY

9.1 A lady aged 55 years presented for eye checkup. She has been having visual difficulty over the past few months, and lately she had started noticing 'halos' around the lights. She also has dull chronic ache in the forehead region. Tonometry revealed her intraocular pressure (i.o.p.) to be 22 and 24 mm Hg respectively in the left and right eye.

(a) Which mydriatic will be suitable for dilating her pupil for fundus examination and why? (see Appendix-1 for solution)

Chapter 10 Antiadrenergic Drugs (Adrenergic Receptor Antagonists) and Drugs for Glaucoma

These are drugs which antagonize the receptor action of adrenaline and related drugs. They are competitive antagonists at α or β or both α and β adrenergic receptors, and differ in important ways from the "adrenergic neurone blocking drugs", which act by interfering with storage or release of adrenergic transmitter. These differences are given in Table 10.1.

α ADRENERGIC BLOCKING DRUGS

These drugs inhibit adrenergic responses mediated through the α adrenergic receptors without affecting those mediated through β receptors.

GENERAL EFFECTS OF α BLOCKERS

1. Blockade of vasoconstrictor α_1 (also α_2) receptors reduces peripheral resistance and causes pooling of blood in capacitance vessels → venous return and cardiac output are reduced → fall in BP. Postural reflex is interfered with → marked *hypotension* occurs on standing → dizziness and syncope. Hypovolemia accentuates the hypotension. The α blockers abolish the pressor action of Adr (injected i.v. in animals), which then produces only fall in BP due to β_2 mediated vasodilatation (also *see* p. 143). This was first demonstrated by Sir HH Dale (1913)

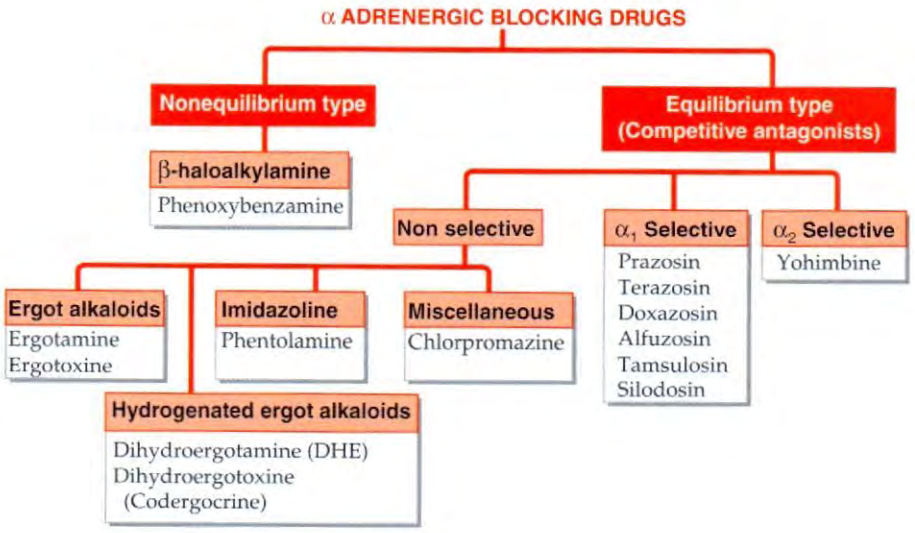


Table 10.1: Differences between antiadrenergic and adrenergic neurone blocking drugs

	Antiadrenergic drugs	*Adrenergic neurone blocking drugs*
1. Locus of action	Adrenergic receptors on effector cells or neurones	Adrenergic neuronal membrane or contents
2. Effects of adrenergic nerve stimulation	Blocked (less completely)	Blocked (more completely)
3. Effect of injected Adr	Blocked	Not blocked (may be potentiated)
4. Type of effects blocked by a single drug	Either α or β (except Labetalol and its congeners)	Sympathetic function decreased irrespective of the receptor type
5. Examples	α—Phentolamine β—Propranolol	Reserpine, Guanethidine, Bretylium, α-methyl-p-tyrosine

and is called *vasomotor reversal of Dale*. Pressor and other actions of selective α agonists (phenylephrine) are suppressed.

2. Reflex *tachycardia* occurs due to fall in mean arterial pressure and increased release of NA from cardiac sympathetic neurons due to blockade of presynaptic α_2 receptors.

3. *Nasal stuffiness* and *miosis* result from blockade of α receptors in nasal blood vessels and in radial muscles of iris respectively.

4. Intestinal motility is increased due to partial inhibition of relaxant sympathetic influences—loose motion may occur.

5. Hypotension produced by α blockers can reduce renal blood flow → g.f.r. is reduced and more complete reabsorption of Na^+ and water occurs in the tubules → *Na^+ retention* and *expansion of blood volume*. This is reinforced by reflex increase in renin release mediated through β_1 receptors.

6. Tone of smooth muscle in bladder trigone, sphincter and prostate is reduced by blockade of α_1 receptors (mostly of the α_{1A} subtype) → *urine flow in patients with* benign hypertrophy of prostate *(BHP) is improved.*

7. Contractions of vas deferens and seminal vesicles which result in ejaculation are coordinated through α receptors. As such, α blockers can *inhibit ejaculation*; this may manifest as *impotence.*

The α blockers have no effect on adrenergic cardiac stimulation, bronchodilatation, vasodilatation and most of the metabolic changes, because these are mediated predominantly through β receptors.

Apart from these common effects, most of which manifest as side effects, many α blockers have some additional actions. The pharmacological profile of an α blocker is mainly governed by its central effects and by the relative activity on α_1 and α_2 receptor subtypes. Only the distinctive features of individual α blockers are described below.

Phenoxybenzamine It is a halogenated alkylamine that cyclizes spontaneously in the body giving rise to a highly reactive ethyleniminium intermediate which reacts with α adrenoceptors and other biomolecules by forming strong covalent bonds. The α blockade is of nonequilibrium (irreversible) type and develops gradually (even after i.v. injection) and lasts for 3–4 days till fresh receptors are synthesized.

Partial blockade of 5-HT, histaminergic and muscarinic receptors, but not β adrenergic receptors, can be demonstrated at higher doses.

The fall in BP caused by phenoxybenzamine is mainly postural because venodilatation is more prominent than arteriolar dilatation. In recumbent subjects cardiac output and blood flow to many organs is increased due to reduction in peripheral resistance and increased venous return. It tends to shift blood from pulmonary to systemic circuit because of differential action on the two vascular beds. It also tends to shift fluid from extravascular to vascular compartment. Phenoxybenzamine is lipid soluble, penetrates brain, and on rapid i.v. injection it can produce CNS stimulation, nausea and vomiting. However, oral doses produce depression, tiredness and lethargy.

Major side effects are postural hypotension, palpitation, nasal blockage, miosis, inhibition of ejaculation.

Pharmacokinetics Oral absorption of phenoxybenzamine is erratic and incomplete; i.m. and s.c. injections are very painful—should not be given. Though most of the dose administered i.v. is excreted in urine in 24 hours, small amounts that have covalently reacted remain in tissues for long periods. Chronic administration leads to accumulation in adipose tissue.

Dose: 20–60 mg/day oral; 1 mg/kg by slow i.v. infusion over 1 hour.

Phenoxybenzamine is used primarily in pheochromocytoma, occasionally in peripheral vascular disease.

FENOXENE 10 mg cap, 50 mg/ml inj. BIOPHENOX 50 mg in 1 ml inj.

Natural and hydrogenated ergot alkaloids (*see* Ch. 12 and Ch. 21) Ergot alkaloids are the adrenergic antagonists with which Dale demonstrated the vasomotor reversal phenomenon. The amino acid alkaloids *ergotamine* and *ergotoxine* are partial agonist and antagonist at α adrenergic, serotonergic and dopaminergic receptors.

The amine alkaloid *ergometrine* has no α blocking activity.

The natural ergot alkaloids produce long lasting vasoconstriction which predominates over their α blocking action—peripheral vascular insufficiency and gangrene of toes and fingers occurs in ergotism. Ergotoxine is a more potent α blocker and less potent vasoconstrictor than ergotamine. Hydrogenation reduces vasoconstrictor and increases α blocking activity.

The α blockade produced by ergot alkaloids is low grade and clinically not useful. Their principal use is in migraine (*see* Ch. 12). Dihydroergotoxine has been used as a cognition enhancer (*see* Ch. 35).

Phentolamine This is a rapidly acting α blocker with short duration of action (in minutes). Because of nonselective α_1 and α_2 blockade, NA release is increased and tachycardia occurs. Venodilatation predominates over arteriolar dilatation. Phentolamine is used for diagnosis and intraoperative management of pheochromocytoma, as well as for control of hypertension due to clonidine withdrawal, cheese reaction, etc. It is the most suitable α blocker for local infiltration to counteract vasoconstriction due to extravasated NA/DA during their i.v. infusion.

Dose: 5 mg i.v. repeated as required;

REGITINE, FENTANOR 10 mg/ml inj.

Prazosin It is first of the highly selective α_1 blockers having $\alpha_1 : \alpha_2$ selectivity ratio 1000:1. All subtypes of α_1 receptor (α_{1A}, α_{1B}, α_{1D}) are blocked equally. It blocks sympathetically mediated vasoconstriction and produces fall in BP which is attended by only mild tachycardia, because NA release is not increased due to absence of α_2 blockade.

Prazosin dilates arterioles more than veins. Postural hypotension is less marked, but may occur in the beginning, causing dizziness and fainting as 'first dose effect'. This can be minimized by starting with a low dose and taking it at bedtime. Subsequently tolerance develops to this side effect due to haemodynamic adjustments. Other α blocking side effects (miosis, nasal stuffiness, inhibition of ejaculation) are also milder. For the above reasons, prazosin (also other α_1 blockers) has largely replaced phenoxybenzamine. Prazosin, in addition, inhibits phosphodiesterase which degrades cAMP. Increase in smooth muscle cAMP could contribute to its vasodilator action.

Prazosin is effective orally (bioavailability ~60%), highly bound to plasma proteins (mainly to α_1 acid glycoprotein), metabolized in liver and excreted primarily in bile. Its plasma t½ is 2–3 hours; effect of a single dose lasts for 6–8 hours.

Prazosin is primarily used as an antihypertensive (*see* Ch. 41). Other uses are in Raynaud's disease and benign hypertrophy of prostate (BHP). Prazosin blocks α_1 receptors in bladder trigone and prostatic smooth muscle, thereby improves urine flow, reduces residual urine in bladder.

PRAZOPRES 0.5, 1.0 and 2.0 mg tabs. Start with 0.5–1 mg at bedtime; usual dose 1–4 mg BD or TDS.

MINIPRESS XL: Prazosin GITS (gastrointestinal therapeutic system) 2.5 mg and 5 mg tablets; 1 tab OD.

Terazosin It is chemically and pharmacologically similar to prazosin; differences are higher oral bioavailability (90%) and longer plasma t½ (~12 hr); a single daily dose lowers BP over 24 hrs. Terazosin is more popular for use in BHP due to single daily dose and a probable

apoptosis promoting effect on prostate. This effect is unrelated to α_1 receptor blockade, but may retard the progression of prostatic hypertrophy.

HYTRIN, TERALFA, OLYSTER 1, 2, 5 mg tab; start with 1 mg OD, increase if required, usual maintenance dose 2–10 mg OD.

Doxazosin Another long acting (t½ 18 hr) congener of prazosin with pharmacological profile, similar to terazosin, including the apoptosis promoting effect on prostate. It is used in hypertension and BHP.

Dose: 1 mg OD initially, increase upto 8 mg BD;

DOXACARD, DURACARD, DOXAPRESS 1, 2, 4 mg tabs.

Alfuzosin This short acting (t½ 3–5 hours) congener of prazosin has been specifically developed for symptomatic treatment of BHP, though it is nonselective for α_{1A}, α_{1B} and α_{1D} subtypes. It is not approved as an antihypertensive. The metabolism of alfuzosin is inhibited by CYP34A inhibitors. Concurrent treatment with erythromycin, ketoconazole, ritonavir etc. is to be avoided.

Dose: 2.5 mg BD-QID or 10 mg OD as extended release (ER) tablet.

ALFUSIN, ALFOO 10 mg ER tab.

Tamsulosin This relatively uroselective α_{1A}/α_{1D} blocker (α_{1A} : α_{1B} affinity 7–38 fold) has been found as effective as terazosin in improving BHP symptoms, because α_{1A} subtype predominate in the bladder base and prostate. However, it lacks the prostatic apoptosis promoting property of terazosin and doxazosin. Tamsulosin does not cause significant changes in BP or HR at doses which relieve urinary symptoms, and it is not used as an antihypertensive. No increase in adverse cardiovascular events has been noted after prolonged use. Postural hypotension is infrequent, dizziness and retrograde ejaculation are the only significant side effects. Problem of floppy iris has been encountered during cataract surgery in patients taking tamsulosin.

Plasma t½ of tamsulosin is 6–9 hrs, but its modified release (MR) cap needs only once daily dosing. It may be a better tolerated α_1 blocker for BHP in patients who continue to suffer postural hypotension with terazosin/doxazosin.

CONTIFLO-OD 0.4 mg Cap, URIMAX, DYNAPRES 0.2, 0.4 mg MR cap; 1 cap (max 2) in the morning with meals. No dose titration is needed in most patients.

Silodosin Another selective α_{1A} blocker developed in Japan, which improves urine flow and relieves symptoms of BHP, but causes little change in BP. Incidence of postural hypotension is low. However, failure of ejaculation is frequent which can cause psychosexual distress. Oral bioavailability is ~30%. It is metabolized by glucuronidation and excreted in urine as well as in faeces. The t½ averages 13 hours.

Dose: 4–8 mg OD; RAPILIF, SILODAL 4, 8 mg caps.

Yohimbine An alkaloid from the West African plant *yohimbe*. It is a relatively selective α_2 blocker with short duration of action. It blocks 5-HT receptors as well. Heart rate and BP are generally elevated due to increased central sympathetic outflow as well as enhanced peripheral NA release. It may cause congestion in genitals and is considered to be an aphrodisiac. This effect is only psychological, but can overcome psychogenic impotence in some patients.

There are no valid indications for clinical use of yohimbine.

Chlorpromazine and some other neuroleptics have significant α adrenergic blocking activity—cause fall in BP, nasal stuffiness and inhibition of ejaculation as side effect.

USES OF α BLOCKERS

1. *Pheochromocytoma* It is a tumour of adrenal medullary cells. Excess CAs are secreted which can cause intermittent or persistent hypertension. Estimation of urinary CA metabolites (VMA, normetanephrine) is diagnostic. In addition, pharmacological tests can be performed.

Phentolamine test Inject phentolamine 5 mg i.v. over 1 min in recumbent subject. A fall in BP > 35 mm Hg systolic and/or > 25 mm Hg diastolic is indicative of pheochromocytoma. However, it is not very reliable, both false positive and false negative results are possible.

Therapeutic Surgical removal of the tumour is the firstline therapeutic approach. Phenoxybenzamine can be used as definitive therapy for inoperable and malignant pheochromocytoma. Prazosin is an alternative. When surgical removal of the tumour is contemplated, it is desirable to give phenoxybenzamine orally for 1–2 weeks preoperatively and infuse it i.v. during surgery. The rationale is:

- Due to excess circulating CAs blood volume is low (they shift fluid from vascular to

SECTION 2

extravascular compartment). Treatment with α blocker normalizes blood volume and distribution of body water.

- Handling of the tumour during surgery may cause outpouring of CAs in blood → marked rise in BP. This is prevented by phenoxybenzamine given pre and intraoperatively. Alternatively, phentolamine or sodium nitroprusside (a rapidly acting vasodilator) drip can be instituted during the operation.
- Removal of the tumour is often attended by marked fall in BP, because blood vessels dilate and the blood volume is low. This does not happen if volume has been restored before hand with the aid of an α blocker.

2. *Hypertension* α blockers other than those selective for α_1 (prazosin-like) have been a failure in the management of essential hypertension, because vasodilatation is compensated by cardiac stimulation. Moreover, postural hypotension, impotence, nasal blockage and other side effects produced by nonselective α blockers are unacceptable. However, phentolamine/phenoxybenzamine are of great value in controlling episodes of rise in BP during clonidine withdrawal and that due to cheese reaction in patients on MAO inhibitors.

3. *Benign hypertrophy of prostate (BHP)* The urinary obstruction caused by BHP has a static component due to increased size of prostate and a dynamic component due to increased tone of bladder neck/prostate smooth muscle. Two classes of drugs are available:

- α_1 adrenergic blockers (prazosin like): they decrease tone of prostatic/bladder neck muscles.
- 5-α reductase inhibitor (finasteride/dutasteride) which arrest growth/reduce size of prostate (*see* Ch. 21).

Since activation of α_1 adrenoceptors in bladder trigone, prostate and prostatic urethra increases smooth muscle tone, their blockade relaxes these structures, reducing dynamic obstruction, increasing urinary flow rate and causing more complete emptying of bladder in many patients of BHP.

Voiding symptoms (hesitancy, narrowing of stream, dribbling and increased residual urine) are relieved better than irritative symptoms like urgency, frequency and nocturia. The α_1 blockers afford faster (within 2 weeks) and greater symptomatic relief than finasteride which primarily affects static component of obstruction and has a delayed onset taking nearly six months for clinical improvement. The α_1 blockers do not affect prostate size, but are more commonly used. However, effects last only till the drug is given. Even with continued therapy, benefit may decline after few years due to disease progression. They may be used concurrently with finasteride.

Terazosin, doxazosin, alfuzosin and tamsulosin are the preferred α_1 blockers because of once daily dosing. There is some evidence that terazosin and doxazosin promote apoptosis in prostate. Tamsulosin appears to cause fewer vascular side effects because of relative α_{1A}/α_{1D} selectivity.

4. *Peripheral vascular diseases* α blockers do increase skin and to some extent muscle blood flow in normal individuals, but these drugs are largely disappointing in peripheral vascular diseases when obstruction is organic (Buerger's disease). However, when vasoconstriction is a prominent feature (Raynaud's phenomenon, acrocyanosis), good symptomatic relief is afforded by prazosin or phenoxybenzamine. Calcium channel blockers are also effective, and preferred by some due to fewer side effects.

5. *Papaverine/Phentolamine Induced Penile Erection (PIPE) therapy for impotence* In patients unable to achieve erection, injection of papaverine (3–20 mg) with or without phentolamine (0.5–1 mg) in the corpus cavernosum has been found to produce penile tumescence to permit intercourse. However, the procedure requires skill and training. Priapism occurs in 2–15% cases, which if not promptly treated leads to permanent damage. Priapism is reversed by aspirating blood from the corpus cavernosum or by injecting phenylephrine locally. Repeated injections can cause penile fibrosis. Other complications are—local haematoma, infection, paresthesia and penile deviation. Oral sildenafil is the preferred drug now, and PIPE therapy should be reserved for selected situations with proper facilities.

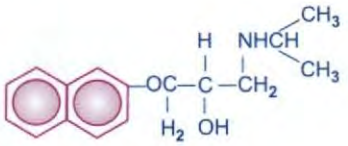
β ADRENERGIC BLOCKING DRUGS

These drugs inhibit adrenergic responses mediated through the β receptors.

The dichloro derivative of isoprenaline was the first compound found in 1958 to block adrenergic responses which could not be blocked till then by the available adrenergic antagonists. However, it was not suitable for clinical use. *Propranolol* introduced in 1963 was a therapeutic breakthrough. Since then, drugs in this class have proliferated and diversified.

All β blockers are competitive antagonists. Propranolol blocks β_1 and β_2 receptors, but has weak activity on β_3 subtype. It is also an inverse agonist: reduces resting heart rate as well. Some β blockers like metoprolol, atenolol, etc. preferentially block β_1 receptors, while few others have additional α_1 receptor blocking and/or vasodilator properties.

The pharmacology of propranolol is described as prototype.



PROPRANOLOL

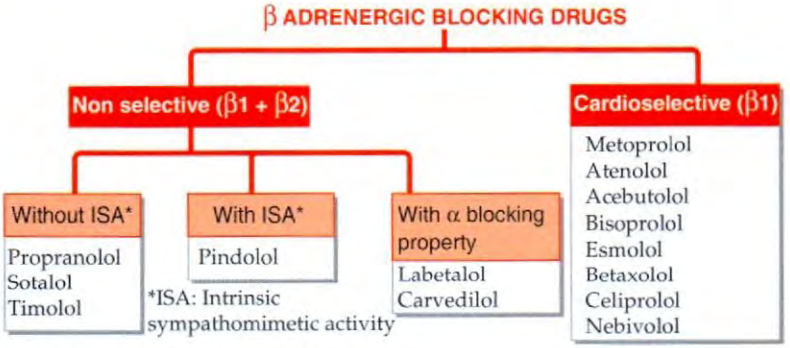
PHARMACOLOGICAL ACTIONS

1. CVS

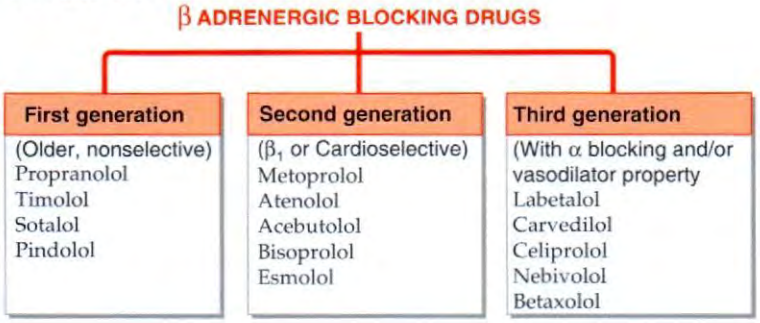
(a) *Heart* Propranolol decreases heart rate, force of contraction (at relatively higher doses) and cardiac output (c.o.). It prolongs systole by retarding conduction so that synergy of contraction of ventricular fibres is disturbed. The effects on a normal resting subject are mild, but become prominent under sympathetic overactivity (exercise, emotion). Ventricular dimensions are decreased in normal subjects, but dilatation can occur in those with reduced reserve—CHF may be precipitated or aggravated.

Cardiac work and oxygen consumption are reduced as the product of heart rate and aortic pressure decreases. Total coronary flow is reduced (blockade of dilator β receptors), but this is largely restricted to the subepicardial region, while perfusion of the subendocardial area (which is the site of ischaemia in angina patients) is not affected. The overall effect in angina patients is improvement of O_2 supply/demand status; exercise tolerance is increased.

Propranolol abbreviates refractory period of myocardial fibres and decreases automaticity—rate of diastolic depolarization in ectopic foci



GENERATION-WISE CLASSIFICATION



is reduced, specially if it had been augmented by adrenergic stimuli. The A-V conduction is slowed. At high doses a direct depressant and membrane stabilizing (quinidine like) action is exerted, but this contributes little to the anti-arrhythmic effect at usual doses. Propranolol blocks cardiac stimulant action of adrenergic drugs but not that of methylxanthines or glucagon.

(b) *Blood vessels* Propranolol blocks vasodilatation and fall in BP evoked by isoprenaline and enhances the rise in BP caused by Adr. There is re-reversal of vasomotor reversal that is seen after α blockade. Propranolol has no direct effect on blood vessels and there is little acute change in BP. On prolonged administration BP gradually falls in hypertensive subjects but not in normotensives. Total peripheral resistance (t.p.r.) is increased initially (due to blockade of β mediated vasodilatation) and c.o. is reduced, so that there is little change in BP. With continued treatment, resistance vessels gradually adapt to chronically reduced c.o, so that t.p.r. decreases and both systolic and diastolic BP gradually fall to some extent. This is considered to be the most likely explanation of the antihypertensive action. Other mechanisms that may contribute are:

- Reduced NA release from sympathetic terminals due to blockade of β receptor mediated facilitation of the release process.
- Decreased renin release from kidney (β_1 mediated): Propranolol causes a more marked fall in BP in hypertensives who have high or normal plasma renin levels and such patients respond at relatively lower doses than those with low plasma renin.
- Central action reducing sympathetic outflow. However, β blockers which penetrate brain poorly are also effective antihypertensives.

2. Respiratory tract Propranolol increases bronchial resistance by blocking dilator β_2 receptors. The effect is hardly discernible in normal individuals because sympathetic bronchodilator tone is minimal. In asthmatics, however, the condition is consistently worsened and a severe attack may be precipitated.

3. CNS No overt central effects are produced by propranolol. However, subtle behavioural changes, forgetfulness, increased dreaming and nightmares have been reported with long-term use of relatively high doses.

Propranolol suppresses anxiety in short-term stressful situations, but this is due to peripheral rather than a specific central action (*see* p. 495).

4. Local anaesthetic Propranolol has membrane stabilizing (Na^+ channel blocking) property and is a potent local anaesthetic. However, it is not a clinically useable local anaesthetic due to irritant action. Ocular irritation and corneal anaesthesia occurs when it is instilled in the eye, making it unsuitable for ocular use.

5. Metabolic Propranolol blocks adrenergically induced lipolysis and consequent increase in plasma free fatty acid levels. Plasma triglyceride level and LDL/HDL-CH ratio tend to increase during propranolol therapy. Glycogenolysis in heart, skeletal muscles and liver that occurs due to sympathetic stimulation is attenuated. As such, recovery from insulin hypoglycaemia that involves sympathetic stimulation is delayed. Though there is no effect on normal blood sugar level, prolonged propranolol therapy may impair carbohydrate tolerance by decreasing insulin release.

6. Skeletal muscle Propranolol inhibits adrenergically provoked tremor. This is a peripheral action exerted directly on the muscle fibres (through β_2 receptors). Propranolol also tends to reduce exercise capacity by attenuating β_2 mediated increase in blood flow to the exercising muscles, as well as by limiting glycogenolysis and lipolysis which provide fuel to working muscles.

7. Eye Instillation of propranolol and some other β blockers reduces secretion of aqueous humor, i.o.t. is lowered. There is no consistent effect on pupil size or accommodation.

8. Uterus Relaxation of uterus in response to isoprenaline and selective β_2 agonists is blocked

by propranolol. However, normal uterine activity is not significantly affected.

PHARMACOKINETICS

Propranolol is well absorbed after oral administration, but has low bioavailability due to high first pass metabolism in liver. Oral: parenteral dose ratio of up to 40:1 has been found. Interindividual variation in the extent of first pass metabolism is marked, therefore equieffective oral doses vary considerably. Propranolol is lipophilic and penetrates into brain easily.

Metabolism of propranolol is dependent on hepatic blood flow. Chronic use of propranolol itself decreases hepatic blood flow: its own oral bioavailability is increased and its t½ is prolonged (by about 30%) on repeated administration. Bioavailability of propranolol is higher when it is taken with meals because food decreases its first pass metabolism. Since metabolism of propranolol is saturable, higher bioavailability and prolongation of t½ is noted when high doses are given.

A number of metabolites of propranolol have been found, of which the hydroxylated product has β blocking activity. The metabolites are excreted in urine, mostly as glucuronides. More than 90% of propranolol is bound to plasma proteins.

Dose: Oral—10 mg BD to 160 mg QID (average 40–160 mg/day). Start with a low dose and gradually increase according to need; i.v.—2 to 5 mg injected over 10 min with constant monitoring. It is not injected s.c. or i.m. because of irritant property.

INDERAL, CIPLAR 10, 40, 80 mg tab, 1 mg/ml inj., BETABLOC 10, 40 mg tab.

INTERACTIONS

1. Additive depression of sinus node and A-V conduction with digitalis and verapamil — cardiac arrest can occur. However, propranolol has been safely used with nifedipine and its congeners.
2. Propranolol delays recovery from hypoglycaemia due to insulin and oral antidiabetics. Warning signs of hypoglycaemia mediated through sympathetic stimulation (tachycardia, tremor) are suppressed.
3. Phenylephrine, ephedrine and other α agonists present in cold remedies can cause marked rise in BP due to blockade of sympathetic vasodilatation.
4. Indomethacin and other NSAIDs attenuate the antihypertensive action of β blockers.
5. Propranolol retards lidocaine metabolism by reducing hepatic blood flow.

ADVERSE EFFECTS AND CONTRAINDICATIONS

Propranolol can produce many adverse effects, but mostly they are mild; β blockers are, in general, well tolerated drugs.

1. Propranolol can accentuate myocardial insufficiency and can precipitate CHF/edema by blocking sympathetic support to the heart, especially during cardiovascular stress. However, when compensation has been restored, careful addition of certain β_1 blockers is now established therapy to prolong survival.
2. Bradycardia: It is the most common side effect, resting HR may be reduced to 60/min or less. Patients of sick sinus are more prone to severe bradycardia.
3. Propranolol worsens chronic obstructive lung disease, can precipitate life-threatening attack of bronchial asthma: contraindicated in asthmatics. The β_1 selective agents may be safer in this regard.
4. Propranolol exacerbates variant (vasospastic) angina due to unopposed α mediated coronary constriction. In some patients, even classical angina may be worsened if ventricular dilatation and asynergy of contraction occurs—specially with high doses.
5. Propranolol is better avoided in diabetics, because risk of hypoglycaemic episodes may be increased. However, the β_1 selective agents may be less risky. Carbohydrate tolerance may be impaired in prediabetics.
6. Plasma lipid profile is altered on long-term use: total triglycerides tend to increase while HDL-cholesterol falls. This may enhance risk of coronary artery disease. Cardioselective β blockers and those with intrinsic

sympathomimetic activity have little/no deleterious effect on blood lipids.
7. Withdrawal of propranolol after chronic use should be gradual, otherwise rebound hypertension, worsening of angina and even sudden death can occur. This appears to be due to upregulation of β receptors occurring as a result of long-term reduction in agonist stimulation.
8. Propranolol is contraindicated in partial and complete heart block: arrest may occur.
9. Tiredness and reduced exercise capacity may be felt due to blunting of β_2 mediated increase in blood flow to the exercising muscles as well as attenuation of glycogenolysis and lipolysis.
10. Cold hands and feet may be noticed during winter due to blockade of vasodilator β_2 receptors. Peripheral vascular disease is worsened.
11. Side effects not overtly due to β blockade are—g.i.t. upset, lack of drive, nightmares, forgetfulness. Incidence of mental depression was found to be higher among patients taking β blockers, especially the lipid soluble agents like propranolol. Male patients more frequently complain of sexual distress.

OTHER β BLOCKERS

A number of β blockers have been developed having some special features. Their comparative properties are presented in Table 10.2. The associated properties alongwith their significance can be summarized as:

Cardioselectivity (in metoprolol, atenolol, acebutolol, bisoprolol, nebivolol).

These drugs are more potent in blocking cardiac (β_1) than bronchial (β_2) receptors. However, selectivity is only relative and is lost at high doses. Their features are:
1. Lower propensity to cause bronchoconstriction, but even these drugs should usually be avoided in asthmatics and COPD patients. However, a coexisting cardiac condition may warrant their use, which may be initiated at low dose and under supervision.
2. Less interference with carbohydrate metabolism and less inhibition of glycogenolysis during hypoglycaemia—safer in diabetics. However, tachycardia in response to hypoglycaemia is blocked.
3. Lower incidence of cold hands and feet, less chances of precipitating Raynaud's phenomenon.
4. No/less deleterious effect on blood lipid profile.
5. Ineffective in suppressing essential tremor (it occurs through β_2 action on muscle fibres).
6. Less liable to impair exercise capacity.

Partial agonistic (intrinsic sympathomimetic) action (in pindolol, celiprolol, acebutolol). These drugs themselves activate β_1 and/or β_2 receptors submaximally. The benefits of this property are controversial.
1. Bradycardia and depression of contractility at rest are not prominent, but exercise tachycardia is blocked; may be preferred in those prone to severe bradycardia (elderly patients; sick sinus) or with low cardiac reserve.
2. Withdrawal is less likely to exacerbate hypertension or angina; continued agonistic action on β receptors (of the drug itself) prevents development of supersensitivity.
3. Plasma lipid profile is not/less worsened.
4. Not effective in migraine prophylaxis—they dilate cerebral vessels.
5. Not suitable for secondary prophylaxis of MI.

Membrane stabilizing activity (in propranolol, oxprenolol, acebutolol). This activity is claimed to contribute to the antiarrhythmic action, but appears to be insignificant. β blockers with membrane stabilizing action cannot be used topically for glaucoma, because they anaesthetize cornea.

Low lipid solubility (atenolol, celiprolol, bisoprolol, sotalol)
1. They are less likely to produce sleep disturbances, nightmares, or to increase the incidence of mental depression.
2. They are incompletely absorbed orally, but do not undergo first pass metabolism and are primarily excreted unchanged in urine: are longer acting (t½ 6–20 hours) and tend to be effective in a narrow dose range. In contrast, the lipid soluble agents are primarily metabolized in liver and have shorter t½ (2–6 hours).

Table 10.2: Comparative properties of β blockers

β–BLOCKER	Potency (on β_1)	Partial agonistic action	Membrane stabilizing action	Lipid solubility	Daily dose (mg)	Oral bioavailability (%)	First pass metabolism	Major route of elimination	Plasma t½ (hours)
NONSELECTIVE									
1. Propranolol	1	–	++	+++	40–480	~30	Yes	Hep.*	3–5
2. Sotalol	1/3	–	–	±	160–480	~ 80	No	Ren.†	6–12
3. Timolol	6	–	–	++	10–40	50–75	Partial	Ren.+Hep.	4–5
4. Pindolol	6	+++	±	+	10–30	90	No	Ren.+Hep.	3–4
CARDIOSELECTIVE									
1. Metoprolol	1	–	±	++	100–400	40–50	Yes	Hep.	3–6
2. Atenolol	1	–	–	–	25–100	50–60	No	Ren.	6–9
3. Acebutolol	1/3	+	+	±	400–1200	40–60	Yes	Hep.+Ren.	3–4
4. Bisoprolol	6	–	–	–	2.5–10	80	No	Hep.+Ren.	9–12
α + β BLOCKER									
1. Labetalol	1/3	+	+	±	300–600	~30	Yes	Hep.	4–6

*Hep—Hepatic metabolism; †Ren.—Renal excretion

SECTION 2

Salient features of important β blockers are given below.

1. Sotalol A nonselective β blocker with low lipid solubility. It has additional cardiac rectifier K^+ channel blocking and class III antiarrhythmic property.

SOTAGARD 40, 80 mg tab.

2. Timolol Due to absence of local anaesthetic activity and good lipid solubility, it is the first ocular β blocker to be used topically for glaucoma (*see* p. 167).

Orally it is a potent β blocker which is indicated in hypertension, angina and prophylaxis of myocardial infarction.

Betaxolol, Levobunolol, Cartiolol and *Metipranolol* are β blockers employed exclusively for topical application to the eye (*see* p. 168).

3. Pindolol A potent β blocker with prominent intrinsic sympathomimetic activity. It has been used primarily as antihypertensive which may be advantageous in patients who develop marked bradycardia with propranolol. Chances of rebound hypertension on withdrawal are also less. Plasma lipid profile may not worsen.

PINADOL 5 mg tab, VISKEN 10, 15 mg tab.

4. Metoprolol It is the prototype of cardioselective (β_1) blockers; nearly 50 times higher dose is needed to block isoprenaline induced vasodilatation. Some measure of inverse agonistic activity on β_1 receptors has also been demonstrated. It is less likely to worsen asthma, but is not entirely safe. It may be preferred in diabetics receiving insulin or oral hypoglycaemics. Patients who complain of cold hands and feet while on propranolol do better on metoprolol.

First pass metabolism of metoprolol is less marked than propranolol, but 90% or more is ultimately hydroxylated by CYP2D6 before excretion. There are 'extensive' and 'poor' hydroxylators of metoprolol (CYP2D6 alleles); the latter may require a lower dose.

Side effects of metoprolol are milder. It is generally given orally for hypertension, angina and CHF, but i.v. injection (5–15 mg) has been used in myocardial infarction provided bradycardia is absent.

BETALOC 25, 50, 100 mg tab, 5 mg/ml inj. LOPRESOR, METOLAR 50, 100 mg tab.

S(–) Metoprolol is the active enantiomer, now available as a single enantiomer product. It is to be used at half the dose as the racemate.

Dose: 12.5–50 mg OD–BD.

METPURE-XL 12.5, 25, 50 mg extended release tabs.

5. Atenolol A relatively selective β_1 blocker having low lipid solubility. It is incompletely absorbed orally, but first pass metabolism is not significant. Because of longer duration of

action, once daily dose is often sufficient. Side effects related to CNS action are less likely. No deleterious effects on lipid profile have been noted. Effective dose for most individuals falls in a narrow range. It is one of the most commonly used β blockers for hypertension and angina, but is not approved for CHF.

BETACARD, ATEN, TENORMIN 25, 50, 100 mg tab.

S(–) Atenolol This pure active enantiomer is effective at half the dose and may be better tolerated.

Dose: 12.5–50 mg OD;

ATPURE, ADBETA 12.5, 25, 50 mg tabs.

6. Acebutolol Another cardioselective agent with significant partial agonistic and membrane stabilizing properties. The side effect profile is like that of metoprolol, but resting heart rate is not decreased as much. Acebutolol is rapidly metabolized to an active metabolite diacetolol which is primarily excreted by kidney and has a longer t½ (8–12 hours). As such, a single daily dose is sufficient in many patients.

SECTRAL 200, 400 mg tab., 10 mg/2 ml amp. Intravenous dose for arrhythmias 20–40 mg.

7. Bisoprolol A cardioselective β_1 blocker lacking intrinsic sympathomimetic activity; suitable for once daily administration in angina, hypertension and CHF.

CONCOR, CORBIS 5 mg tab; ½ to 2 tab OD.

8. Esmolol It is an ultra-short acting β_1 blocker devoid of partial agonistic or membrane stabilizing actions. Due to inactivation by esterases in blood its plasma t½ is < 10 min; action disappears 15–20 min after terminating i.v. infusion. The degree of β blockade can be titrated by regulating the rate of infusion. Rapid onset, short lasting fall in BP attends i.v. infusion of esmolol.

A loading dose of 0.5 mg/kg is given followed by 0.05–0.2 mg/kg/min infusion. It has been used to terminate supraventricular tachycardia, episodic atrial fibrillation or flutter and arrhythmia during anaesthesia. Esmolol is also very useful for reducing HR and BP during and after cardiac surgery, in aortic dissection and in early treatment of myocardial infarction.

MINIBLOCK 100 mg/10 ml, 250 mg/10 ml inj.

9. Nebivolol This highly selective β_1 blocker is regarded as a *third generation* β blocker, because in addition to β receptor blockade, it activates endothelial nitric oxide (NO) synthase and enhances NO production. It thus causes vasodilatation and has the potential to improve endothelial function, which may delay atherosclerosis. Absence of deleterious effect on plasma lipids and on carbohydrate metabolism is another advantage. It tends to increase insulin sensitivity, instead of decreasing it. In contrast to older β blockers, hypotensive response to nebivolol has a rapid onset. Nebivolol is indicated in hypertension as well as in CHF.

Dose: 5 mg (elderly 2.5 mg) OD;

NEBICARD 2.5, 5 mg tabs, NODON 5 mg tab.

10. Celiprolol Another third generation selective β_1 blocker having additional weak β_2 agonistic activity which reduces vascular resistance and holds promise of safety in asthmatics. Nonadrenoceptor mediated vasodilatation (due to NO production) adds to its antihypertensive action.

Dose: 200–600 mg OD; CELIPRES 100, 200 mg tab.

USES

1. *Hypertension* β blockers are relatively mild antihypertensives. All agents, irrespective of associated properties, are nearly equally effective. They were one of the first choice drugs, but are less favoured now for initiating therapy as the single drug (*see* Ch. 41).

2. *Angina pectoris* All β blockers benefit angina of effort. Taken on a regular schedule they decrease frequency of attacks and increase exercise tolerance. High doses, however, may worsen angina in some patients by increasing ventricular size and reducing coronary flow. β blockers are not suitable for variant (vasospastic) angina (*see* Ch. 40).

3. *Cardiac arrhythmias* β blockers (mainly propranolol) suppress extrasystoles and tachycardias, both supraventricular and ventricular, especially those mediated adrenergically (during anaesthesia, digitalis induced): Propranolol may be used i.v. for this purpose. It also controls ventricular rate in atrial fibrillation and flutter,

but only occasionally restores sinus rhythm. Esmolol is an alternative drug for paroxysmal supraventricular tachycardia (*see* Ch. 39).

4. *Myocardial infarction (MI)* In relation to MI, β blockers, particularly propranolol and metoprolol, have been used for two purposes:

(a) *Secondary prophylaxis of MI:* There is now firm evidence of benefit. Long-term use after recovery from MI has been found to decrease subsequent mortality by 20%. They may act by:

- Preventing reinfarction
- Preventing sudden ventricular fibrillation at the subsequent attack of MI.

High risk patients (those who had large infarcts) should be put on these β blockers (if there are no haemodynamic contraindications) for at least 2 years. Other β blockers, especially those with partial agonistic action, are considered less suitable for this purpose.

(b) *Myocardial salvage during evolution of MI:* Administered i.v. within 4–6 hours of an attack followed by continued oral therapy, one of the above two β blockers—

- May limit infarct size by reducing O_2 consumption—marginal tissue which is partially ischaemic may survive.
- May prevent arrhythmias including ventricular fibrillation.

However, β blockers can be given to only those patients not in shock or cardiac failure and who have heart rate > 50/min along with not higher than first degree heart block (P-R interval < 0.24 sec). In megatrials such therapy has been found to reduce mortality by 20–25%.

5. *Congestive heart failure* Although β blockers can acutely worsen heart failure, several studies have reported beneficial haemodynamic effects of certain β blockers, namely *metoprolol, bisoprolol, nebivolol* and *carvedilol* over long-term in selected patients with dilated cardiomyopathy. Introduced gradually and maintained for long term, these drugs retard the progression of CHF and prolong life. The benefit may result from antagonism of deleterious effects of sympathetic overactivity (invoked reflexly by heart failure) on the myocardium. Overactivation of cardiac β_1 receptors has been found to exert toxic effects on the heart by accelerating myocyte apoptosis and promoting functionally unfavourable remodeling. One of the above named β blockers, used appropriately along with other measures, is now established as standard therapy for most mild to moderate CHF patients. However, these drugs should not be given to patients with marked fluid retention and to those who worsen on initiating the β blocker, or to those requiring i.v. vasodilators/i.v. inotropic drugs (*see* Ch. 38).

6. *Dissecting aortic aneurysm* β blockers help by reducing cardiac contractile force and aortic pulsation. Nitroprusside infusion is often added.

7. *Pheochromocytoma* β blockers may be used to control tachycardia and arrhythmia, but should never be administered unless an α blocker has been given before, otherwise dangerous rise in BP can occur. They suppress cardiomyopathy caused by excess CAs.

8. *Thyrotoxicosis* Propranolol rapidly controls the sympathetic symptoms (palpitation, nervousness, tremor, fixed stare, severe myopathy and sweating) without significantly affecting thyroid status. It also inhibits peripheral conversion of T_4 to T_3 and is highly valuable during thyroid storm. Major use, however, is preoperatively and while awaiting response to antithyroid drugs/radioactive iodine.

9. *Migraine* Propranolol is the most effective drug for chronic prophylaxis of migraine (*see* p. 195).

10. *Anxiety* Propranolol exerts an apparent antianxiety effect, especially under conditions which provoke nervousness and panic, e.g. examination, unaccustomed public appearance, etc. This is probably due to blockade of peripheral manifestations of anxiety (palpitation, tremor) which have a reinforcing effect. Propranolol is largely ineffective in anxiety neurosis, but may benefit the somatic symptoms.

11. *Essential tremor* Nonselective $\beta_1+\beta_2$ blockers have now an established place in treating essential tremor. However, they do not benefit parkinsonian tremor.

12. *Glaucoma* Ocular β blockers are widely used for chronic simple (wide angle) glaucoma. They are also used as adjuvant in angle closure glaucoma (*see* p. 167, 170).

13. *Hypertrophic obstructive cardiomyopathy* The subaortic region is hypertrophic. Forceful contraction of this region under sympathetic stimulation (exercise, emotion) increases outflow resistance which has incapacitating haemodynamic consequence. β blockers improve c.o. in these patients during exercise by reducing left ventricular outflow obstruction, though they have little effect while at rest.

α + β ADRENERGIC BLOCKERS

Labetalol It is the first adrenergic antagonist capable of blocking both α and β receptors. There are 4 diastereomers of labetalol, each of which has a distinct profile of action on subtypes of α and β receptors. The commercial racemic preparation has equal parts of each diastereomer and displays $\beta_1 + \beta_2 + \alpha_1$ blocking as well as weak β_2 agonistic activity. The β blocking potency is about 1/3 that of propranolol, while α blocking potency is about 1/10 of phentolamine.

Labetalol is 3–5 times more potent in blocking β than α receptors. As such, effects of a low dose resemble those of propranolol alone while at higher dose they are like a combination of propranolol and prazosin. Fall in BP (both systolic and diastolic) is due to α_1 and β_1 blockade as well as β_2 agonism (vasodilatation). Relatively high doses reduce both c.o. and t.p.r. Heart rate is unchanged or slightly decreased or increased. In contrast to propranolol, limb blood flow increases with labetalol. It has also been shown to inhibit NA uptake by adrenergic nerve endings.

Labetalol is orally effective but undergoes considerable first pass metabolism.

It is a moderately potent antihypertensive that is particularly useful in pheochromocytoma, clonidine withdrawal, pregnancy induced hypertension (preeclampsia) and hypertensive emergencies, as well as in essential hypertension.

Most important side effect is postural hypotension, but this is significant only in some patients. Failure of ejaculation and other side effects of α and β blockers can also occur, but plasma lipid levels are not altered. Rashes and liver damage have been reported.

Dose: Start with 50 mg BD, increase to 100–200 mg TDS oral. In hypertensive emergencies 20–40 mg i.v. every 10 min till desired response is obtained.

NORMADATE 50, 100, 200 mg tab, LABESOL, LABETA 50 mg tab, 20 mg/amp and 100 mg/amp inj.

Carvedilol It is a $\beta_1 + \beta_2 + \alpha_1$ adrenoceptor blocker which produces vasodilatation due to α_1 blockade as well as calcium channel blockade, Antioxidant property has also been demonstrated, but its clinical relevance is uncertain. It has been used in hypertension and is the β blocker especially employed as cardioprotective in CHF. Oral bioavailability of carvedilol is 30%. It is primarily metabolized CYP2D6 of which there are 'poor' or 'extensive' metabolizer alleles. Interaction with CYP2D6 inhibitors can occur. Carvedilol has a t½ of 6–8 hrs.

CHF: Start with 3.125 mg BD for 2 weeks, if well tolerated gradually increase to max. of 25 mg BD.

Hypertension/angina: 6.25 mg BD initially, titrate to max. of 25 mg BD.

CARVIL, CARLOC, CARVAS 3.125, 6.25, 12.5, 25 mg tabs; ORICAR 12.5, 25 mg tabs.

DRUGS FOR GLAUCOMA

Glaucoma is a group of diseases characterized by a progressive form of optic nerve damage. This is generally, but not necessarily, associated with raised (> 21 mmHg) intraocular tension (i.o.t), but the etiology is unknown and there are many risk factors. The chief therapeutic measure is to lower i.o.t., either by reducing secretion of aqueous humour or by promoting its drainage. Lowering of i.o.t. retards progression of optic nerve damage even in normal/low i.o.t. glaucoma.The site of formation and pathway of drainage of aqueous humour as well as sites of action of antiglaucoma drugs is illustrated in Fig. 10.1. Major amount of aqueous (~90%) drains through the *trabecular route*, while ~10% fluid passes into the connective tissue

spaces within the ciliary muscle—then *via* suprachoroid into episcleral vessels *(uveoscleral outflow)*. Glaucoma is seen in *two* principal clinical forms; *viz.* 'open angle' and 'angle closure' glaucoma.

A. Open angle (wide angle, chronic simple) glaucoma

It is probably a genetically predisposed degenerative disease affecting patency of the trabecular meshwork which is gradually lost past middle age. The i.o.t. rises insidiously and progressively. Ocular hypotensive drugs are used on a long-term basis and constitute the definitive treatment in majority of cases. The mode of ocular hypotensive action of topical antiglaucoma drugs is summarized in Table 10.3.

1. β Adrenergic blockers

Topical β blockers have been the first line drugs till recently, but PG $F_{2\alpha}$ analogues are the preferred drugs now. In contrast to miotics, the β blockers do not affect pupil size, tone of ciliary muscle or outflow facility, but lower i.o.t. by reducing aqueous formation. This probably results from down regulation of

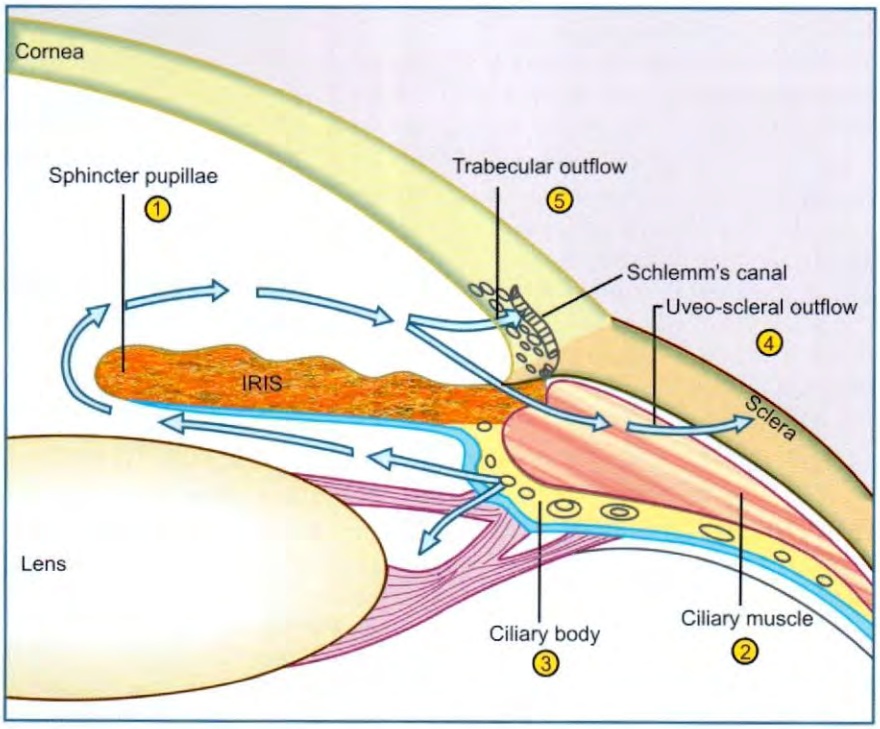


Fig. 10.1: Illustration of aqueous humour dynamics and the sites of action of ocular hypotensive drugs
(1) Site of action of miotics in angle closure glaucoma: contraction of sphincter pupillae removes pupillary block and reverses obliteration of iridocorneal angle
(2) Site of action of miotics in open angle glaucoma: contraction of ciliary muscle pulls on scleral spur and improves trabecular patency
(3) Site of action of (a) β blockers (b) α_1 agonists (c) α_2 agonists (d) carbonic anhydrase inhibitors: all reduce aqueous secretion by ciliary body
(4) Site of action of prostaglandins and adrenaline (α agonist action): increase uveoscleral outflow by altering permeability and/or pressure gradients
(5) Site of action of adrenaline (β_2 agonist action): possibly increases aqueous conductivity of trabecular filtering cells

TOPICAL DRUGS FOR GLAUCOMA

β-Adrenergic blockers	α-Adrenergic agonists	Prostaglandin analogues	Carbonic anhydrase inhibitors	Miotics
Timolol	Dipivefrine	Latanoprost	Dorzolamide	Pilocarpine
Betaxolol	Apraclonidine	Travoprost	Brinzolamide	Physostigmine
Levobunolol	Brimonidine	Bimatoprost		Echothiophate
Carteolol				

adenylylcyclase due to β_2 receptor blockade in the ciliary epithelium (*see* Fig. 10.2) and a secondary effect due to reduction in ocular blood flow. They are as effective as miotics and produce less ocular side effects. Ocular β blockers are lipophilic with high ocular capture (to reduce systemic effects) and have no/weak local anaesthetic activity (to avoid corneal hypoesthesia and damage).

Ocular side effects of β blockers These are generally mild and infrequent—stinging, redness and dryness of eye, corneal hypoesthesia, allergic blepharoconjunctivitis and blurred vision.

Systemic adverse effects These are the major limitations in the use of ocular β blockers, and occur due to absorption through nasolacrimal duct. Life-threatening bronchospasm has been reported in asthmatic and COPD patients. Bradycardia, accentuation of heart block and CHF are likely to occur, especially in the elderly. In fact all adverse effects and contraindications of systemic β blocker therapy (*see* p. 160-61) apply to ocular β blockers as well. Systemic adverse effects can be minimized by applying mild pressure on the inner canthus of the eye for about 5 min. after instilling the eye drop to prevent entry of the drug into nasolacrimal duct from where it is mainly absorbed.

Timolol It is the prototype of ocular β blockers; is nonselective (β_1 + β_2) and has no local anaesthetic or intrinsic sympathomimetic activity. The ocular hypotensive action (20–35% fall in i.o.t.) becomes evident within 1 hour and lasts for ~12 hours. After chronic dosing,

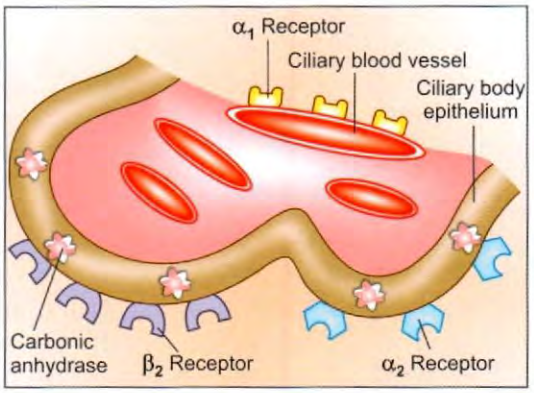


Fig. 10.2: Location of α_1, α_2 and β_2 adrenergic receptors and of carbonic anhydrase enzyme (molecules which are targets of drug action for reducing aqueous formation) in the processes of the ciliary body
α_1 adrenoceptors constrict ciliary vessels and reduce aqueous production: are activated by adrenaline.
α_2 adrenoceptors located on ciliary epithelium reduce aqueous secretion: are activated by adrenaline/apraclonidine/brimonidine.
β_2 adrenoceptors located on ciliary epithelium enhance aqueous secretion *via* increased cAMP. Their blockade by timolol/betaxolol reduces secretion.
Carbonic anhydrase present within ciliary epithelial cells generates HCO_3^- ion which is secreted into aqueous humor. Acetazolamide/dorzolamide inhibit it and reduce aqueous secretion.

Advantages of topical β blockers over miotics

- No change in pupil size: no diminution of vision in dim light and in patients with cataract
- No induced myopia which is especially troublesome in young patients
- No headache/brow pain due to persistent spasm of iris and ciliary muscles
- No fluctuations in i.o.t. as occur with pilocarpine drops
- Convenient twice/once daily application sufficient

the action is smooth and well sustained. Some effect on i.o.t. persists for 1–2 weeks following discontinuation. This feature, in contrast to pilocarpine drops, gives a high level of clinical safety, i.e. 1 or 2 missed doses will not affect i.o.t. control. However, ~30% cases of open angle glaucoma fail to achieve the desired level of i.o.t. with timolol alone, and may need additional medication.

GLUCOMOL, OCUPRES, IOTIM, LOPRES 0.25% and 0.5% eye drops; start with 0.25% drops BD, change to 0.5% drops in case of inadequate response. TIMOLAST 0.5% as gelforming eyedrop for OD use.

Betaxolol It is a β_1 selective blocker offering the advantage of less bronchopulmonary and probably less cardiac, central and metabolic side effects. In addition, it appears to exert a protective effect on retinal neurones independent of i.o.t. lowering, by blocking some Ca^{2+} channels and reducing Na^+/Ca^{2+} influx. This action is more prominent in betaxolol than in timolol. However, betaxolol is less efficacious in lowering i.o.t. than timolol, because ocular β receptors are predominantly of the β_2 subtype. Transient stinging and burning in the eye is more common with it. Most ophthalmologists prefer to start with betaxolol and change over to timolol (or a similar drug) only if i.o.t. control is insufficient or there is local intolerance to betaxolol.

OPTIPRESS, IOBET, OCUBETA 0.5% eye drops; 1 drop in each eye BD.

Levobunolol It has been introduced as a once daily alternative to timolol. The ocular and systemic effects are very similar to timolol except for longer duration of action.

BETAGAN 0.5% ophthalmic soln., 1 drop OD.

Carteolol and *Metipranolol* are the other ocular β blockers.

2. α Adrenergic agonists

Dipivefrine It is a prodrug of Adr; penetrates cornea and is hydrolysed by the esterases present there into Adr, which itself has poor corneal penetration and causes ocular smarting, reactive hyperemia. The released Adr (from dipivefrine) lowers i.o.t. by augmenting uveoscleral outflow, β_2 receptor mediated increase in hydraulic conductivity of trabecular filtering cells, as well as by reducing aqueous formation (α_1 + α_2 receptor mediated). Though better tolerated and longer acting than Adr, dipivefrine still produces significant ocular burning and other side effects. It is used only for add-on therapy in selected patients.

PROPINE 0.1% eye drop; 1 drop in each eye BD.

Apraclonidine It is a polar clonidine congener which does not cross blood-brain barrier, but applied topically (0.5–1%) it lowers i.o.t. by ~25%. It decreases aqueous production by primary α_2 and subsidiary α_1 action in the ciliary body. Itching, lid dermatitis, follicular conjunctivitis, mydriasis, eyelid retraction, dryness of mouth and nose are common side effects. Its use is restricted to short-term control of spikes of i.o.t. after laser trabeculoplasty or iridotomy.

ALFADROPS DS 1% eyedrops.

Brimonidine This clonidine congener is more α_2 selective and more lipophilic than apraclonidine. It lowers i.o.t. by 20–27% by reducing aqueous production and by increasing uveoscleral flow. Peak effect on i.o.t. occurs after 2 hours of instillation. Allergic conjunctivitis and other ocular side effects are similar to but less frequent than with apraclonidine.

Table 10.3: Mode of action of ocular hypotensive drugs

Drug/class	*Aqueous secretion*	*Trabecular outflow*	*Uveoscleral outflow*
1. β-blockers (Timolol)	↓	–	–
2. Adrenaline/ Dipivefrine	↓	↑	↑
3. Brimonidine/ apraclonidine	↓	–	↑
4. Prostaglandins (Latanoprost)	–	↑	↑
5. Miotics (Pilocarpine)	–	↑	–
6. Carbonic anhydrase inhibitors	↓	–	–

Because of weaker α_1 action, side effects like mydriasis, eyelid retraction, conjunctival blanching followed by hyperemia are less prominent, but dry mouth, sedation and a small fall in BP have been noted.

Brimonidine is indicated both for short-term (prophylaxis of i.o.t. spikes post laser/post surgery) as well as long-term use in glaucoma. It is generally used for add-on therapy only.

ALPHAGAN-P, BRIMODIN-P 0.15% eye drops, IOBRIM 0.2% eyedrops; 1 drop in each eye TDS.

3. Prostaglandin analogues

Low concentration of $PGF_{2\alpha}$ was found to lower i.o.t without inducing ocular inflammation. It acts by increasing uveoscleral outflow, possibly by increasing permeability of tissues in ciliary muscle or by an action on episcleral vessels. An effect on trabecular outflow has also been demonstrated, but is less marked. Ciliary body COX-2 has been found to be down regulated in wide angle glaucoma indicating a physiological role of PGs in aqueous humour dynamics.

Latanoprost Instilled in the eye, this $PGF_{2\alpha}$ derivative has shown efficacy similar to timolol (i.o.t. reduction by 25–35%) and the effect is well sustained over long-term. It reduces i.o.t. in normal pressure glaucoma also. Though ocular irritation and pain are relatively frequent, no systemic side effects are reported. Blurring of vision, increased iris pigmentation, thickening and darkening of eyelashes have occurred in some cases. Macular edema can develop during treatment with any $PGF_{2\alpha}$ analogue, especially in aphakic patients; a watch should be kept to detect it early.

Because of good efficacy, once daily application and absence of systemic complications, PG analogues have become the first choice drugs for open angle glaucoma. High cost is a disadvantage.

LACOMA, XALATAN, LATOPROST, 0.005% eye drops, one drop in each eye OD in the evening; LACOMA-T, LAPROST PLUS, LATOCHECK-T eye drops with timolol 0.5% eye drops. (To be stored in cold)

Travoprost Another selective FP-prostanoid receptor agonist which lowers i.o.t. mainly by increasing uveoscleral outflow and a minor effect on trabecular outflow. The effect starts within 2 hours, peaks at 12 hours and lasts for 24 hours or more. The i.o.t. lowering efficacy and side effects are comparable to latanoprost. Some patients not responding well with one may respond to the other.

TRAVATAN 0.004% eye drops. One drop in each eye in the evening; refrigeration of the eye drop is not required; TRAVACOM 0.004% with timolol 0.5% eye drop.

Bimatoprost A synthetic prostamide derivative found to be equally or more effective than latanoprost in lowering i.o.t. Ocular side effects are also similar, but some patients may tolerate it better.

LUMIGAN, CAREPROST 0.03% eye drops; one drop in each eye OD in the evening. The eye drop need not be stored in refrigerator.

4. Carbonic anhydrase inhibitors

Acetazolamide (*see* Ch. 42) Oral treatment with acetazolamide (0.25 g 6–12 hourly) reduces aqueous formation by limiting generation of bicarbonate ion in the ciliary epithelium. It is used to supplement ocular hypotensive drugs for short-term indications like angle closure, before and after ocular surgery/laser therapy. Systemic side effects—paresthesia, anorexia, hypokalaemia, acidosis, malaise and depression restrict long-term use to few cases in which target i.o.t. is not achieved even by concurrent use of 2–3 topical drugs.

Dorzolamide (2% eye drops BD-TDS) It is a topically useful carbonic anhydrase inhibitor developed to circumvent systemic side effects of acetazolamide. It lowers i.o.t. by ~20%; somewhat less efficacious than timolol. Ocular stinging, burning, itching, corneal edema and bitter taste are the usual side effects. Systemic adverse effects are also possible. Dorzolamide is used only as add on drug to topical β blockers/PG analogues, or when these drugs are contraindicated.

DORTAS, DORZOX 2% eye drops.

Brinzolamide is another ocular carbonic anhydrase inhibitor.

5. Miotics: Till the 1970s topical pilocarpine alone or combined with antiChEs were the standard antiglaucoma drugs (*see* Ch. 7). However, because of several drawbacks (*see* box on p. 167), they are now used only as the last option. In open angle glaucoma, they lower i.o.t. by increasing ciliary muscle tone thereby improving patency of trabeculae.

The current approach to treatment of open angle glaucoma can be summarized as—start monotherapy with latanoprost/another PG analogue, or a topical β blocker; if target i.o.t. is not attained, either change over to the alternative drug or use both the above concurrently. Brimonidine/dorzolamide (occasionally dipivefrine) are used only when there are contraindications to PG analogues and/or β blockers, or to supplement their action. Topical miotics and oral acetazolamide are added only as the last resort.

B. Angle closure (narrow angle, acute congestive) glaucoma

It occurs in individuals with a narrow iridocorneal angle and shallow anterior chamber. The i.o.t. remains normal until an attack is precipitated, usually by mydriasis (Fig. 10.3A,B). The i.o.t. rises rapidly to very high values (40–60 mmHg). It is an emergent condition with marked congestion of eyes and severe headache. Failure to lower i.o.t. quickly may result in loss of sight.

Vigorous therapy employing several measures to reduce i.o.t. is instituted.

1. *Hypertonic mannitol (20%) 1.5–2 g/kg or glycerol (10%):* infused i.v. decongest the eye by osmotic action. A retention enema of 50% glycerine is also some times used.
2. *Acetazolamide*: 0.5 g i.v. followed by oral twice daily is started concurrently.
3. *Miotic:* Once the i.o.t. starts falling due to the above i.v. therapy, pilocarpine 1–4% is instilled every 10 min initially and then at longer intervals. Contraction of sphincter pupillae changes the direction of forces in the iris to lessen its contact with the lens and spreads the iris mass centrally → pupillary block is removed and iridocorneal angle is freed (Fig. 10.3C). However, when i.o.t. is very high, the iris muscle fails to respond to miotics; tension should be reduced by other measures before miotics can act.
4. *Topical β blocker:* Timolol 0.5% is instilled 12 hourly in addition.
5. *Apraclonidine* (1%)/latanoprost 0.005% instillation may be added.

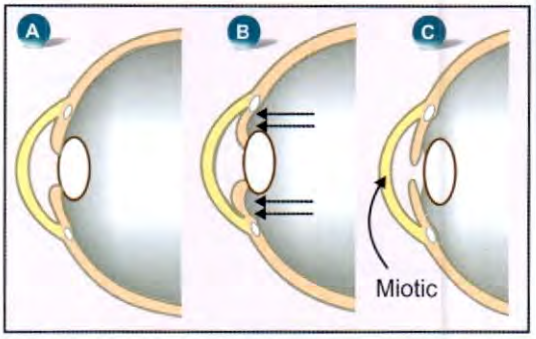


Fig. 10.3: Development of angle closure glaucoma and its reversal by miotic

A. Mydriasis occurs in an eye with narrow iridocorneal angle and iris makes contact with lens blocking passage of aqueous from posterior to anterior chamber.

B. Pressure builds up behind the iris which bulges forward and closes the iridocorneal angle thus blocking aqueous outflow.

C. Miotic makes the iris thin and pulls it away from the lens removing the pupillary block and restoring aqueous drainage

Drugs are used only to terminate the attack of angle closure glaucoma. Definitive treatment is surgical or laser iridotomy. Few cases, who have chronic narrow angle glaucoma, may be treated with a miotic/other ocular hypotensive drug for long periods, but often surgery/laser therapy is ultimately required.

☞ PROBLEM DIRECTED STUDY

10.1 A 70-year-male presented with the complaints of weak stream of urine, sense of incomplete bladder voiding, urinary frequency and nocturia. After physical examination and ultrasound, he was diagnosed to have developed benign hypertrophy of prostate and was prescribed:

Tab. Terazosin 5 mg, one tab daily at bed time.

He took the medicine as advised and went off to sleep. At night, when he got up to pass urine, he felt giddy and fainted. On being laid flat on the bed, he regained consciousness within 2 minutes. Later, he was gradually propped up on the bed to the sitting position and then got up slowly and walked without any problem.

(a) What is the rationale of prescribing terazosin to this patient?

(b) What is the likely explanation for the fainting attack?

(c) What precautions could have avoided the fainting episode?

10.2 A lady aged 55 years was brought at night to the hospital emergency with severe breathlessness and wheezing. Chest auscultation revealed marked bronchoconstriction. She was managed with 100% O_2 inhalation and nebulized salbutamol + ipratropium bromide. The asthmatic attack was controlled in about 6 hours. Next day, history taking revealed that she was having mild episodic asthma off and on, but never had such a severe attack. Day before she had visited an ophthalmologist for visual difficulty and frontal headache. The intraocular pressure was measured to be 24 and 25 mmHg in right and left eye respectively. She was prescribed:

Timolol 0.5% eye drops in each eye twice a day.

(a) What is the most likely explanation for the precipitation of severe attack of asthma?

(b) How could such a complication be avoided?

(see Appendix-1 for solutions)

SECTION 3

AUTACOIDS AND RELATED DRUGS

Autacoid This term is derived from Greek: *autos*—self, *akos*—healing substance or remedy.

Autacoids are diverse substances produced by a *wide variety of cells* in the body, having intense biological activity, but generally *act locally* (e.g. within inflammatory pockets) at the site of synthesis and release.

They have also been called 'local hormones'. However, they differ from 'hormones' in two important ways—hormones are produced by *specific cells,* and are transported through circulation to act on *distant target tissues*.

Autacoids are involved in a number of physiological and pathological processes (especially reaction to injury and immunological insult). Some autacoids, in addition, serve as transmitters or modulators in the nervous system, but their role at many sites is not precisely known. A number of useful drugs act by modifying their action or metabolism. The classical autacoids are—

Amine autacoids Histamine, 5-Hydroxytryptamine (Serotonin)

Lipid derived autacoids Prostaglandins, Leukotrienes, Platelet activating factor

Peptide autacoids Plasma kinins (Bradykinin, Kallidin), Angiotensin

In addition, cytokines (interleukins, TNFα, GM-CSF, etc.) and several peptides like gastrin, somatostatin, vasoactive intestinal peptide, endothelins and many others may be considered as autacoids.

Chapter 11 Histamine and Antihistaminics

HISTAMINE

Histamine, meaning 'tissue amine' (*histos*—tissue) is almost ubiquitously present in animal tissues and in certain plants, e.g. stinging nettle. Its pharmacology was studied in detail by Dale in the beginning of the 20th century when close parallelism was noted between its actions and the manifestations of certain allergic reactions. Histamine was implicated as a mediator of hypersensitivity phenomena and tissue injury reactions. It is now known to play important physiological roles.

Histamine is present mostly within storage granules of *mast cells*. Tissues rich in histamine are skin, gastric and intestinal mucosa, lungs, liver and placenta. Nonmast cell histamine occurs in brain, epidermis, gastric mucosa and growing regions. Turnover of mast cell histamine is slow, while that of nonmast cell histamine is fast. Histamine is also present in blood, most body secretions, venoms and pathological fluids.

Synthesis, storage and destruction

Histamine is β imidazolylethylamine. It is synthesized locally from the amino acid histidine and degraded rapidly by oxidation and methylation (Fig. 11.1). In mast cells, histamine (positively charged) is held by an acidic protein and heparin (negatively charged) within intracellular granules. When the granules are extruded by exocytosis, Na^+ ions in e.c.f. exchange with histamine to release it free (Fig. 11.2). Increase in intracellular cAMP (caused by β adrenergic agonists and methylxanthines) inhibits histamine release. Histamine is inactive orally because liver degrades all histamine that is absorbed from the intestines.

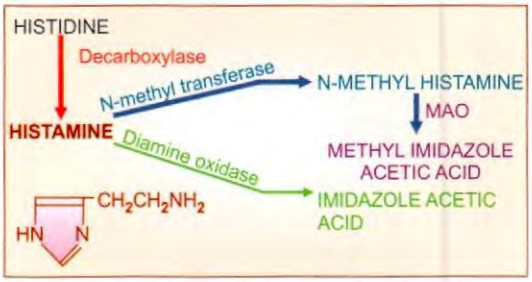


Fig. 11.1: Synthesis and degradation of histamine
MAO—Monoamine oxidase

Histamine receptors

Four types of histaminergic receptors have now been clearly delineated and cloned. Analogous to adrenergic α and β receptors, histaminergic receptors were classified by Asch and Schild (1966) into H_1 and H_2 : those blocked by then available antihistamines were labelled H_1. Sir James Black (1972) produced the first H_2 blocker burimamide and confirmed this classification. Till now, only these two receptors are clinically relevant. A third H_3 receptor, which serves primarily as an autoreceptor controlling histamine release from neurones in the brain was identified in 1983. Though some selective H_3 agonists and antagonists have been produced, none has found any clinical application. Features of these 3 types of histaminergic receptors are compared in Table 11.1.

Molecular cloning has revealed yet another (H_4) receptor in 2001. It has considerable homology with H_3 receptor and binds many H_3 ligands. 4-Methyl histamine, earlier

Table 11.1: Distinctive features of three types of histaminergic receptors

	H_1	H_2	H_3
1. Selective agonists (relative selectivity H_1: H_2)	2-Methyl histamine (8:1) 2-Pyridylethylamine (30:1) 2-Thiazolyl ethylamine (90:1)	Dimaprit (1:2000) Impromidine (1:10,000)	(R) α-Methyl histamine (H_1: H_3 1:3000) Imetit
2. Selective antagonists (relative selectivity H_1: H_2)	Mepyramine (6000:1) Chlorpheniramine (15000:1)	Cimetidine (1: 500) Ranitidine (l : >500)	Thioperamide (H_1: H_3 1: 23000) Impromidine (also H_2 agonist) Tiprolisant, Clobenpropit
3. Receptor type	Gq-protein coupled	Gs-protein coupled	Gi/Go-protein coupled
4. Effector pathway	PIP_2 hydrolysis → IP_3/DAG : Release of Ca^{2+} from intracellular stores; Protein kinase-C activation NO release→cGMP	Adenylyl cyclase activation — cAMP ↑—phosphorylation of specific proteins	a. Restricting Ca^{2+} influx b. K^+ channel activation c. cAMP ↓
5. Distribution in body: actions mediated	a. Smooth muscle (intestine, airway, uterus)—contraction b. Blood vessels • Endothelium: Release of NO and, PGI_2—vasodilatation. widening of gap junctions—increased capillary permeability • Smooth muscle of larger vessels—vasoconstriction. c. Afferent nerve endings—stimulation. d. Ganglionic cell—stimulation. e. Adrenal medulla—release of CAs. f. Brain (postsynaptic)—impulse.	a. Gastric glands—acid secretion b. Blood vessels (smooth muscle)—dilatation c. Heart Atria: +ive chronotropy Ventricles: +ive inotropy d. Uterus (rat)—relaxation e. Brain (postsynaptic)—impulse	a. Brain (presynaptic)—inhibition of histamine release—sedation b. Lung, spleen, skin, gastric mucosa —decrease histamine release c. Ileum—inhibition of ACh release from myenteric plexus neurones d. Certain blood vessels—inhibit NA release—vasodilatation

PIP_2—Phosphatidyl inositol bisphosphate; IP_3—Inositol trisphosphate; DAG—Diacylglycerols;
NO—Nitric oxide; PGI_2—Prostacyclin;
CAs—Catecholamines; cAMP —Cyclic 3', 5' adenosine monophosphate; ACh—Acetylcholine

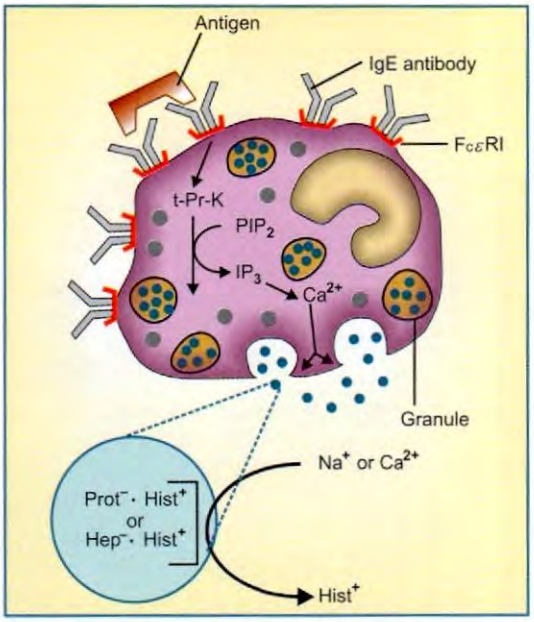


Fig. 11.2: Mechanism of antigen-antibody reaction induced release of histamine from mast cell
In sensitized atopic individual, specific reaginic (IgE) antibody is produced and gets bound to Fc epsilon receptor I (FcεRI) on the surface of mast cells. On challenge, the antigen bridges IgE molecules resulting in transmembrane activation of a tyrosine-protein kinase (t-Pr-K) which phosphorylates and activates phospholipaseCγ. Phosphatidyl inositol bisphosphate (PIP_2) is hydrolysed and inositol trisphosphate (IP_3) is generated which triggers intracellular release of Ca^{2+}. The Ca^{2+} ions induce fusion of granule membrane with plasma membrane of the mast cell resulting in exocytotic release of granule contents. In the granule, positively charged histamine ($Hist^+$) is held complexed with negatively charged protein ($Prot^-$) and heparin (Hep^-) molecules. Cationic exchange with extracellular Na^+ (and Ca^{2+}) sets histamine free to act on the target cells.

considered to be a specific H_2 agonist, has shown greater affinity and selectivity for the H_4 receptor, and is now labelled a H_4 agonist. Eosinophils, mast cells and basophils are the primary cells expressing H_4 receptors. Activation of H_4 receptors enhances chemotaxis of these cells. The H_4 receptor may be playing a role in allergic inflammation. Some H_4 antagonists are being explored as potential drugs for allergic inflammatory conditions like rhinitis and asthma. Intestines and brain are the other sites where H_4 receptors have been located.

PHARMACOLOGICAL ACTIONS

1. Blood vessels Histamine causes marked dilatation of smaller blood vessels, including arterioles, capillaries and venules. On s.c. injection flushing, especially in the blush area, heat, increased heart rate and cardiac output, with little or no fall in BP are produced. Rapid i.v. injection causes fall in BP which has an early short lasting H_1 and a slow but more persistent H_2 component. With low doses only the H_1 component is manifest since H_1 receptors have higher affinity. Fall in BP due to large doses is completely blocked only by a combination of H_1 and H_2 antagonists. Dilatation of cranial vessels causes pulsatile headache.

Like many other autacoids and ACh, vasodilatation caused by histamine is partly (H_1 component) indirect, mediated through 'endothelium dependent relaxing factor' (EDRF), i.e. NO; the receptor being located on the endothelial cells. H_2 receptors mediating vasodilatation are located directly on the vascular smooth muscle.

Larger arteries and veins are constricted by histamine. This is mediated by H_1 receptor on vascular smooth muscle. Histamine also causes increased capillary permeability due to separation of endothelial cells resulting in exudation of plasma. This is primarily a H_1 response.

Injected intradermally, it elicits the *triple response* consisting of:

Red spot: due to intense capillary dilatation.
Wheal: due to exudation of fluid from capillaries and venules.
Flare: i.e. redness in the surrounding area due to arteriolar dilatation mediated by axon reflex.

2. Heart Direct effects of histamine on *in situ* heart are not prominent, but the isolated heart, especially of guinea pig, is stimulated—rate as well as force of contraction is increased. These are primarily H_2 responses but a H_1 mediated negative dromotropic (slowing of A-V conduction) effect has also been demonstrated.

3. Visceral smooth muscle Histamine causes bronchoconstriction; guinea pigs and patients of asthma are highly sensitive. Large doses cause abdominal cramps and colic by increasing intestinal contractions. Guineapig uterus is contracted while that of rat is relaxed; human uterus is not much affected as are most other visceral smooth muscles.

Smooth muscle contraction is a H_1 response. In few instances H_2 mediated relaxation is also seen, e.g. bronchial muscle of sheep, human bronchi after H_1 blockade when H_2 response is unmarked.

4. Glands Histamine causes marked increase in gastric secretion—primarily of acid but also of pepsin (*see* Ch. 47). This is a direct action exerted on parietal cells through H_2 receptors, and is mediated by increased cAMP generation, which in turn activates the membrane proton pump (H^+ K^+ ATPase).

Histamine can increase other secretions also, but the effect is hardly discernable.

5. Sensory nerve endings Itching occurs when histamine is injected i.v. or intracutaneously. Higher concentrations injected more deeply cause pain. These are reflections of the capacity of histamine to stimulate nerve endings.

6. Autonomic ganglia and adrenal medulla These are stimulated and release of Adr occurs, which can cause a secondary rise in BP.

7. CNS Histamine does not penetrate blood-brain barrier—no central effects are produced on i.v. injection. However, intracerebroventricular administration produces rise in BP, cardiac stimulation, behavioural arousal, hypothermia, vomiting and ADH release. These effects are mediated through both H_1 and H_2 postsynaptic receptors.

PATHOPHYSIOLOGICAL ROLES

1. Gastric secretion Histamine has dominant physiological role in mediating secretion of HCl in the stomach (*see* Fig. 47.1). Nonmast cell histamine occurs in gastric mucosa, possibly in cells called 'histaminocytes' situated close to the parietal cells. This histamine has high turnover rate. It is released locally under the influence of all stimuli that evoke gastric secretion (feeding, vagal stimulation, cholinergic drugs and gastrin) and activates the proton pump (H^+K^+ ATPase) through H_2 receptors.

H_2 blockers not only suppress acid secretion induced by histamine but also markedly diminish that in response to ACh and gastrin. By a mutually synergistic interaction the three secretagogues amplify responses to each other with histamine playing the dominant role. As such, antimuscarinic drugs dampen the response to histamine and gastrin as well. All three secretagogues activate the same proton pump (H^+K^+ATPase) in the parietal cell membrane, but through their own receptors.

2. Allergic phenomena Mediation of hypersensitivity reactions was the first role ascribed to histamine. It is an important, but only one of the mediators of such phenomena. Released from mast cells following AG : AB reaction on their surface (involving IgE type of reaginic antibodies; Fig. 11.2) in immediate type of hypersensitivity reactions, histamine is causative in urticaria, angioedema, bronchoconstriction and anaphylactic shock. The H_1 antagonists are effective in controlling these manifestations to a considerable extent, except asthma and to a lesser extent anaphylactic fall in BP in which leukotrienes (especially LTD_4) and PAF appear to be more important. Histamine is not involved in delayed or retarded type of allergic reactions.

3. As transmitter Histamine is believed to be the afferent transmitter which initiates the sensation of itch and pain at sensory nerve endings.

Nonmast cell histamine occurs in brain, especially hypothalamus and midbrain. It is involved in maintaining wakefulness; H_1 antihistaminics owe their sedative action to blockade of this function. In the brain H_1 agonism suppresses appetite. This may explain the appetite promoting action of certain H_1 antagonists. Histamine also appears to participate as a transmitter regulating body temperature, cardiovascular function, thirst, and possibly other functions, mainly through H_2 (postsynaptic receptors) and H_3 (presynaptic autoreceptors and heteroreceptors).

4. Inflammation Histamine is a mediator of vasodilatation and other changes that occur during inflammation. It promotes adhesion of leukocytes to vascular endothelium by expressing adhesion molecule *P-selectin* on endothelial cell surface, sequestrating leukocytes at the

inflammatory site. It may also regulate microcirculation according to local needs.

5. Tissue growth and repair Because growing and regenerating tissues contain high concentrations of histamine, it has been suggested to play an essential role in the process of growth and repair.

6. Headache Histamine has been implicated in certain vascular headaches, but there is no conclusive evidence.

USES

Histamine has no therapeutic use. In the past it has been used to test acid secreting capacity of stomach, bronchial hyperreactivity in asthmatics, and for diagnosis of pheochromocytoma, but these pharmacological tests are risky and obsolete now.

Betahistine It is an orally active, somewhat H_1 selective histamine analogue, which is used to control vertigo in patients of Meniéré's disease. It possibly acts by causing vasodilatation in the internal ear. It is contraindicated in asthmatics and ulcer patients.

VERTIN 8 mg tab., 1/2 to 1 tab. QID.

HISTAMINE RELEASERS

A variety of mechanical, chemical and immunological stimuli are capable of releasing histamine from mast cells.
1. Tissue damage: trauma, stings and venoms, proteolytic enzymes, phospholipase A.
2. Antigen: antibody reaction involving IgE antibodies.
3. Polymers like dextran, polyvinyl pyrrolidone (PVP).
4. Some basic drugs—tubocurarine, morphine, atropine, pentamidine, polymyxin B, vancomycin and even some antihistaminics release histamine by displacing it from the binding site, and not by an immunological reaction. This release is not exocytotic, and does not require Ca^{2+}.
5. Surface acting agents like Tween 80, compound 48/80 etc. The primary action of these substances is release of histamine from mast cells, therefore they are called *'histamine liberators'*. They produce an 'anaphylactoid' reaction—itching and burning sensation, flushing, urticaria, fall in BP, tachycardia, headache, colic and asthma.

H_1 ANTAGONISTS (Conventional antihistaminics)

These drugs competitively antagonize actions of histamine at the H_1 receptors. Recent evidence indicates that histamine H_1 receptor exhibits some degree of constitutive activity at certain sites, and few H_1 antagonists are also inverse agonists. The first H_1 antagonists were introduced in the late 1930s and have subsequently proliferated into an unnecessary motley of drugs. Nevertheless, they are frequently used for a variety of purposes. More commonly employed now are the less sedating/nonsedating second generation H_1 antihistamines added after 1980. Seemingly, H_1 antihistaminics have diverse chemical structures, but majority have a substituted ethylamine side chain. They are classified and listed in Table 11.2.

PHARMACOLOGICAL ACTIONS

Qualitatively all H_1 antihistaminics have similar actions, but there are quantitative differences, especially in the sedative property.

1. Antagonism of histamine The H_1 antagonists effectively block histamine induced bronchoconstriction, contraction of intestinal and other smooth muscle and triple response—especially wheal, flare and itch. Fall in BP produced by low doses of histamine is blocked, but additional H_2 antagonists are required for complete blockade of that caused by higher doses. Pretreatment with these drugs protects animals from death due to i.v. injection of large doses of histamine. Release of Adr from adrenal medulla in response to histamine is abolished. Constriction of larger blood vessel by histamine is also antagonized. Action of histamine on gastric secretion is singularly not affected by these drugs. Cyproheptadine had additional 5-HT_2 receptor blocking activity (*see* p. 189).

2. Antiallergic action Many manifestations of immediate hypersensitivity (type I reactions) are suppressed. Urticaria, itching and angioedema are well controlled. Anaphylactic fall in BP is only partially prevented. Asthma in man is practically unaffected, though anaphylactic bronchoconstriction in guinea pig is largely prevented. This tissue and species dependence of response probably reflects extent of involvement of histamine in the reaction. It is now well established that leukotrienes (LTC_4, LTD_4) and PAF are more important mediators for human asthma.

Table 11.2: Clinical classification, doses and preparations of H_1 antihistaminics

Drug	*Dose and route*	*Preparations*
I. *HIGHLY SEDATIVE*		
Diphenhydramine	25–50 mg oral	BENADRYL 25, 50 mg cap., 12.5 mg/5 ml syr.
Dimenhydrinate	25–50 mg oral	DRAMAMINE 16 mg/5 ml syr, 50 mg tab, GRAVOL 50 mg tab
Promethazine	25–50 mg oral, i.m. (1 mg/kg)	PHENERGAN 10, 25 mg tab., 5 mg/ml elixir, 25 mg/ml inj
Hydroxyzine	25–50 mg oral, i.m.	ATARAX 10, 25 mg tab., 10 mg/5 ml syr, 6 mg/ml drops, 25 mg/ml inj.
II. *MODERATELY SEDATIVE*		
Pheniramine	20–50 mg oral, i.m.	AVIL 25 mg, 50 mg tab, 15 mg/5 ml syr, 22.5 mg/ml inj.
Cyproheptadine	4 mg oral	PRACTIN, CIPLACTIN 4 mg tab., 2 mg/5 ml syrup
Meclozine (Meclizine)	25–50 mg oral	In DILIGAN 12.5 mg + niacin 50 mg tab In PREGNIDOXIN 25 mg + Caffeine 20 mg tab
Cinnarizine	25–50 mg oral	STUGERON, VERTIGON 25 and 75 mg tab.
III. *MILD SEDATIVE*		
Chlorpheniramine	2–4 mg (0.1 mg/kg) oral, i.m.	PIRITON, CADISTIN 4 mg tab
Dexchlorpheniramine	2 mg oral	POLARAMINE 2 mg tab, 0.5 mg/ 5 ml syr
Triprolidine	2.5–5 mg oral	ACTIDIL 2.5 mg tab.
Clemastine	1–2 mg oral	TAVEGYL 1 mg tab., 0.5 mg/5 ml syr
IV. *SECOND GENERATION ANTIHISTAMINICS*		
Fexofenadine	120–180 mg oral	ALLEGRA, ALTIVA, FEXO 120, 180 mg tab
Loratadine	10 mg oral	LORFAST, LORIDIN, LORMEG, 10 mg tab, 1 mg/ml susp.
Desloratadine	5 mg oral	DESLOR, LORDAY, NEOLORIDIN 5 mg tab
Cetirizine	10 mg oral	ALERID, CETZINE, ZIRTIN, SIZON 10 mg tab, 5 mg/5 ml syr.
Levocetirizine	5–10 mg oral	LEVOSIZ, LEVORID, TECZINE 5, 10 mg tab LEVOCET 5 mg tab, 2.5 mg/5 ml syr.
Azelastine	4 mg oral 0.28 mg intranasal	AZEP NASAL SPRAY 0.14 mg per puff nasal spray
Mizolastine	10 mg oral	ELINA 10 mg tab
Ebastine	10 mg oral	EBAST 10 mg tab
Rupatadine	10 mg oral	RUPAHIST 10 mg tab

3. CNS The older antihistamines produce variable degree of CNS depression. This appears to depend on the compound's ability to penetrate the blood-brain barrier and its affinity for the central (compared to peripheral) H_1 receptors. Individual susceptibility to different agents varies considerably. The same drug and dose may incapacitate some subjects, while others may remain alert. An overall grading of the sedative property of H_1 antihistaminics is presented in Table 11.2. Some individuals also experience stimulant effects like restlessness and insomnia. Excitement and convulsions are frequently seen at toxic doses. The second generation antihistaminics are practically nonsedating.

Certain (*see* below) H_1 antihistamines are effective in preventing *motion sickness*. It is not clear whether this is due to antagonism of histamine in the brain or reflects antimuscarinic property of these drugs. Promethazine also controls vomiting of pregnancy and other causes.

Promethazine and few other antihistaminics reduce tremor, rigidity and sialorrhoea of *parkinsonism*. Anticholinergic and sedative properties underlie the benefit.

Some older antihistamines, especially cyproheptadine, have *appetite stimulating* effect.

Some H_1 antihistamines are also effective *antitussives* (*see* Ch. 16).

4. Anticholinergic action Many H_1 blockers in addition antagonize muscarinic actions of ACh. The antimuscarinic action can be graded as:

High	*Low*	*Minimal/ Absent*
Promethazine	Chlorpheniramine	Fexofenadine
Diphenhydramine	Triprolidine	Astemizole
Dimenhydrinate	Cyproheptadine	Loratadine
Pheniramine	Cinnarizine	Cetirizine
		Mizolastine

If used concurrently with atropine or its substitutes, phenothiazines, tricyclic antidepressants or disopyramide, the anticholinergic action adds up.

5. Local anaesthetic Some drugs like pheniramine, promethazine, diphenhydramine have strong while others have weak membrane stabilizing property. However, they are not clinically suitable local anaesthetics because they cause irritation when injected s.c.

Membrane stabilizing activity confers antiarrhythmic property to these compounds.

6. BP Most antihistaminics cause a fall in BP on i.v. injection (direct smooth muscle relaxation or α adrenergic blockade). Promethazine has significant α blocking activity. However, this is not evident on oral administration, though postural hypotension can occur in susceptible individuals.

PHARMACOKINETICS

The conventional H_1 antihistaminics are well absorbed from oral and parenteral routes, metabolized in the liver and excreted in urine. They are widely distributed in the body and enter brain. The newer compounds penetrate brain poorly accounting for their low/absent sedating action. Duration of action of most agents is 4–6 hours, except meclozine, chlorpheniramine, mesolastine, loratadine, cetirizine and fexofenadine which act for 12–24 hours or more. The H_1 antihistaminics are mainly administered orally, but few are available for i.m./i.v. use as well.

SIDE EFFECTS AND TOXICITY

Side effects of first generation H_1 antihistaminics are frequent, but generally mild. Individuals show marked differences in susceptibility to side effects with different drugs. Some tolerance to side effects develops on repeated use.

Sedation, diminished alertness and concentration, light headedness, motor incoordination, fatigue and tendency to fall asleep are the most common. Objective testing shows impairment of psychomotor performance. Patients should be cautioned not to operate motor vehicles or machinery requiring constant attention. Alcohol synergises in producing these effects as do other CNS depressants. Few individuals, however, become restless, nervous and are unable to sleep. Second generation compounds are largely free of CNS effects.

Regular use of conventional antihistamines is not advisable in children, because the CNS depressant property may interfere with learning and academic tasks.

Dryness of mouth, alteration of bowel movement, urinary hesitancy and blurring of vision can be ascribed to anticholinergic property of older antihistaminics.

Epigastric distress and headache may be felt. Local application can cause contact dermatitis. Some drugs like hydroxyzine, cyclizine and fexofenadine are teratogenic in animals; but there is no evidence of excess malformations in humans. Caution is nevertheless to be exercised in prescribing an antihistaminic during pregnancy.

Acute overdose produces central excitation, tremors, hallucinations, muscular incordination, convulsions, flushing, hypotension, fever and some other features of belladonna poisoning. Death is due to respiratory and cardiovascular failure.

SECOND GENERATION ANTIHISTAMINICS

The second generation antihistaminics (SGAs) may be defined as those H_1 receptor blockers marketed after 1980 which have one or more of the following properties:

- Absence of CNS depressant property.
- Higher H_1 selectivitiy: no anticholinergic side effects.
- Additional antiallergic mechanisms apart from histamine blockade: some also inhibit late phase allergic reaction by modifying release/action of leukotrienes, platelet activating factor (PAF) and cytokines, etc.

As per an international consensus group of experts, no compound developed so far merits labelling as 'third generation antihistaminic'.

These newer drugs have the advantage of not impairing psychomotor performance (driving, etc. need not be contraindicated), produce no subjective effects, no sleepiness, do not potentiate alcohol or benzodiazepines. Some patients do complain of sedation, but incidence is similar to that with placebo. However, they have a narrow spectrum of therapeutic usefulness which is limited by the extent of involvement of histamine (acting through H_1 receptors) in the disease state. Their principal indications are:

(i) Allergic rhinitis and conjunctivitis, hay fever, pollinosis: they control sneezing, runny but not blocked nose, and red-watering-itchy eyes.
(ii) Urticaria, dermographism, atopic eczema.
(iii) Acute allergic reactions to drugs and foods.

The SGAs have poor antipruritic, antiemetic and antitussive actions.

Fexofenadine It is the active metabolite of terfenadine, the first nonsedating SGA that was withdrawn because of several deaths due to polymorphic ventricular tachycardia *(Torsades de pointes)* occurring with its higher doses or when it was coadministered with CYP3A4 inhibitors (erythromycin, clarithromycin, ketoconazole, itraconazole, etc.). This toxicity is based on blockade of delayed rectifier K^+ channels in the heart at higher concentrations. Astemizole is another SGA banned for the same reason. Fexofenadine has a low propensity to block delayed rectifier K^+ channels, does not prolong QTc interval. Since it is minimally metabolized, no interaction with CYP3A4 inhibitors have been reported. It is largely free of arrhythmogenic potential, but some cases of ventricular arrhythmia in patients with preexisting long QT interval have been reported. Thus, it is not entirely safe in patients with long QT, bradycardia or hypokalemia.

Fexofenadine penetrates blood-brain barrier poorly; produces minimal sedation or impairment of psychomotor performance. It is free of atropinic side effects. Oral absorption is rapid. It is mainly excreted unchanged in urine and bile, has plasma t½ 11–16 hours and duration of action 24 hours.

Dose: For allergic rhinitis 120 mg OD; for urticaria and other skin allergies 180 mg OD.

Loratadine Another long-acting selective peripheral H_1 antagonist which lacks CNS depressant effects and is fast acting. It is partly metabolized by CYP3A4 to an active

metabolite with a longer t½ of 17 hr, but has not produced cardiac arrhythmia in overdose, though seizures are reported. No interaction with macrolides or antifungals has been noted. Good efficacy has been reported in urticaria and atopic dermatitis.

Desloratadine It is the major active metabolite of loratadine effective at half the dose. Noninterference with psychomotor performance and cardiac safety are documented.

Cetirizine It is a metabolite of hydroxyzine with marked affinity for peripheral H_1 receptors; penetrates brain poorly, but mild sedation and subjective somnolence is experienced by many recipients. It is not metabolized; does not prolong cardiac action potential or produce arrhythmias when given with erythromycin/ketoconazole.

Cetirizine in addition inhibits release of histamine and of cytotoxic mediators from platelets as well as eosinophil chemotaxis during the secondary phase of the allergic response. Thus, it may benefit allergic disorders by other actions as well. It attains high and longer lasting concentration in skin, which may be responsible for superior efficacy in urticaria/atopic dermatitis, as well as for once daily dosing despite elimination t½ of 7–10 hr. It is indicated in upper respiratory allergies, pollinosis, urticaria and atopic dermatitis; also used as adjuvant in seasonal asthma.

Levocetirizine is the active R(–) enantiomer of cetirizine. It is effective at half the dose and appears to produce less sedation and other side effects.

Azelastine This newer H_1 blocker has good topical activity; in addition it inhibits histamine release and inflammatory reaction triggered by LTs and PAF. After intranasal application it has been shown to down regulate intracellular adhesion molecule-1 (ICAM-1) expression on nasal mucosa. Its t½ is 24 hr, but action lasts longer due to active metabolite. Its metabolism is inhibited by CYP 3A4 inhibitors. Given by nasal spray for seasonal and perennial allergic rhinitis it provides quick symptomatic relief lasting 12 hr. Stinging in the nose and altered taste perception are the local side effects. Some somnolence has been reported on nasal application and a tendency to weight gain noted after oral use.

Mizolastine This nonsedating antihistaminic is effective in allergic rhinitis and urticaria by single daily dosing despite a t½ of 8–10 hr and no active metabolite.

Ebastine Another newer SGA that rapidly gets converted to the active metabolite carbastine having a t½ of 10–16 hr. It is nonsedating and active in nasal and skin allergies. Animal studies have found it to prolong Q-Tc interval which makes it liable to arrhythmogenic potential and CYP3A4 interaction, but actual reports are still few.

Rupatadine This recently introduced antihistaminic has additional PAF antagonistic property, and is indicated in allergic rhinitis.

USES

The uses of H_1 antihistaminics are based on their ability to block certain effects of histamine released endogeneously, as well as on their sedative and anticholinergic properties.

1. *Allergic disorders* Antihistaminics do not suppress AG: AB reaction, but block the effects of released histamine—are only palliative. They effectively control certain immediate type of allergies, such as itching, urticaria, seasonal hay fever, allergic conjunctivitis and angioedema of lips, eyelids, etc. However, their action is slow, therefore Adr alone is life-saving in laryngeal angioedema, while intravenously administered antihistaminic may have adjuvant value. Similarly, they cannot be relied upon in anaphylactic shock and have a secondary place to Adr. Benefits are less marked in perennial vasomotor rhinitis, atopic dermatitis and chronic urticarias; combination with an H_2 antagonist succeeds in some cases of chronic urticaria not responding to H_1 antagonist alone.

The antihistaminics are ineffective in bronchial asthma: reasons may be—

- Leukotrienes (LTC_4, D_4) and PAF are more important mediators in humans than histamine.
- Concentration of antihistamines attained at the site may not be sufficient to block high concentration of histamine released locally in the bronchi.

Certain newer compounds like cetirizine have adjuvant role in seasonal asthma.

Antihistaminics are also ineffective in other types of humoral and cell mediated allergies because histamine is not involved. They do suppress urticaria and swellings in serum sickness, but have no effect on other components of the syndrome.

Type I hypersensitivity reactions to drugs (except asthma and anaphylaxis) are suppressed. Some skin rashes also respond.

2. *Other conditions involving histamine* Antihistaminics block symptoms produced by histamine releasers (*see* p. 178); afford symptomatic relief in insect bite and ivy poisoning. Abnormal dermographism is suppressed. They also have prophylactic value in blood/saline infusion induced rigor.

3. *Pruritides* Many conventional antihistamines have antipruritic action independent of H_1 antagonism. Though relief is often incomplete, older antihistaminics chlorpheniramine, diphenhydramine, cyproheptadine remain the first choice drugs for idiopathic pruritus.

4. *Common cold* Antihistaminics do not affect the course of the illness but may afford symptomatic relief by anticholinergic (reduce rhinorrhoea) and sedative actions. The newer nonsedating antihistamines are less effective in this respect.

5. *Motion sickness* Promethazine, diphenhydramine, dimenhydrinate and meclozine have prophylactic value in milder types of motion sickness; should be taken one hour before starting the journey. Promethazine can also be used in morning sickness, drug induced and postoperative vomiting, radiation sickness.

An 'off label' (unapproved) use of cyproheptadine is often made in anorectic/convalescent patients for improving appetite. Such use in underweight children is inappropriate, because its CNS depressant action can affect learning.

6. *Vertigo* Vertigo is typically felt as a spinning sensation or rotation of surroundings, or sense of movement when there is none. Mild vertigo is often reported as 'dizziness'. Vertigo is mostly of vestibular origin, but may also be due to a variety of peripheral or central causes, and is generally accompanied by nausea and vomiting.

The long term therapy of vertigo occurring in Ménière's disease and other conditions is imperfect. A variety of approaches have been tried.

1. Labyrinthine suppressants These drugs suppress end-organ receptors or inhibit central cholinergic pathway (in vestibular nuclei).
   - *Antihistaminics* (with anticholinergic action)—cinnarizine, dimenhydrinate, diphenhydramine, promethazine.
   - *Anticholinergics*— hyoscine, atropine.
   - *Antiemetic phenothiazines*—prochlorperazine.
2. Vasodilators They improve blood flow to labyrinth and brainstem—betahistine is quite frequently used in Ménière's disease.
3. Diuretics They decrease labyrinthine fluid pressure —acetazolamide, thiazides, amiloride.
4. Anxiolytics, antidepressants These drugs appear to modify the sensation of vertigo; may also depress end-organ receptors—diazepam, amitriptyline.
5. Corticosteroids They decrease intralabyrinthine edema due to viral infection or other causes.

Labyrinthine (vestibular) suppressant medications are the principal drugs for management of vertigo as well as that of attendant nausea and vomiting. The H_1 antihistaminic *cinnarizine* and *dimenhydrinate* are the most commonly used vestibular suppressants in this condition. Betahistine (*see* p. 178) is specifically used in Mènière's disease.

Cinnarizine: This H_1 antihistamine has additional weak antimuscarinic, anti-5HT, sedative and vasodilator properties. It modulates Ca^{2+} fluxes and attenuates vasoconstrictor action of many endogenous mediators. The antivertigo property may be due to calcium channel blockade. Cinnarizine inhibits vestibular sensory nuclei in the inner ear, suppresses postrotatory labyrinthine

reflexes, possibly by reducing stimulated influx of Ca^{2+} from endolymph into the vestibular sensory cells. Beneficial effects have been reported in Ménière's disease and other types of vertigo. Side effects are sedation and mild g.i. upset.

Prochlorperazine: This D2 receptor blocking neuroleptic has additional H_1 antihistaminic and labyrinthine suppressant property which is useful in the short-term control of vertigo as well as the associated nausea and vomiting.

Parenteral prochlorperazine is the most effective drug for controlling violent vertigo and vomiting. It is also used in other types of nausea and vomiting (*see* Ch. 48)

7. *Preanaesthetic medication* Promethazine has been used for its anticholinergic and sedative properties.

8. *Cough* Antihistaminics like chlorpheniramine, diphenhydramine and promethazine are constituents of many popular cough remedies. They have no selective cough suppressant action, but may afford symptomatic relief by sedative and anticholinergic property (*see* Ch. 16).

9. *Parkinsonism* Promethazine and some others afford mild symptomatic relief in early cases—based on anticholinergic and sedative property.

10. *Acute muscle dystonia* Caused by antidopaminergic-antipsychotic drugs is promptly relieved by parenteral promethazine, diphenhydramine or hydroxyzine. This is again based on central anticholinergic action of the drugs.

11. *As sedative, hypnotic, anxiolytic* Antihistamines with CNS depressant action have been used as sedative and to induce sleep, especially in children. However, promethazine has produced serious respiratory depression in young children; few deaths are on record; it is not indicated in children aged 2 years or less. For promoting sleep, antihistaminics are not as dependable as benzodiazepines. Hydroxyzine has been used in anxiety associated with autonomic manifestations.

(Combinations of antihistaminics with antidiarrhoeals or bronchodilators, or those containing more than one antihistaminic are banned in India.)

H_2 antagonist The first H_2 blocker *Burimamide* was discovered by Black in 1972. *Metiamide* was the next, but both were not found suitable for clinical use. *Cimetidine* was introduced in 1977 and gained wide usage. *Ranitidine, famotidine, roxatidine,* and many others have been added subsequently. They are primarily used in peptic ulcer, gastroesophageal reflux and other gastric hypersecretory states. They are described in Ch. 47.

H_3 antagonist Though some selective H_3 antagonists have been produced, they have not found any clinical utility.

PROBLEM DIRECTED STUDY

11.1 A taxi driver aged 30 years presented with sudden onset running and itchy nose, bouts of sneezing, partial nasal blockage, redness and watering from the eyes, but no fever, bodyache or malaise. He gave history of similar episodes occurring off and on during the spring season. A diagnosis of seasonal allergic rhinitis was made and the doctor prescribed an oral antiallergic medication to be taken once a day till symptoms subside.

(a) Which antiallergic medicine would be suitable for this patient? Which antiallergic drugs should be avoided?

(b) Will the above medication prevent/reduce recurrent episodes of rhinitis that this patient gets during spring. If not, can some medications be added to prevent/subdue the episodes during the vulnerable season.

(see Appendix-1 for solution).

Chapter 12 5-Hydroxytryptamine, its Antagonists and Drug Therapy of Migraine

5-HYDROXYTRYPTAMINE (5-HT, Serotonin)

Serotonin was the name given to the vasoconstrictor substance which appeared in the serum when blood clotted and *Enteramine* to the smooth muscle contracting substance present in enterochromaffin cells of gut mucosa. In the early 1950s both were shown to be *5-hydroxytryptamine* (5-HT). About 90% of body's content of 5-HT is localized in the enterochromaffin cells of stomach and intestines; most of the rest is in platelets and brain. It is also found in wasp and scorpion sting, and is widely distributed in invertebrates and plants (banana, pear, pineapple, tomato, stinging nettle, cowhage).

SYNTHESIS, STORAGE AND DESTRUCTION

5-HT is β-aminoethyl-5-hydroxyindole. It is synthesized from the amino acid tryptophan and degraded primarily by MAO and to a small extent by a dehydrogenase (Fig. 12.1).

There is close parallelism between CAs and 5-HT. The decarboxylase is non-specific, acts on DOPA as well as 5-hydroxytryptophan (5-HTP) to produce DA and 5-HT respectively. Like NA, 5-HT is actively taken up by an amine pump *serotonin transporter (SERT),* a Na^+ dependent carrier, which operates at the membrane of platelets (therefore, 5-HT does not circulate in free form in plasma) and serotonergic nerve endings. This pump is inhibited by selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). Platelets do not synthesize 5-HT but acquire it by uptake during passage through intestinal blood vessels. Again like CAs, 5-HT is stored within storage vesicles, and its uptake at the vesicular membrane by *vesicular monoamine transporter (VMAT-2)* is inhibited by reserpine, which causes depletion of CAs as well as 5-HT. The degrading enzyme MAO is also common for both. The isoenzyme MAO-A preferentially metabolizes 5-HT.

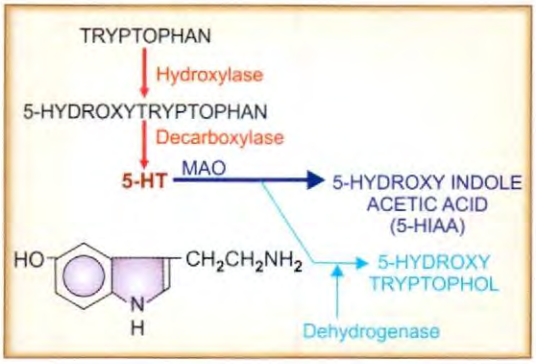


Fig. 12.1: Synthesis and degradation of 5-hydroxytryptamine (5-HT)

SEROTONERGIC (5-HT) RECEPTORS

Gaddum and Picarelli (1957) classified 5-HT receptors into musculotropic (D type) and neurotropic (M type) on the basis of their blockade by *D*ibenzyline (phenoxybenzamine) and *M*orphine. The classical 5-HT antagonists methysergide and cyproheptadine blocked D

type receptors. Subsequently 5-HT receptors were differentiated by their high or low affinity for [^{3}H] 5-HT in radioligand binding studies. The present system of classifying 5-HT receptors is based on molecular characterization and cloning of the receptor cDNAs. Some subtypes of 5-HT receptors have specific tissue distribution, but certain tissues express more than one subtype.

Four families of 5-HT receptors (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_{4-7}) comprising of 14 receptor subtypes have so far been recognized. However, only some of these have been functionally correlated. Selective agonists/antagonists have been defined only for these subtypes. Knowledge of subtypes of 5-HT receptors has assumed importance because some newly developed therapeutically useful drugs can only be described in terms of 5-HT receptor subtype selective agonists or antagonists.

All 5-HT receptors (except 5-HT_3) are G protein coupled receptors which function through decreasing (5-HT_1) or increasing (5-HT_4, 5-HT_6, 5-HT_7) cAMP production, or by generating IP_3/DAG (5-HT_2) as second messengers. The 5-HT_3 is a ligand gated cation (Na^+,K^+) channel which on activation elicits fast depolarization.

5-HT_1 Receptors Six subtypes (5-$HT_{1A, B, D, E, F, P}$) have been identified. The 5-HT_{1C} receptor is now designated 5HT_{2C}. All subtypes of 5-HT_1 receptor couple with Gi/Go protein and inhibit adenylyl cyclase; 5-HT_{1A} in addition activates K^+ channels (resulting in hyperpolarization) and inhibits Ca^{2+} channels. These receptors function primarily as autoreceptors in brain—inhibit firing of 5-HT neurones or release of 5-HT from nerve endings.

The most important location of 5-HT_{1A} receptor is somato-dendritic synapses in raphe nuclei of brainstem; their activation serves to reduce firing of raphe neurones. Hippocampus is another important site. The antianxiety drug *buspirone* acts as a partial agonist of 5-HT_{1A} receptor. The 5-HT_{1D} receptor has been shown to regulate dopaminergic tone in substantia nigra–basal ganglia, and 5-$HT_{1D/1B}$ (the same receptor is 5-HT_{1B} in rat) to cause constriction of cranial blood vessels. The antimigraine drug *sumatriptan* is a selective 5-$HT_{1D/1B}$ agonist. Other functions subserved by 5-HT_{1D} receptors are inhibition of 5-HT release from forebrain serotonergic neurones, NA release from sympathetic nerve endings and that of inflammatory neuropeptides from nerve endings in cranial blood vessels.

The peripheral 5-HT_{1P} receptors expressed on neurones of enteric nervous system mediate their slow depolarization.

5-HT_2 Receptors There are 3 subtypes of 5-HT_2 receptor; all are coupled to Gq protein→activate phospholipase C and function through generation of IP_3/DAG. 5-HT_{2A} receptor also inhibits K^+ channels resulting is slow depolarization of neurones. α-methyl 5-HT is a selective agonist for all 3 subtypes.

5-HT_{2A} is the most widely expressed postjunctional 5-HT receptor (designated earlier as D type) located on vascular and visceral smooth muscle, platelets and cerebral neurones especially prefrontal cortex. It mediates most of the direct actions of 5-HT like vasoconstriction, intestinal, uterine and bronchial muscle contraction, platelet aggregation and activation of cerebral neurones. *Ketanserin* is a 5-HT_2 antagonist more selective for 5-HT_{2A}.

Contraction of rat gastric fundus is mediated by 5-HT_{2B} receptor.

5-HT_{2C} receptor is located on vascular endothelium—elicits vasodilatation through EDRF release. Choroid plexus expresses large number of 5-HT_{2C} receptors which may regulate CSF formation.

5-HT_3 Receptor This is the neuronal 5-HT receptor which rapidly depolarizes nerve endings by opening the cation channel located within it and corresponds to the original M type receptor. It mediates the indirect and reflex effects of 5-HT at:

(i) Somatic and autonomic nerve endings mediating pain, itch, coronary chemoreflex (bradycardia, fall in BP due to withdrawal of sympathetic tone, respiratory stimulation or apnoea elicited by stimulation of receptors in the coronary bed), and other visceral reflexes.

(ii) Nerve endings in myenteric plexus eliciting augmentation of peristalsis, emetic reflex.

(iii) Area postrema and nucleus tractus solitarious in brainstem inducing nausea, vomiting.

Ondansetron is a selective 5-HT_3 antagonist which inhibits vomiting by blocking these receptors in the brainstem as well as in gut wall. 2-Methyl 5-HT is a selective 5-HT_3 agonist.

5-HT_{4-7} Receptors The 5-HT_4 receptor couples to Gs protein, activates adenylyl cyclase and has been demonstrated in the mucosa, plexuses and smooth muscle of the gut where it is probably involved in augmenting intestinal secretion and peristalsis. It is also located in brain, especially hippocampus and the colliculi where it causes slow depolarization by decreasing K^+ conductance.

Cisapride and *renzapride* are selective 5-HT_4 agonists.

The recently cloned 5-HT_5, 5-HT_6 and 5-HT_7 receptors are closely related to the 5-HT_4 receptor. These are mainly located in specific brain areas, but their functional role is not known. An interesting finding is that *clozapine* (atypical antipsychotic) has high affinity for 5-HT_6 and 5-HT_7 receptors in addition to being a 5-$HT_{2A/2C}$ antagonist.

Salient features of important 5-HT receptor subtypes

5-HT$_1$	:	Autoreceptors; inhibit serotonergic neural activity in brain. *5-HT$_{1A}$*—present in raphe nuclei and hippocampus; buspirone (antianxiety) may act through these receptors. *5-HT$_{1D/1B}$*—Constricts cranial blood vessels and inhibits release of inflammatory neuropeptides in them; sumatriptan (antimigraine) acts through these receptors.
5-HT$_{2A}$	:	Previously D type receptor; most important postjunctional receptor mediating direct actions of 5-HT like vascular and visceral smooth muscle contraction, platelet aggregation, neuronal activation in brain; ketanserin blocks these receptors.
5-HT$_3$	:	Previously M type receptor; depolarizes neurones by gating cation channels; elicits reflex effects of 5-HT—emesis, gut peristalsis, bradycardia, transient hypotension, apnoea, pain, itch; ondansetron (antiemetic) acts by blocking these receptors.
5-HT$_4$	:	Mediate intestinal secretion, augmentation of peristalsis. Renzapride (prokinetic) is a selective 5-HT$_4$ agonist.

ACTIONS

5-HT is a potent depolarizer of nerve endings. It thus exerts direct as well as reflex and indirect effects. Tachyphylaxis is common with repeated doses of 5-HT. The overall effects therefore are often variable.

1. CVS Arteries are constricted (by direct action on vascular smooth muscle) as well as dilated (through EDRF release) by 5-HT, depending on the vascular bed and the basal tone. In addition, 5-HT releases Adr from adrenal medulla, affects ganglionic transmission and evokes cardiovascular reflexes. The net effect is complex. Larger arteries and veins are characteristically constricted. In the microcirculation 5-HT dilates arterioles and constricts venules: capillary pressure rises and fluid escapes. The direct action to increase capillary permeability is feeble.

Isolated heart is stimulated by 5-HT: both directly and by release of NA from nerve endings. In intact animals, bradycardia is mostly seen due to activation of coronary chemoreflex (Bezold Jarisch reflex) through action on vagal afferent nerve endings in the coronary bed, evoking bradycardia, hypotension and apnoea. BP: a triphasic response is classically seen on i.v. injection of 5-HT in animals.

- Early sharp fall in BP—due to coronary chemoreflex.
- Brief rise in BP—due to vasoconstriction and increased cardiac output.
- Prolonged fall in BP—due to arteriolar dilatation and extravasation of fluid.

However, 5-HT is not involved in the physiological regulation of BP.

5-HT receptor function in the gut

5-HT$_{2A}$	:	intestinal smooth muscle—contraction.
5-HT$_3$	:	fast depolarization of enteric plexus neurones; release of 5-HT from enterochromaffin cells.
5-HT$_4$	:	lower esophageal sphincter—contraction; enteric plexus—ACh release—enhanced peristalsis; intestinal mucosa—secretion.
5-HT$_{1P}$	:	slow depolarization of enteric plexus neurones.

2. Visceral smooth muscles 5-HT is a potent stimulator of g.i.t., both by direct action as well as through enteric plexuses. Several subtypes of 5-HT receptors are present in the gut (*See* box). Peristalsis is increased and diarrhoea can occur (also due to increased secretion).

5-HT constricts bronchi, but is less potent than histamine. Action on other smooth muscles in man are feeble and inconsistent.

3. Glands 5-HT inhibits gastric secretion (both acid and pepsin), but increases mucus production. It thus has ulcer protective property. Effect on other glandular secretions is not significant.

4. Nerve endings and adrenal medulla Afferent nerve endings are activated by 5-HT

causing tingling and pricking sensation, as well as pain. Depolarization of visceral afferents elicits respiratory and cardiovascular reflexes, nausea and vomiting. 5-HT is less potent than histamine in releasing CAs from adrenal medulla.

5. Respiration A brief stimulation of respiration (mostly reflex from bronchial afferents) and hyperventilation are the usual response, but large doses injected i.v. can cause transient apnoea through coronary chemoreflex.

6. Platelets By acting on 5-HT_{2A} receptors 5-HT causes changes in shape of platelets, but is a weak aggregator. However, it does not induce the release reaction.

7. CNS Injected i.v., 5-HT does not produce central effects because of poor entry across blood-brain barrier. However, it serves as a transmitter, primarily inhibitory. Direct injection in the brain produces sleepiness, changes in body temperature, hunger and a variety of behavioural effects.

PATHOPHYSIOLOGICAL ROLES

1. *Neurotransmitter* 5-HT is an established neurotransmitter in the brain. The brain 5-HT has a fast turnover rate. Cells containing 5-HT are present in the raphe nuclei of brainstem, substantia nigra and few other sites. They send axons rostrally (to limbic system, cortex and neostriatum) as well as caudally to spinal cord. 5-HT appears to be involved in sleep, temperature regulation, thought, cognitive function, behaviour and mood, appetite, vomiting and pain perception. Some serotonergic neurones are present in intestines also.

Experimental evidence from pharmacological manipulation of 5-HT metabolism, genetic models (like knock out mice), as well as therapeutic effect of selective serotonin reuptake inhibitors (SSRIs) and TCAs, etc. strongly suggest a role of 5-HT in the pathogenesis of anxiety, depression, aggression and other behavioural disorders in humans.

2. *Precursor of melatonin* 5-HT is the precursor of melatonin in pineal gland. It is believed to regulate the biological clock and maintain circadian rhythm.

3. *Neuroendocrine function* The hypothalamic neurones that control release of anterior pituitary hormones are probably regulated by serotonergic mechanism.

4. *Nausea and vomiting* Especially that evoked by cytotoxic drugs or radiotherapy is mediated by release of 5-HT and its action on 5-HT_3 receptors in the gut, area postrema and nucleus tractus solitarious.

5. *Migraine* 5-HT is said to initiate the vasoconstrictor phase of migraine and to participate in neurogenic inflammation of the affected blood vessels. Methysergide (5-HT antagonist) is an effective prophylactic and sumatriptan (5-$HT_{1D/1B}$ agonist) can control an attack. However, the role of 5-HT in this condition is not precisely known.

6. *Haemostasis* Platelets release 5-HT during aggregation at the site of injury to blood vessel. Acting in concert with collagen and other mediators, this 5-HT accelerates platelet aggregation and clot formation. Thus, it serves to amplify the response. Its contractile action appears to promote retraction of the injured vessel. Both the above actions contribute to haemostasis.

7. *Raynaud's phenomenon* Release of 5-HT from platelets may trigger acute vasospastic episodes of larger arteries involved in Raynaud's phenomena. Ketanserin has prophylactic value.

8. *Variant angina* Along with thromboxaneA_2, 5-HT released from platelets has been implicated in causing coronary spasm and variant angina. However, the inefficacy of anti 5-HT drugs in this condition points to the involvement of other mediators.

9. *Hypertension* Increased responsiveness to 5-HT, as well as its reduced uptake and clearance by platelets has been demonstrated in hypertensive patients. Ketanserin has antihypertensive property. 5-HT has been held responsible for preeclamptic rise in BP.

10. *Intestinal motility* Enterochromaffin cells and 5-HT containing neurones may regulate peristalsis and local reflexes in the gut. This

system appears to be activated by intestinal distension and vagal efferent activity.

11. *Carcinoid syndrome* The carcinoid tumours produce massive quantities of 5-HT. Bowel hypermotility and bronchoconstriction are features of carcinoid which appear to be due to 5-HT, but flushing and hypotension are probably caused by other mediators. Pellagra in carcinoid may occur due to diversion of tryptophan for synthesizing 5-HT.

Use Due to widespread and variable actions, 5-HT has no therapeutic use.

DRUGS AFFECTING 5-HT SYSTEM

1. *5-HT precursor* Tryptophan increases brain 5-HT and produces behavioural effects because tryptophan hydroxylase in brain is not saturated by the amount of tryptophan available physiologically.

2. *Synthesis inhibitor* p-Chlorophenylalanine (PCPA) selectively inhibits tryptophan hydroxylase (rate limiting step) and reduces 5-HT level in tissues. It is not used clinically due to high toxicity.

3. *Uptake inhibitor* Tricyclic antidepressants inhibit 5-HT uptake along with that of NA. The selective serotonin reuptake inhibitors (SSRI) like fluoxetine, sertraline, etc. inhibit only 5-HT reuptake and have antidepressant-antianxiety property.

4. *Storage inhibitor* Reserpine blocks 5-HT (as well as NA) uptake into storage vesicles by inhibiting VMAT-2, and causes depletion of all monoamines. Fenfluramine selectively releases 5-HT by promoting its reverse transport at serotonergic nerve endings in the brain, followed by its prolonged depletion. It has anorectic property.

5. *Degradation inhibitor* Nonselective MAO inhibitor (tranylcypromine) and selective MAO-A inhibitor (clorgyline) increase 5-HT content by preventing its degradation.

6. *Neuronal degeneration* 5, 6 dihydroxytryptamine selectively destroys 5-HT neurones.

7. *5-HT receptor agonists* A diverse range of compounds producing a variety of actions have been found to activate one or more subtypes of 5-HT receptors. Notable among these are:

(i) *D-Lysergic acid diethyl amide (LSD)*—Synthesized as an ergot derivative, LSD was found to be an extremely potent hallucinogen. It is a nonselective 5-HT agonist—activates many subtypes of 5-HT receptors including 5-HT_{1A} on raphe cell bodies, $5\text{-HT}_{2A/2C}$ (probably responsible for the hallucinogenic effect) and $5\text{-HT}_{5\text{-}7}$ in specific brain areas. However, LSD inhibits 5-HT_{2A} receptors in the ileum. A number of other hallucinogens also interact with brain 5-HT receptors.

(ii) *Azapirones* like buspirone, gepirone and ipsapirone are a novel class of antianxiety drugs which do not produce sedation. They act as partial agonists of 5-HT_{1A} receptors in the brain.

(iii) *Sumatriptan* and other triptans are selective $5\text{-HT}_{1D/1B}$ agonists. They constrict cerebral blood vessels and have emerged as the most effective treatment of acute migraine attacks.

(iv) *Cisapride* This prokinetic drug, which increases gastrointestinal motility, is a selective 5-HT_4 agonist. Renzapride is still more selective for 5-HT_4 receptors.

8. *5-HT receptor antagonists* A variety of drugs block serotonergic receptors; many are nonselective, but some newer ones are highly subtype selective.

5-HT ANTAGONISTS

The ability to antagonize at least some actions of 5-HT is found in many classes of drugs, e.g. ergot derivatives (ergotamine, LSD, 2-bromo LSD, methysergide), adrenergic α blockers (phenoxybenzamine), antihistaminics (cyproheptadine, cinnarizine), chlorpromazine, morphine, etc., but these are nonselective and interact with receptors for other signal molecules as well. Many are partial agonists or antagonize certain actions of 5-HT but mimic others. The salient features of drugs which have been used clinically as 5-HT antagonists and some newer selective antagonists are described below:

1. Cyproheptadine It primarily blocks 5-HT_{2A} receptors and has additional H_1 antihistaminic, anticholinergic and sedative properties (*see* Ch. 11). Like other antihistaminics, it has been used in allergies and is a good antipruritic, but the anti 5-HT action has no role in these conditions. It increases appetite and has been used in children as well as in poor eaters to promote weight gain. The H_1 antihistaminic action and an action on growth hormone secretion has been suggested to account for this property.

The anti 5-HT activity of cyproheptadine has been utilized in controlling intestinal manifestations of carcinoid and postgastrectomy dumping syndromes, as well as in antagonizing priapism/orgasmic delay caused by 5-HT uptake inhibitors like fluoxetine and trazodone.

Side effects drowsiness, dry mouth, confusion, ataxia, weight gain.

2. Methysergide It is chemically related to ergot alkaloids; antagonizes action of 5-HT on vascular and visceral smooth muscles, without producing other ergot like effects. It does not interact with α adrenergic or dopamine receptors. Methysergide is a potent 5-$HT_{2A/2C}$ antagonist with some tissue specific agonistic actions as well. Introduced briefly for migraine prophylaxis, carcinoid and postgastrectomy dumping syndrome, it went into disuse because it caused abdominal, pulmonary and endocardial fibrosis.

3. Ketanserin It has selective 5-HT_2 receptor blocking property with negligible action on 5-HT_1, 5-HT_3 and 5 HT_4 receptors and no partial agonistic activity. 5-HT induced vasoconstriction, platelet aggregation and contraction of airway smooth muscle are antagonized. Weak H_1 and dopaminergic blocking activities are also present.

Ketanserin has significant α_1 adrenergic blocking activity and was introduced as antihypertensive, but did not gain popularity.

Ritanserin is a relatively more 5-HT_{2A} selective congener of ketanserin.

4. Clozapine In addition to being a weak dopaminergic antagonist, this atypical antipsychotic is a 5-$HT_{2A/2C}$ blocker (*see* Ch. 32). Clozapine may also exert inverse agonist activity at cerebral 5-$HT_{2A/2C}$ receptors which may account for its efficacy in resistant cases of schizophrenia.

5. Risperidone This atypical antipsychotic is a combined 5-HT_{2A} + dopamine D2 antagonist, similar to clozapine. Like the latter, it especially ameliorates negative symptoms of schizophrenia, but produces extrapyramidal side effects.

Other atypical antipsychotics like *olanzapine* and *quetiapine* are also combined 5-HT and DA antagonists, but interact with other neurotransmitter receptors as well.

6. Ondansetron It is the prototypical selective 5-HT_3 antagonist that has shown remarkable efficacy in controlling nausea and vomiting following administration of highly emetic anticancer drugs and radiotherapy. The 5-HT_3 antagonists are described in Ch. 48.

ERGOT ALKALOIDS

Ergot is a fungus *Claviceps purpurea* which grows on rye, millet and some other grains. The grain is replaced by a purple, hard, curved body called 'sclerotium'. Epidemics of ergot poisoning (ergotism), due to consumption of contaminated grains, have been recorded from the beginning of history. It still occurs in epidemic and sporadic forms. Painful dry gangrene of hands and feet which become black (as if burnt) occurs due to vasospastic ischemia. Miscarriages occur in women and cattle.

Some suffer hallucinations and a convulsive type is also described.

Ergot had been used by midwives to quicken labour since the middle ages. This use received medical sanction in the 19th century, but its dangers were recognized by the beginning of the 20th century and then it was advocated only after delivery. Dale and Barger (1906 onwards) isolated the ergot alkaloids and studied their pharmacology. Ergometrine was isolated in 1935.

Ergot contains a host of pharmacologically active substances—alkaloids, LSD, histamine, ACh, tyramine and other amines, sterols, etc.

Natural ergot alkaloids

These are tetracyclic indole containing compounds which may be considered as derivatives of *lysergic acid*. They are divided into—

(a) *Amine alkaloid* Ergometrine (Ergonovine): which is oxytocic.

(b) *Amino acid alkaloids* Ergotamine, Ergotoxine (mixture of ergocristine + ergocornine + ergocryptine): they are vasoconstrictor and α adrenergic blocker/partial agonist.

Semisynthetic derivatives

(a) Dihydroergotamine (DHE), Dihydroergotoxine (Codergocrine): are antiadrenergic, cerebroactive.

(b) 2-Bromo-α-ergocryptine (Bromocriptine): is a dopaminergic D2 agonist (*see* Ch. 17).

(c) Methysergide: it is mainly anti 5-HT.

The ergot alkaloid related compounds have diverse pharmacological properties. They act as agonists, partial agonists and antagonists on certain subtypes of α adrenergic, serotonergic and dopaminergic receptors in a tissue specific manner.

Actions

Ergotamine It acts as a partial agonist and antagonist at α adrenergic and all subtypes of 5-HT_1 and 5-HT_2 receptors, but does not interact with 5-HT_3 or dopamine receptors. Sustained vasoconstriction (because of very slow dissociation from the receptors), visceral smooth muscle contraction, vasomotor centre depression are produced, and the action of NA and 5-HT on smooth muscles is antagonized. However, the overall effect of oral/rectal doses of ergotamine on BP is insignificant. It is a potent emetic (through CTZ and vomiting centre) and moderately potent oxytocic. At high doses CNS stimulation and paresthesias may be experienced. On chronic exposure (ergot poisoning) vasoconstriction is accompanied by damage to capillary endothelium resulting in thrombosis, vascular stasis and gangrene.

Dihydroergotamine (DHE) Hydrogenation of ergotamine reduces serotonergic and α-adrenergic agonistic actions, but enhances α-receptor blocking property. Consequently DHE is a less potent vasoconstrictor; primarily constricts capacitance vessels and causes less intimal damage. It is a weaker emetic and oxytocic, but has some antidopaminergic action as well.

Dihydroergotoxine (Codergocrine) This hydrogenated mixture of ergotoxine group of alkaloids is a more potent α blocker and a very weak vasoconstrictor. In the brain, a variety of partial agonistic/antagonistic actions on 5-HT receptors, as well as metabolic and vascular effects are produced. In addition, ACh release in cerebral cortex may be enhanced. Dihydroergotoxine has been advocated for treatment of dementia (*see* Ch. 35).

Bromocriptine The 2-bromo derivative of ergocryptine is a relatively selective dopamine D2 agonist with prominent action on pituitary lactotropes (inhibits prolactin release), in striatum (antiparkinsonian) and in CTZ (emetic). The emetic action is weaker than that of ergotamine. In certain brain areas weak antidopaminergic action has also been shown. It has very weak anti 5-HT or α blocking actions and is not an oxytocic.

Ergometrine (Ergonovine) This amine ergot alkaloid has very weak agonistic and practically no antagonistic action on α adrenergic receptors: vasoconstriction is not significant. Partial agonistic action on 5-HT_2 receptors is most probably responsible for its powerful uterotonic effect. It is a moderately potent 5-HT_2 antagonist in g.i. smooth muscle and a weak dopaminergic agonist on the pituitary lactotropes as well as CTZ; emetic potential is low. The most prominent action of ergometrine is contraction of myometrium, because of which it is used exclusively in obstetrics (*see* Ch. 23).

Pharmacokinetics Oral bioavailability of amino acid ergot alkaloids and their hydrogenated derivatives is poor (< 1%) due to slow and incomplete absorption as well as high firstpass metabolism. Bioavailability is higher after sublingual and rectal administration, but still often erratic. They are metabolized in liver and excreted primarily in bile. Ergotamine is sequestrated in tissues—produces longer lasting actions compared to its plasma t½ of 2 hours. Ergot alkaloids effectively cross blood-brain barrier.

Adverse effects Nausea, vomiting, abdominal pain, muscle cramps, weakness, paresthesias, coronary and other vascular spasm, chest pain (due to coronary vasoconstriction) are the frequent side effects. These drugs are contraindicated in presence of sepsis, ischaemic heart disease, peripheral vascular disease, hypertension, pregnancy, liver and kidney disease.

Preparations and dose

Ergotamine: For migraine 1–3 mg oral/sublingual, repeat as required (max 6 mg in a day); rarely 0.25–0.5 mg i.m. or s.c.; ERGOTAMINE 1 mg tab, 0.5 mg/ml inj.

Dihydroergotamine: For migraine 2–6 mg oral (max 10 mg/day), 0.5–1 mg i.m., s.c. repeat hourly (max 3 mg); DIHYDERGOT, DHE 1 mg tab, MIGRANIL 1 mg/ml inj.

Dihydroergotoxine (codergocrine) For dementia 1–1.5 mg oral or sublingual, 0.15–0.6 mg i.m., HYDERGINE 1.5 mg tab, CERELOID 1 mg tab.

DRUG THERAPY OF MIGRAINE

Migraine is a mysterious disorder characterized by pulsating headache, usually restricted to one side, which comes in attacks lasting 4–48 hours and is often associated with nausea, vomiting, sensitivity to light and sound, flashes of light, vertigo, loose motions and other symptoms. Two major types are—*migraine with aura* (classical migraine) in which headache is preceded by visual or other neurological symptoms, and *migraine without aura* (common migraine). Pulsatile dilatation of certain large cranial vessels is the immediate cause of pain. The pathogenic mechanisms are not well understood.

The *Vascular theory* holds that initial vasoconstriction or shunting of blood through carotid arterio-venous anastomoses produces cerebral ischaemia and starts the attack. The *Neurogenic theory* considers it to be a spreading depression of cortical electrical activity followed by vascular phenomena. Some triggering event appears to produce neurogenic inflammation of the affected blood vessel wall which is amplified by retrograde transmission in the afferent nerves and release of mediators like 5-HT, neurokinin, substance P, calcitonin gene related peptide (CGRP), nitric oxide, etc. Perivascular edema occurs due to leakage of plasma from the inflamed cranial vessels, and pain nerve endings in the dura are activated by stretching.

Changes in blood/urinary levels of 5-HT and its metabolites during migraine attack, its precipitation by 5-HT releasers and efficacy of drugs having actions in the serotonergic system to prevent/abort/terminate migraine attacks suggests a pivotal role of 5-HT in this disorder.

Drug therapy of migraine

Severity		*Drug therapy*
Mild	:	Simple analgesics/NSAIDs or their combinations (± antiemetic)
Moderate	:	NSAIDs combinations/a triptan/ ergot alkaloids (+ antiemetic)
Severe	:	a Triptan/ergot alkaloids (+ antiemetic) + Prophylaxis • Propranolol/other β blockers • Amitriptyline/other tricyclic antidepressants • Flunarizine/other Ca^{2+} channel blockers • Valproate/topiramate

Drug therapy of migraine has to be individualized: severity and frequency of attacks and response of individual patients to drugs used earlier determine the choice. The strategy mostly adopted is summarized in the box.

Mild migraine Cases having fewer than one attack per month of throbbing but tolerable headache lasting upto 8 hours which does not incapacitate the individual, may be classified as mild migraine.

(i) *Simple analgesics* like paracetamol (0.5–1 g) or aspirin (300–600 mg) taken at the first indication of an attack and repeated 4–6 hourly abort and suppress most mild attacks.

(ii) *Nonsteroidal antiinflammatory drugs (NSAIDs) and their combinations* Drugs like ibuprofen (400–800 mg 8 hourly), naproxen (500 mg followed by 250 mg 8 hourly), diclofenac (50 mg 8 hourly), mephenamic acid (500 mg 8 hourly), indomethacin (50 mg 6–8 hourly) either alone or combined with paracetamol/codeine/diazepam or another sedative/diphenhydramine or another antihistaminic/caffeine are found more satisfactory by some patients. Dispersible or effervescent formulations of the analgesic should be preferred, because gastric stasis attending migraine attack may hamper absorption from the regular tablet. Analgesics are more effective in migraine without aura, but certain patients of migraine with aura also prefer them over specific antimigraine drugs (triptans/ergot alkaloids). Analgesics are taken only till the attack passes off. Excessive use of analgesic may itself cause headache. Taken in the prodromal stage they can also abort an attack, but long-term treatment on a regular schedule to ward off migraine attacks is not advised.

(iii) *Antiemetics* Gastric stasis occurs during migraine which delays absorption of oral drugs. Metoclopramide (10 mg oral/i.m.) is frequently used. It relieves nausea, vomiting and gastric stasis. When the patient has already vomited, it is better to give the antiemetic by injection. Domperidone (10–20 mg oral) and prochlorperazine (10–25 mg oral/i.m.) are also effective. Diphenhydramine or promethazine exert sedative as well as antiemetic action.

Moderate migraine Migraine may be labelled as moderate when the throbbing headache is more intense, lasts for 6–24 hours, nausea/vomiting and other features are more prominent and the patient is functionally impaired. One or more attacks occur per month.

Simple analgesics are usually not effective, but stronger NSAIDs or their combinations mentioned above are beneficial in many cases. The remaining are treated with a specific antimigraine drug, i.e. a triptan or an ergot preparation. Antiemetics are almost regularly needed. Prophylactic therapy is advised only when attacks are more frequent than 2–3 per month.

Severe migraine These patients suffer 2–3 or more attacks per month of severe throbbing headache lasting 12–48 hours, often accompanied by vertigo, vomiting and other symptoms; the subject is grossly incapacitated during the attack.

Analgesics/NSAIDs and their combinations usually do not afford adequate relief—specific antimigraine drugs have to be prescribed along with antiemetics. Combination of a longer acting analgesic like naproxen with a triptan may be more suitable for patients who have prolonged migraine attacks and suffer recurrences when treated with a triptan alone. Prophylactic regimens lasting 6 months or more are recommended.

SPECIFIC ANTIMIGRAINE DRUGS

Ergotamine It is the most effective ergot alkaloid for migraine. Given early in attack, lower doses generally suffice, and relief is often dramatic. However, when pain has become severe—larger doses are needed and control may be achieved only after few hours. Oral/sublingual route is preferred, 1 mg is given at half hour intervals till relief is obtained or a total of 6 mg is given. Parenteral administration, though rapid in action is more hazardous.

Ergotamine acts by constricting the dilated cranial vessels and/or by specific constriction of carotid A-V shunt channels. Ergotamine and DHE have also been shown to reduce neurogenic inflammation and leakage of plasma in duramater that occurs due to retrograde stimulation of perivascular afferent nerves. These actions appear to be mediated through partial agonism at $5\text{-HT}_{1D/1B}$ receptors in and around cranial vessels.

Dihydroergotamine (DHE) It is nearly as effective as ergotamine and preferred for parenteral administration because injected DHE is less hazardous.

Current status Because of erratic oral absorption, frequent side effects, especially nausea, vomiting, muscle cramps and availability of triptans, ergot preparations are rarely used now, except for considerations of cost or when triptans fail. Ergot alkaloids have no prophylactic value: regular use is not justified, which may itself produce a dull background headache and an attack may be precipitated on discontinuation. *Caffeine* 100 mg taken with ergotamine enhances its absorption from oral and rectal routes and adds to the cranial vasoconstricting action. Many combination preparations are available.

MIGRIL: Ergotamine 2 mg, caffeine 100 mg, cyclizine 50 mg tab.

VASOGRAIN: Ergotamine 1 mg, caffeine 100 mg, paracetamol 250 mg, prochlorperazine 2.5 mg tab.

Selective $5\text{-HT}_{1D/1B}$ agonists (Triptans)

This novel class of antimigraine drugs selectively activate $5\text{-HT}_{1D/1B}$ receptors, and are called 'triptans'. Currently, they are the first line drugs for patients who fail to respond to analgesics. Ergot alkaloids are now required only in few cases. Because these drugs have been designed to act on the same subtype of 5-HT receptor, pharmacodynamic differences among them are minor, but there are significant pharmacokinetic differences. All others triptans have higher oral bioavailability than the prototype drug sumatriptan. Fewer headache recurrences in an attack are reported with naratriptan and frovatriptan due to their longer t½, but they may be slower in affording initial pain relief.

Sumatriptan It is the first selective $5\text{-HT}_{1D/1B}$ receptor agonist; activates other subtypes of 5-HT_1 receptors only at very high concentrations, and does not interact with 5-HT_2, 5-HT_3, $5\text{-HT}_{4\text{-}7}$, α or β adrenergic, dopaminergic, cholinergic or GABA receptors. Administered at the onset of an attack of migraine, sumatriptan is as effective and better tolerated than ergotamine. About 3/4 patients obtain complete/significant relief

within 2–3 hours. However, recurrence of headache within 24 hr has been noted in 20–40% patients, probably due to short t½ of sumatriptan. A distinct advantage is that it tends to suppress nausea and vomiting of migraine, while ergotamine accentuates these symptoms.

The antimigraine activity of sumatriptan has been ascribed to 5-$HT_{1D/1B}$ receptor mediated constriction of dilated cranial blood vessels, especially the arterio-venous shunts in the carotid artery, which express 5-$HT_{1D/1B}$ receptors. Dilatation of these shunt vessels during migraine attack is believed to divert blood flow away from brain parenchyma. Consistent with the fact that 5-$HT_{1D/1B}$ receptors are presynaptic autoreceptors, sumatriptan can reduce 5-HT release at these blood vessels. Alternatively or in addition, it may inhibit inflammatory neuropeptide release around the affected vessels as well as extravasation of plasma proteins across dural vessels. Like ergotamine, the triptans have been found to suppress neurogenic inflammation of cranial vessels. The use of sumatriptan (or other triptans) should be restricted to treatment of acute attacks of moderate to severe migraine not responding to analgesics or their combinations.

Pharmacokinetics: Sumatriptan is absorbed rapidly and completely after s.c. injection. Oral bioavailability averages only 15%. Absorption is faster after intranasal spray, but bioavailability remains almost the same. It is the only triptan available for nasal and parenteral administration as well. Sumatriptan is rapidly metabolized by MAO-A isoenzyme and metabolites are excreted in urine; elimination t½ is ~2 hours.

Side effects of sumatriptan are usually mild. Tightness in head and chest, feeling of heat and other paresthesias in limbs, dizziness, weakness are short lasting, but dose related side effects. These are more common after s.c. injection, which is painful. Slight rise in BP occurs, but has little clinical relevance, because sumatriptan is not a drug for regular use. Bradycardia, coronary vasospasm and risk of myocardial infarction are the serious, but infrequent adverse effects. Few sudden deaths have been ascribed to sumatriptan. Seizures and hypersensitivity reactions are rare.

Contraindications: Ischaemic heart disease, hypertension, epilepsy, hepatic or renal impairment and pregnancy are the contraindications. Patients should be cautioned not to drive.

Sumatriptan and ergotamine should not be administered within 24 hours of each other. Interaction with 5-HT reuptake inhibitors, MAO inhibitors and lithium has been reported.

Dose: 50–100 mg oral at the onset of migraine attack, may be repeated once within 24 hours if required. Those not responding to the first dose should not be given the second dose. It is the only triptan available for parenteral use; 6 mg s.c. may be given to patients who cannot take the drug orally or in whom the pain develops very rapidly. After injection, it acts in 10–20 min and is more consistently effective. Alternatively, for rapid action and in patients who vomit out the oral tablet, 25 mg nasal spray can be used. It may be repeated once after 2 hours. A bitter taste may be felt after the nasal spray.

MIGRATAN, 50, 100 mg tabs, SUMINAT 25, 50, 100 mg tab, 25 mg nasal spray, 6 mg/0.5 ml inj. SUMITREX 25, 50, 100 mg tab, 6 mg/0.5 ml inj.

Rizatriptan: This congener of sumatriptan is more potent, has higher oral bioavailability with slightly faster onset of action.

Dose: 5-10 mg; repeat once after 2 hr (if required).

RIZACT, RIZATAN 5, 10 mg tab.

Naratriptan, Zolmitriptan, Almotriptan, Frovatriptan and *Eletriptan* are other triptans used in some countries.

Features of some triptans are compared in the box.

PROPHYLAXIS OF MIGRAINE

Regular medication to reduce the frequency and/or severity of attacks is recommended for moderate-to-severe migraine when 2–3 or more attacks occur per month, or when attacks are disabling despite treatment, or in patients with contraindications for triptans/ergotamine. Diverse classes of drugs are used, but none is effective in all cases, and none abolishes the attacks totally. It may be prudent to discontinue pophylaxis every 6 months to check whether its continuation is needed or not. It is important to avoid the precipitating factor(s).

Comparative features of triptans

		Suma.	*Frova.*	*Riza.*	*Nara.*	*Zolmi.*
1.	Oral bioavailability (%)	15	25	45	70	40
2.	T*max** (hr)	1.5–2	2–4	1–1.5	2–3	1.5–2
3.	Plasma t½ (hr)	~2	26	2–3	6	2–3
4.	Oral dose					
	Initial (mg)	50–100	2.5	5–10	2.5	2.5
	Max. in 24 hr (mg)	200	5–7.5	20	5	10

* T*max*: Time to peak plasma concentration after oral dosing.

(i) *β-Adrenergic blockers* Propranolol is the most commonly used drug. It reduces frequency as well as severity of attacks in upto 70% patients. Effect is generally seen in 4 weeks and is sustained during prolonged therapy. The starting dose is 40 mg BD, which may be increased upto 160 mg BD if required. The mechanism of action is not clear; that it is due to β adrenergic blockade has been questioned. Other nonselective (timolol) and β_1 selective (metoprolol, atenolol) agents are also effective, but pindolol and others having intrinsic sympathomimetic action are not useful.

(ii) *Tricyclic antidepressants* Many tricyclic compounds, of which *amitriptyline* (25–50 mg at bed time) has been most extensively tried, reduce migraine attacks. It is effective in many patients but produces more side effects than propranolol. Whether its 5-HT (and other monoamine) uptake blocking property is causally related to the prophylactic effect is not known. The antimigraine effect is independent of antidepressant property, but this class of drugs are better suited for patients who concurrently suffer from depression.

(iii) *Calcium channel blockers* Verapamil was found to reduce migraine attacks, but was judged inferior to propranolol.

Flunarizine is a relatively weak Ca^{2+} channel blocker that inhibits Na^+ channels as well. It is claimed to be as effective as propranolol, but convincing proof is lacking. Frequency of attacks is often reduced, but effect on intensity and duration of attacks is less well documented. It is claimed to be a cerebro-selective Ca^{2+} channel blocker, which may benefit migraine by reducing intracellular Ca^{2+} overload due to brain hypoxia and other causes. Side effects are sedation, constipation, dry mouth, hypotension, flushing, weight gain and rarely extrapyramidal symptoms.

Dose: Flunarizine 10–20 mg OD, children 5 mg OD, NOMIGRAIN, FLUNARIN 5 mg, 10 mg caps/tab.

(iv) *Anticonvulsants* *Valproic acid* (400–1200 mg/day) and *gabapentin* (300–1200 mg/day) have some prophylactic effect in migraine. The newer drug *topiramate* has recently been approved for migrain prophylaxis. A 50% reduction in the number of attacks in half of the patients was noted in 2 randomized trials. Start with topiramate 25 mg OD and gradually increase to 50 mg OD or BD. Efficacy of anticonvulsants in migraine is lower than that of β blockers. They are indicated in patients refractory to other drugs or when propranolol is contraindicated.

(v) *CGRP antagonist* A fully human monoclonal antibody *Erenumab* which blocks calcitonin gene-related peptide (CGRP) receptor has been recently found to reduce number of migraine attacks when injected s.c. once a month in patients with severe migraine (*see* p. 555). It has now been approved by US-FDA.

(vi) *5-HT antagonists* The prophylactic effect of methysergide and cyproheptadine is less impressive than β blockers. They are not used now for migraine.

☞ PROBLEM DIRECTED STUDY

12.1 A 36 years lady presents with the complaint of episodes of unilateral pulsatile headache for the past 2 years or so. During the initial episodes, the headache was mild, was relieved by paracetamol/ibuprofen tablets, and did not interfere with her daily activities. However, the severity and frequency of pain episodes has progressively increased, so that now episodes recur nearly every 1-2 weeks, especially at the beginning of her periods. Headache is preceded by lethargy, anorexia, nausea and is accompanied by blurred vision, flashes of light seen on closing the eyes, unsteadiness and frequent vomiting. The pain lasts for 12–18 hours and she is incapacitated for nearly 24 hours. The headache is not relieved now by over-the-counter analgesics or combination analgesics.

(a) What medication can be prescribed to treat the headache episodes. What instructions should be given regarding timing, dose, etc. of this medication?

(b) What specific medical history needs to be elicited, physical examination/investigation performed before prescribing the above medication?

(c) Apart from treatment of pain episodes, can this patient be put on some regular medication to prevent/minimise the episodes?

Chapter 13 Prostaglandins, Leukotrienes (Eicosanoids) and Platelet Activating Factor

PROSTAGLANDINS AND LEUKOTRIENES (Eicosanoids)

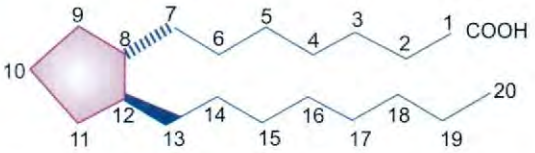
Prostaglandins (PGs) and Leukotrienes (LTs) are biologically active derivatives of 20 carbon atom polyunsaturated essential fatty acids that are released from cell membrane phospholipids. They are the major lipid derived autacoids.

In the 1930s human semen was found to contract isolated uterine and other smooth muscle strips and to cause fall in BP in animals. The active principle was termed 'prostaglandin', thinking that it was derived from prostate. Only in the 1960s it was shown to be a mixture of closely related compounds, the chemical structures were elucidated and widespread distribution in the body was revealed. In 1970s it became clear that aspirin like drugs act by inhibiting PG synthesis, and that in addition to the classical PGs (PGEs and PGFs), thromboxane (TX), prostacyclin (PGI) and leukotrienes (LTs) were of great biological importance. Bergstrom, Samuelsson and Vane got the Nobel prize in 1982 for their work on PGs and LTs. Over the past 40 years PGs and LTs have been among the most intensely investigated substances.

CHEMISTRY, BIOSYNTHESIS AND DEGRADATION

Chemically, PGs may be considered to be derivatives of *prostanoic acid,* though prostanoic acid does not naturally occur in the body. It has a five membered ring and two side chains projecting in opposite directions at right angle to the plane of the ring. There are many series of PGs and thromboxanes (TXs) designated A, B, C....I, depending on the ring structure and the substituents on it. Each series has members with subscript 1, 2, 3 indicating the number of double bonds in the side chains.

Leukotrienes are so named because they were first obtained from leukocytes (*leuko*) and have



PROSTANOIC ACID

3 conjugated double bonds (*triene*). They have also been similarly designated A, B, C.....F and given subscripts 1, 2, 3, 4.

In the body PGs, TXs and LTs are all derived from eicosa (referring to 20 C atoms) tri/tetra/penta enoic acids. Therefore, they can be collectively called *eicosanoids.* In human tissues, the fatty acid released from membrane lipids in largest quantity is *5,8,11,14 eicosa tetraenoic acid (arachidonic acid).* During PG, TX and prostacyclin synthesis, 2 of the 4 double bonds of arachidonic acid get saturated in the process of cyclization, leaving 2 double bonds in the side chain. Thus, subscript 2 PGs are the most important in man, e.g. PGE_2, $PGF_{2\alpha}$, PGI_2, TXA_2. No cyclization or reduction of double bonds occurs during LT synthesis—the LTs of biological importance are LTB_4, LTC_4, LTD_4.

Eicosanoids are the most universally distributed autacoids in the body. Practically every cell and tissue is capable of synthesizing one or more types of PGs or LTs. As such, they have potent and a very wide range of biological activity. The pathways of biosynthesis of eicosanoids are summarized in Fig. 13.1.

There are no preformed stores of PGs and LTs. They are synthesized locally and the rate of synthesis is governed by the rate of release of arachidonic acid from membrane lipids in

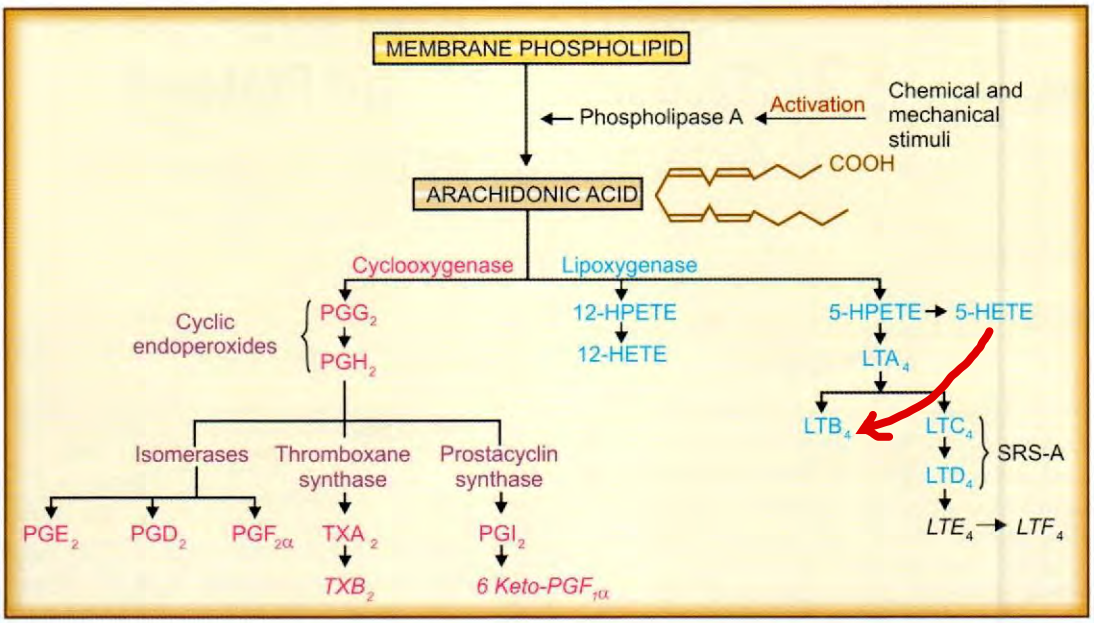


Fig. 13.1: Biosynthesis of prostaglandins (PGs) and leukotrienes (LTs). Less active metabolites are shown in italics
TX—Thromboxane; PGI—Prostacyclin; HPETE—Hydroperoxy eicosatetraenoic acid (Hydroperoxy arachidonic acid); HETE—Hydroxyeicosatetraenoic acid (Hydroxy arachidonic acid); SRS-A—Slow reacting substance of anaphylaxis

response to appropriate stimuli. These stimuli activate hydrolases, including phospholipase A, probably through increased intracellular Ca^{2+}.

Cyclooxygenase (COX) *pathway* It generates eicosanoids with a ring structure (PGs, TXs, prostacyclin) while *lipoxygenase* (LOX) produces open chain compounds (LTs). All tissues have COX—can form cyclic endoperoxides PGG_2 and PGH_2 which are unstable compounds. Further course in a particular tissue depends on the type of isomerases or other enzymes present in it. PGE_2 and $PGF_{2\alpha}$ are the primary prostaglandins (name based on the separation procedure: PGE partitioned into *Ether* while PGF into phosphate [*Fosfat* in Swedish] buffer; α in $PGF_{2\alpha}$ refers to orientation of OH group on the ring). PGs A, B and C are not found in the body: they are artifacts formed during extraction procedures. Lung and spleen can synthesize the whole range of COX products. Platelets primarily synthesize TXA_2 which is—chemically unstable, spontaneously changes to TXB_2. Endothelium mainly generates prostacyclin (PGI_2) which is also chemically unstable and rapidly converts to 6-keto $PGF_{1\alpha}$.

Cyclooxygenase is known to exist in two isoforms COX-1 and COX-2. While both isoforms catalyse the same reactions, COX-1 is a constitutive enzyme in most cells—it is synthesized and is active in the basal state; the level of COX-1 activity is not much changed once the cell is fully grown. On the other hand, COX-2 normally present in insignificant amounts, is inducible by cytokines, growth factors and other stimuli during the inflammatory response. It is believed that eicosanoids produced by COX-1 participate in physiological (house keeping) functions such as secretion of mucus for protection of gastric mucosa, haemostasis and maintenance of renal function, while those produced by COX-2 lead to inflammatory and other pathological changes. However, certain sites in kidney, brain and the foetus constitutively express COX-2 which may play physiological role.

A splice variant of COX-1 (designated COX-3) has been found in the dog brain. This isoenzyme is inhibited by paracetamol and is implicated in the genesis of fever, but the exact role in humans is not known.

Lipoxygenase pathway This pathway appears to operate mainly in the lung, WBC and platelets. Its most important products are the LTs, (generated by 5-LOX) particularly LTB_4 (potent chemotactic) and LTC_4, LTD_4 which together constitute the *'slow reacting substance of anaphylaxis' (SRS-A)* described in 1938 to be released during anaphylaxis. A membrane associated transfer protein called FLAP (five lipoxygenase activating protein) carrys arachidonic acid to 5-LOX, and is essential for the synthesis of LTs. Platelets have only 12-LOX.

Apart from PGs and LTs, a number of other active products can be generated from arachidonic acid at certain sites.

HPETEs produced by LOX can also be converted to *hepoxilins, trioxilins* and lipoxins. A third enzymatic pathway involving cytochrome P450 can metabolize arachidonic acid into *19-* and *20-HETEs* and *epoxyeicosatrienoic acids*. Free radicals can attack arachidonic acid to produce *isoprostanes* nonenzymatically. Brain cells couple arachidonic acid with ethanolamine to produce *anandamide* and a few other related eicosanoids which are now recognized to be the endogenous cannabinoid receptor ligands. Accordingly, they produce cannabis like effects. Like the other eicosanoids, they are synthesized only when needed at the site of action.

Inhibition of synthesis Synthesis of COX products can be inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs). Aspirin acetylates COX at a serine residue and causes irreversible inhibition, while other NSAIDs are competitive and reversible inhibitors. Most NSAIDs are nonselective COX-1 and COX-2 inhibitors, but some later ones like celecoxib, etoricoxib are selective for COX-2.

The sensitivity of COX in different tissues to inhibition by these drugs varies; selective inhibition of formation of certain products may be possible at lower doses. NSAIDs do not inhibit the production of LTs. Rather, LT production may be increased since all the arachidonic acid becomes available to the LOX pathway.

Zileuton inhibits LOX and decreases the production of LTs. It was used briefly in asthma, but has been withdrawn.

Glucocorticosteroids inhibit the release of arachidonic acid from membrane lipids (by enhancing production of proteins called *annexins* which inhibit phospholipase A_2). Production of all eicosanoids—PGs, TXs and LTs is indirectly curtaited. Moreover, steroids inhibit the induction of COX-2 by cytokines at the site of inflammation.

Degradation Biotransformation of arachidonates occurs rapidly in most tissues, but fastest in the lungs. Most PGs, TXA_2 and prostacyclin have plasma t½ of a few seconds to a few minutes. First a specific carrier mediated uptake into cells occurs, the side chains are then oxidized and double bonds are reduced in a stepwise manner to yield inactive metabolites. Metabolites are excreted in urine. PGI_2 is catabolized mainly in the kidney.

ACTIONS AND PATHOPHYSIOLOGICAL ROLES

Prostaglandins, thromboxanes and prostacyclin

The cyclic eicosanoids produce a wide variety of actions depending upon the particular PG (or TX or PGI), species on which tested, tissue, hormonal status and other factors. PGs differ in their potency to produce a given action and different PGs sometimes have opposite effects. Even the same PG may have opposite effects under different circumstances. The important actions of PGs and TXA_2 are summarized in Table 13.1. Since virtually all cells and tissues are capable of forming one or more PGs, these autacoids have been implicated as mediators or modulators of a number of physiological processes and pathological states.

1. CVS PGE_2 causes vasodilatation in most, but not all, vascular beds. $PGF_{2\alpha}$ constricts many larger veins including pulmonary vein and artery. Fall in BP occurs when PGE_2 is injected i.v., but $PGF_{2\alpha}$ has little effect on BP.

- PGI_2 is uniformly vasodilatory and is more potent hypotensive than PGE_2.
- TXA_2 consistently produces vasoconstriction.
- PGE_2 and $F_{2\alpha}$ stimulate heart by weak direct but more prominent reflex action due to fall in BP. The cardiac output increases.

Role

- PGs do not circulate in blood and have no role in regulating systemic vascular resistance. However, PGI_2 generated in the vascular endothelium, mainly by COX-2, appears to be involved in the regulation of local vascular tone as a dilator.
- PGE_2 is continuously produced locally in the ductus arteriosus by COX-2 during foetal life and keeps it patent. At birth its synthesis stops and closure occurs. Aspirin and indomethacin induce closure when it fails to occur spontaneously.
- PGs, generated mainly by COX-2, along with LTs and other autacoids may mediate vasodilatation and exudation at the site of inflammation.

2. Platelets TXA_2, which can be produced locally by platelets, is a potent inducer of aggregation and release reaction. On the other hand PGI_2 (generated by vascular endothelium) is a potent inhibitor of platelet aggregation. PGE_2 has dose dependent pro- and anti-aggregatory effects

Role TXA_2 produced by platelets and PGI_2 produced by vascular endothelium probably constitute a mutually antagonistic system: preventing aggregation of platelets while in circulation and inducing aggregation on injury, when plugging and thrombosis are needed.

Aspirin interferes with haemostasis by inhibiting platelet aggregation. TXA_2 produced by platelet COX-1 plays an important role in amplifying aggregation. Before it is deacetylated in liver, aspirin acetylates COX-1 in platelets while they are in portal circulation. Further, platelets are unable to regenerate fresh COX-1 (lack nucleus: do not synthesize protein), while vessel wall is able to do so (fresh enzyme is synthesized within hours). Thus, at low doses, aspirin selectively inhibits TXA_2 production and has antithrombotic effect lasting > 3 days.

3. Uterus PGE_2 and $PGF_{2\alpha}$ consistently contract human uterus *in vivo*, both pregnant as well as nonpregnant. The sensitivity is higher during pregnancy and there is progressive modest increase with the advance of pregnancy. However, even during early stages, uterus is quite sensitive to PGs though not to oxytocin. PGs increase basal tone as well as amplitude of uterine contractions.

At term, PGs soften the cervix at low doses and make it more compliant.

Role

- Foetal tissues produce PGs. At term $PGF_{2\alpha}$ has been detected in maternal blood. It is postulated that PGs mediate initiation and progression of labour. Aspirin has been found to delay the initiation of labour and also prolong its duration.
- Dysmenorrhoea in many women is associated with increased PG synthesis by the endometrium. This apparently induces uncoordinated uterine contractions which compress blood vessels causing uterine ischaemia and pain. Aspirin group of drugs are highly effective in relieving dysmenorrhoea in most women.

4. Bronchial muscle $PGF_{2\alpha}$, PGD_2 and TXA_2 are potent bronchoconstrictors (more potent than histamine) while PGE_2 is a powerful bronchodilator. PGI_2 produces mild dilatation. Asthmatics are more sensitive to constrictor as well as dilator effects of PGs. PGE_2 and PGI_2 also inhibit histamine release and are effective by aerosol. However, these antiasthmatic effects of PGE_2 and PGI_2 cannot be exploited clinically because they produce irritation of the respiratory tract and have brief action.

Role Asthma may be due to an imbalance between constrictor PGs ($F_{2\alpha}$, PGD_2, TXA_2) and cysteinyl LTs on one hand and dilator ones (PGE_2, PGI_2) on the other. In few individuals aspirin-like drugs consistently induce asthma, possibly by diverting arachidonic acid to produce excess LTC_4 and D_4. This sensitivity

Table 13.1 : A summary of the actions of major prostaglandins, prostacyclin and thromboxane

Organ	*Prostaglandin E_2 (PGE_2)*	*Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)*	*Prostacyclin (PGI_2)*	*Thromboxane A_2 (TXA_2)*
1. Blood vessels	Vasodilatation, ↓ BP	Constricts larger veins and some arteries, little effect on BP	Vasodilatation (marked and widespread), ↓↓ BP	Vasoconstriction
2. Heart	Weak inotropic, reflex cardiac stimulation	Weak inotropic	—	—
3. Platelets	Variable effect	—	Antiaggregatory	Aggregation and release reaction
4. Uterus	Contraction (*in vivo*), softening of cervix	Contraction (*in vivo* and *in vitro*), softening of cervix	—	Contraction (*in vitro*)
5. Bronchi	Dilatation, Inhibit histamine release	Constriction	Dilatation (mild), inhibit histamine release	Constriction
6. Stomach	↓ acid secretion, ↑ mucus production	—	↓ acid secretion (weak), mucosal vasodilatation	—
7. Intestine	Contracts longitudinal & relaxes circular muscles, ↑ peristalsis, ↑ Cl^- & water secretion	Spasmogenic, ↑ fluid & electrolyte secretion (weak)	Weak spasmogenic, inhibits toxin-induced fluid secretion	Weak spasmogenic
8. Kidney	Natriuresis, ↓ Cl^- reabsorption, inhibit ADH action, vasodilatation, renin release	—	Natriuresis, vasodilatation, renin release	Vasoconstriction
9. CNS	Pyrogenic, variety of effects on i.c.v. inj.			
10. Afferent nerves	Sensitize to noxious stimuli → tenderness	—	Same as PGE_2	—
11. Endocrine system	Release of ant. pituitary hormones, steroids, insulin; TSH-like action	—	—	
12. Metabolism	Antilipolytic, insulin like action, mobilization of bone Ca^{2+}	—	—	—

is not shared by selective COX-2 inhibitors, indicating that suppression of COX-1 at the pulmonary site is responsible for the reaction. In allergic human asthma, LTs play a more important role, and COX inhibitors are without any effect in most patients.

5. GIT

(i) In isolated preparations, the longitudinal muscle of gut is contracted by PGE_2 and $PGF_{2\alpha}$ while the circular muscle is either contracted (usually by $PGF_{2\alpha}$) or relaxed (usually by PGE_2). Propulsive activity is enhanced in man, especially by PGE_2. This can cause colic and watery diarrhoea, which are important side effects. PGE_2 acts directly on the intestinal mucosa and increases water, electrolyte and mucus secretion.

Role PGs may be involved in mediating toxin induced increased fluid movement in secretory diarrhoeas. In certain diarrhoeas, aspirin can reduce stool volume, but it is not uniformly effective. PGs appear to play a role in the growth of colonic polyps and cancer. Association of lower incidence of colon cancer with regular intake of aspirin is now established. NSAIDs afford relief in familial colonic polyposis by reducing polyp formation.

(ii) PGE_2 markedly reduces acid secretion in the stomach. Volume of juice and pepsin content are also decreased. It inhibits fasting as well as stimulated secretion. Release of gastrin is suppressed (*see* Fig. 47.1). The gastric pH may rise upto 7.0. PGI_2 also reduces gastric secretion, but is less potent. Secretion of mucus and HCO_3^- by gastric mucosal epithelial cells is increased, as is mucosal blood flow. Thus, PGs are antiulcerogenic.

Role PGs (especially PGI_2) appear to be involved in the regulation of gastric mucosal blood flow. They may be functioning as natural ulcer protectives by enhancing gastric mucus and HCO_3^- production, as well as by improving mucosal circulation and health. The ulcerogenic action of NSAIDs appears to be due to loss of this protective influence.

Normally, gastric mucosal PGs are produced by COX-1. Selective COX-2 inhibitors are less ulcerogenic. However, COX-2 gets induced during ulcer healing, and COX-2 inhibitors have the potential to delay healing.

6. Kidney PGE_2 and PGI_2 increase water, Na^+ and K^+ excretion and have a diuretic effect. PGE_2 has a furosemide-like inhibitory effect on Cl^- reabsorption as well. They cause renal vasodilatation and inhibit tubular reabsorption. PGE_2 attenuates ADH action, and this adds to the diuretic effect. In contrast, TXA_2 causes renal vasoconstriction. PGI_2, PGE_2 and PGD_2 evoke release of renin.

Role

- PGE_2 and PGI_2 produced mainly by COX-2 in the kidney appear to function as intrarenal regulators of blood flow as well as tubular reabsorption in kidney. Accordingly, the NSAIDs, including selective COX-2 inhibitors, tend to retain salt and water. The diuretic action of furosemide is blunted by indomethacin—indicating a facilitatory role of PGs by increasing renal blood flow and/or augmenting inhibition of tubular reabsorption.
- Renin release in response to sympathetic stimulation, low salt intake and other influences may be facilitated by PGs.

7. CNS PGs injected i.v. penetrate brain poorly, so that central actions are not prominent. However, injected intracerebroventricularly PGE_2 produces a variety of effects—sedation, rigidity, behavioural changes and marked rise in body temperature. PGI_2 also induces fever, but TXA_2 is not pyrogenic.

Role

- PGE_2 may mediate pyrogen induced fever and malaise. Aspirin and other inhibitors of PG synthesis are antipyretic. Pyrogens, including cytokines, released during bacterial infection trigger synthesis of PGE_2 in the hypothalamus which resets the thermostat to cause fever. COX-2 is the major isoenzyme involved; selective COX-2 inhibitors are equally efficacious antipyretics. A role of COX-3 has also been proposed.

- PGs may be functioning as neuromodulators in the brain by regulating neuronal excitability. A role in pain perception, sleep and some other functions has been suggested.

8. Sympathetic nerves Depending on the PG, species and tissue, both inhibition as well as augmentation of NA release from sympathetic nerve endings has been observed. However, PGE_2 mostly inhibits NA release.

Role PGs may modulate sympathetic neurotransmission in the periphery.

9. Peripheral nerves PGs (especially E_2 and I_2) sensitize afferent nerve endings to pain inducing chemical and mechanical stimuli (Fig. 13.2). They irritate mucous membranes and produce long lasting dull pain on intradermal injection.

Role PGs serve as algesic agents during inflammation. They cause tenderness and amplify the action of other algesics. Inhibition of PG synthesis is a major antiinflammatory mechanism. Aspirin injected locally decreases pain produced by injection of bradykinin at the same site. Moreover, PGs released in the dorsal horn of spinal cord by painful stimuli sensitise the neurones to pain perception.

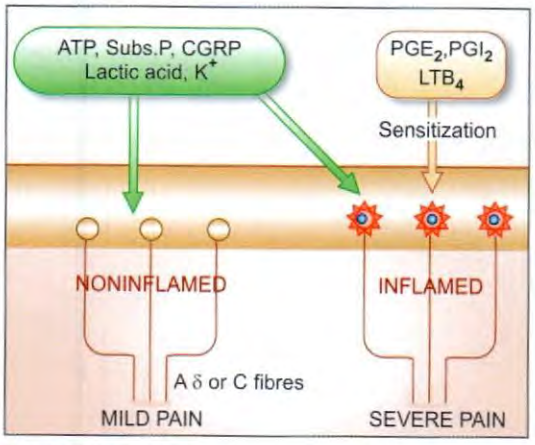


Fig. 13.2: Sensitization of nociceptors (pain receptors) to mediators of pain by prostaglandins at the inflammatory site. Subs. P—Substance P; CGRP—Calcitonin gene related peptide

10. Eye: $PGF_{2\alpha}$ induces ocular inflammation and lowers i.o.t by enhancing uveoscleral and trabecular outflow. Nonirritating congeners like *latanoprost* are now first line drugs in wide angle glaucoma (*see* p. 169).

Role Locally produced PGs appear to facilitate aqueous humor drainage. The finding that COX-2 expression in the ciliary body is deficient in wide angle glaucoma patients supports this contention.

11. Endocrine system PGE_2 facilitates the release of anterior pituitary hormones (growth hormone, prolactin, ACTH, FSH and LH) as well as that of insulin and adrenal steroids. It has a TSH-like effect on the thyroid.

12. Metabolism PGEs are antilipolytic, exert an insulin like effect on carbohydrate metabolism and mobilize Ca^{2+} from bone. They may facilitate hypercalcaemia due to bony metastasis.

Leukotrienes

The straight chain lipoxygenase products of arachidonic acid are produced by a more limited number of tissues (LTB_4 mainly by neutrophils; LTC_4 and LTD_4—the cysteinyl LTs—mainly by macrophages), but probably they are pathophysiologically as important as PGs.

1. CVS and blood LTC_4 and LTD_4 injected i.v. evoke a brief rise in BP followed by a more prolonged fall. The fall in BP is not due to vasodilatation because no relaxant action has been seen on blood vessels. It is probably a result of coronary constriction induced decrease in cardiac output and reduction in circulating volume due to increased capillary permeability. These LTs markedly increase capillary permeability and are more potent than histamine in causing local edema formation.

LTB_4 is highly chemotactic for T-lymphocytes, neutrophils and monocytes; this property is not shared by other LTs. Migration of neutrophils through capillaries and their clumping at sites of inflammation in tissues is also promoted by LTB_4. The cysteinyl LTs (C_4, D_4) are chemotactic for eosinophils and T-lymphocytes.

Role LTs are important mediators of inflammation. They are produced (along with PGs) locally at the site of injury. While LTC_4 and D_4 cause exudation of plasma, LTB_4 attracts the

inflammatory cells which reinforce the reaction. They play greater role in chronic inflammatory states. 5-HPETE and 5-HETE may facilitate local release of histamine from mast cells.

2. Smooth muscle LTC_4 and D_4 contract most smooth muscles. They are potent bronchoconstrictors and induce spastic contraction of g.i.t. at low concentrations.

They also increase mucus secretion in the airways.

Role The cysteinyl LTs (C_4 and D_4) are the most important mediators of human allergic asthma. They are released along with PGs and other autacoids during AG: AB reaction in the lungs. In comparison to other mediators, they are more potent and are metabolized slowly in the lungs, therefore exert a long lasting action. LTs may also be responsible for abdominal colics during systemic anaphylaxis.

3. Afferent nerves Like PGE_2 and I_2, the LTB_4 also sensitizes afferents carrying pain impulses—contributes to pain and tenderness of inflammation.

PROSTANOID RECEPTORS

PGs, TX and prostacyclin act on their own specific receptors located on cell membrane. Five families of prostanoid receptors (DP, EP, FP, IP and TP) have been designated, each after the endogenous PG for which it has the greatest affinity. This has been supported by receptor cloning. All prostanoid receptors are G-protein coupled receptors which can be functionally categorized into 'excitatory' or 'contractile', 'relaxant' and 'inhibitory' groups (Fig. 13.3).

The *contractile group* (EP_1, FP, TP) couple primarily with Gq protein and activate PLC_β

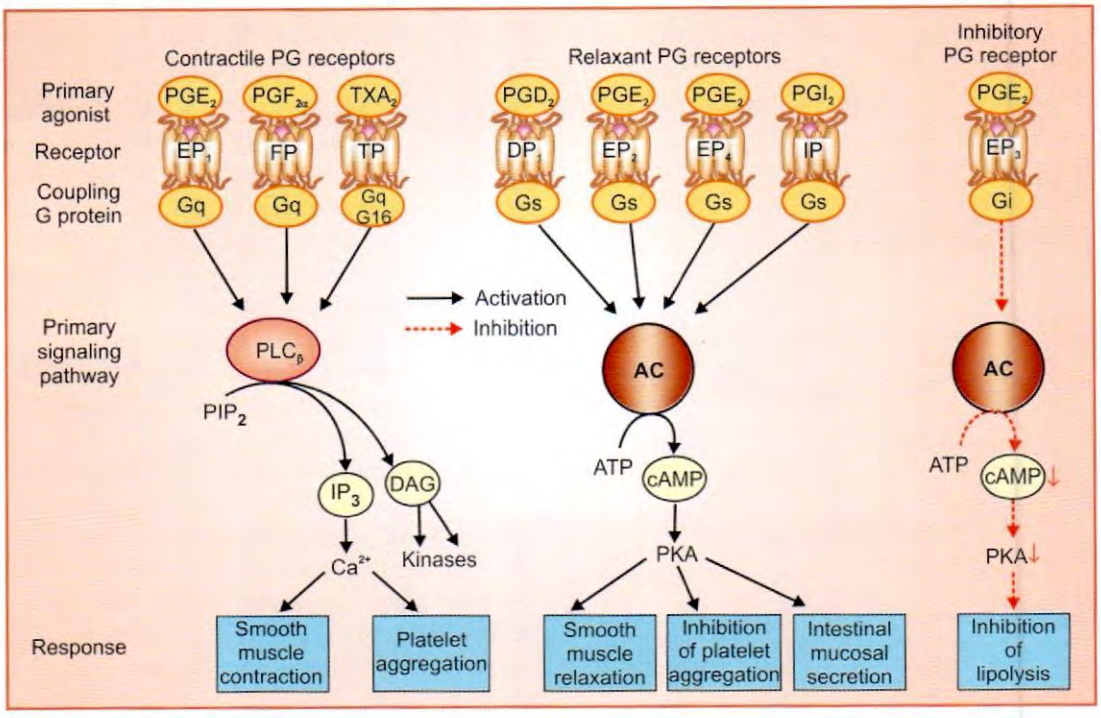


Fig. 13.3: Prostanoid receptors, their primary signaling pathways and major responses elicited through them.
All prostanoid receptors are G-protein coupled receptors. On the basis of their functional characterization, prostanoid receptors have been grouped into *contractile, relaxant* and *inhibitory* groups.
PLC_β—Phospholipase Cβ; IP_3—Inositol trisphosphate; DAG—Diacyl glycerol; AC—Adenylyl cyclase; cAMP—Cyclic AMP; PKA—Protein kinase A.

to generate IP_3 and DAG. These second messengers release Ca^{2+} intracellularly resulting in excitatory responses like smooth muscle contraction, platelet aggregation, etc. The *relaxant group* (DP_1, EP_2, EP_4 and IP) couple with Gs protein—activate adenylyl cyclase to generate intracellular second messenger cAMP. Smooth muscle relaxation, inhibition of platelet aggregation, etc. are produced through cAMP dependent protein kinase (PK_A). The *inhibitory* (EP_3) receptor couples with Gi protein, inhibits adenylyl cyclase and exerts antilipolytic action. The major characteristics of subtypes of prostanoid receptors are:

DP This receptor has strongest affinity for PGD_2, but PGE_2 can also activate it. Two subtypes DP_1 and DP_2 have been identified, but both have limited distribution in the body; DP_1 is a relaxant receptor which dilates certain blood vessels and inhibits platelet aggregation. The DP_2 receptor couples with Gi protein and inhibits cAMP generation.

EP This receptor is characterized by highest affinity for PGE_2; *enprostil* is a selective agonist. Four subtypes have been recognized:

EP_1 is a contactile receptor—contracts visceral smooth muscle, but is less abundant in the body.

EP_2 and EP_4 are relaxant in nature, act by increasing cAMP in smooth muscle, but the same second messenger enhances Cl^- and water secretion by the intestinal mucosa. While EP_2 is present in few organs, EP_4 has wide distribution.

EP_3 is inhibitory, decreases cAMP generation by coupling with Gi protein. The antilipolytic action of PGE_2 is exerted by opposing cAMP generation in adipose tissue. Distribution of EP_3 receptor in the body is wide.

FP This contactile receptor is highly expressed in the female genital tract, and is present in many other organs. It exhibits strong affinity for $PGF_2\alpha$; *fluprostenol* is a selective agonist.

IP This relaxant receptor is defined by highest affinity for PGI_2, but PGE_2 also acts on it; *cicaprost* is a selective agonist. It is expressed in heart, lungs, kidney, platelet (antiaggregatory), etc., but the highest density is in the vasculature.

TP Characterized by high affinity for TxA_2, this contractile receptor is abundant in platelets (aggregatory), cardiovascular system, immune cells and many other organs. PGH_2 can also activate TP. The TP receptor functions by activating PLC_β through G_q and G_{16} proteins. Apart from IP_3/DAG—Ca^{2+}—PKc pathway, it utilizes other kinases as well to exert certain biological effects.

LEUKOTRIENE RECEPTORS

Separate receptors for LTB_4 (BLT_1 and BLT_2) and for the cysteinyl LTs (LTC_4, LTD_4) have been defined. Two subtypes, *cys*LT_1 and *cys*LT_2 of the cysteinyl LT receptor have been cloned. All LT receptors couple with Gq protein and function through the IP_3/DAG transducer mechanism. The BLT receptors are chemotactic and primarily expressed in leucocytes and spleen. BLT_1 receptor has high, while BLT_2 receptor has lower affinity for LTB_4. The *cys*LT_1 receptor is mainly expressed in bronchial and intestinal muscle and has higher affinity for LTD_4 than for LTC_4. The primary location of *cys*LT_2 receptor is leucocytes and spleen, and it shows no preference for LTD_4 over LTC_4. The *cys*LT_1 receptor antagonists, *viz. Montelukast, Zafirlukast,* etc. are now valuable drugs for bronchial asthma (*see* Ch. 16).

USES

The clinically useful natural and synthetic prostaglandins are listed in the chart below.

PROSTAGLANDINS (PGs)

Natural PGs	Prostaglandin analogues
Dinoprostone (PGE_2)	Carboprost
Gemeprost	(15-methyl $PGF_{2\alpha}$)
Dinoprost ($PGF_{2\alpha}$)	Misoprostol
Alprostadil (PGE_1)	(methyl PGE_1 ester)
Prostacyclin (PGI_2)	Latanoprost
(Epoprostenol)	(PGE_2 analogue)
	Travoprost
	Bimatoprost

Clinical application of PGs and their analogues is rather restricted because of limited availability, short lasting action, cost and frequent side effects. However, their use in glaucoma and in obstetrics is now commonplace. Their indications are:

1. *Abortion* During the first trimester, termination of pregnancy by transcervical suction is the procedure of choice. Intravaginal PGE_2 pessary inserted 3 hours before attempting dilatation can minimise trauma to the cervix by reducing resistance to dilatation.

Medical termination of pregnancy of upto 7 weeks has been achieved with high success rate by administering mifepristone (antiprogestin) 600 mg orally 2 days before a single oral dose of misoprostol 400 µg. This is now a valuable alternative to suction-evacuation. Uterine contractions are provoked and the conceptus is expelled within the next few hours. Intravaginal misoprostol is now favoured by many in place of oral, because it produces fewer side effects. Sublingual route is also advocated by some experts. Ectopic pregnancy should be ruled out beforehand and complete expulsion should be confirmed afterwards. Uterine cramps, vaginal bleeding, nausea, vomiting and diarrhoea are the common side effects. Methotrexate administered along with misoprostol is also highly successful for inducing abortion in the first few weeks of pregnancy.

PGs have a place in midterm abortion, missed abortion and molar gestation, though delayed and erratic action and incomplete abortion are a problem. The initial enthusiasm has given way to more considered use. PGs convert the oxytocin resistant midterm uterus to oxytocin responsive one: a single extraamniotic injection (PGE_2) followed by i.v. infusion of oxytocin, or intraamniotic ($PGF_{2\alpha}$) with hypertonic solution produces 2nd trimester abortion in a high percentage without undue side effects. Pretreatment with mifepristone improves the efficacy of PGE_2 as abortifacient.

2. *Induction/augmentation of labour* PGs do not offer any advantage over oxytocin for induction of labour at term. They are less reliable and show wider individual variation in action. PGE_2 and $PGF_{2\alpha}$ (rarely) have been used in place of oxytocin in toxaemic and renal failure patients, because PGs do not cause fluid retention that is possible with oxytocin. PGE_2 may also be used to augment labour if it is slow, particularly in primipara. Intravaginal route is preferred now because side effects are milder; extra/intra amniotic route is infrequently used.

3. *Cervical priming (ripening)* Applied intravaginally or in the cervical canal, low doses of PGE_2, which do not affect uterine motility, make the cervix soft and compliant. This procedure has yielded good results in cases with unfavourable cervix. If needed labour may be induced 12 hours later with oxytocin: chances of failure are reduced.

4. *Postpartum haemorrhage (PPH)* Carboprost (15-methyl $PGF_{2\alpha}$) injected i.m. is an alternative drug for control of PPH due to uterine atony, especially in patients unresponsive to ergometrine and oxytocin.

PGE_2 (Dinoprostone) PROSTIN-E_2 for induction/augmentation of labour, midterm abortion.

Vaginal gel (1 mg or 2 mg in 2.5 ml) 1 mg inserted into posterior fornix, followed by 1–2 mg after 6 hour if required.

Vaginal tab (3 mg) 3 mg inserted into posterior fornix, followed by another 3 mg if labour does not start within 6 hour.

Extraamniotic solution (10 mg/ml in 0.5 ml amp.) infrequently used.

Intravenous solution (1 mg/ml in 0.75 ml amp., 10 mg/ml in 0.5 ml amp) i.v. route is rarely used due to more side effects.

Oral tablet PRIMIPROST 0.5 mg tab, one tab. hourly till induction, max 1.5 mg per hr; rarely used.

Cervical gel CERVIPRIME (0.5 mg in 2.5 ml prefilled syringe) 0.5 mg inserted into cervical canal for preinduction cervical softening and dilatation in patients with poor Bishop's score.

Gemeprost CERVAGEM 1 mg vaginal pessary: for softening of cervix in first trimester—1 mg 3 hr before attempting dilatation; for 2nd trimester abortion/molar gestation—1 mg every 3 hours, max. 5 doses.

$PGF_{2\alpha}$ (Dinoprost) PROSTIN F_2 ALPHA intraamniotic injection 5 mg/ml in 4 ml amp. for midterm abortion/induction of labour (rarely used).

15-methyl $PGF_{2\alpha}$ (Carboprost) PROSTODIN 0.25 mg in 1 ml amp; 0.25 mg i.m. every 30–120 min for PPH, midterm abortion, missed abortion.

T-PILL + MISO, ABORTOM: Mifepristone 200 mg tab (3 tabs) + misoprostol 200 µg (2 tabs) kit: mifepristone 3 tab orally followed 2 days later by misoprostol 2 tab orally, for termination of pregnancy of upto 49 days.

5. *Glaucoma* Topical $PGF_{2\alpha}$ analogues like *latanoprost, travoprost, bimatoprost* that are FP receptor agonists are the first choice drugs in wide angle glaucoma (*see* p. 169). UNOPROSTONE

6. *Peptic ulcer* Stable analogue of PGE_1 (misoprostol) is occasionally used for healing peptic ulcer, especially

in patients who need continued NSAID therapy or who continue to smoke (*see* Ch. 47).

7. *To maintain patency of ductus arteriosus* in neonates with congenital heart defects, till corrective surgery is undertaken. PGE_1 (Alprostadil) is used; apnoea occurs in few cases.

PROSTIN VR, BIOGLANDIN 0.5 mg in 1 ml amp; dilute and infuse i.v.

8. *To avoid platelet damage* PGI_2 (Epoprostenol) can be used to prevent platelet aggregation and damage during haemodialysis or cardiopulmonary bypass. It also improves harvest of platelets for transfusion.

9. *Pulmonary hypertension* PGI_2 lowers pulmonary artery resistance. Accordingly, few cases of primary *pulmonary hypertension* have been successfully maintained on epoprostenol infused continuously in a large vein.

FLOLAN: epoprostenol 0.5 mg vial for reconstitution.

10. *Peripheral vascular diseases* PGI_2 (or PGE_1) infused i.v. can relieve rest pain and promote healing of ischaemic ulcers in severe cases of intermittent claudication and in Raynaud's disease.

11. *Impotence* Alprostadil (PGE_1) injected into the penis causes erection lasting 1–2 hours. However, oral sildenafil/tadalafil is now preferred for erectile dysfunction.

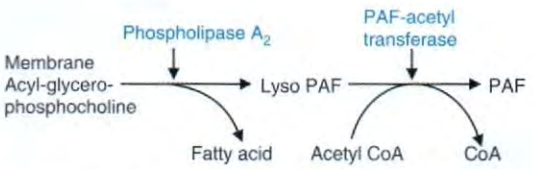
SIDE EFFECTS

Side effects are common in the use of PGs, but their intensity varies with the PG, the dose and the route. These are: nausea, vomiting, watery diarrhoea, uterine cramps, unduly forceful uterine contractions, vaginal bleeding, flushing, shivering, fever, malaise, fall in BP, tachycardia, chest pain.

PLATELET ACTIVATING FACTOR (PAF)

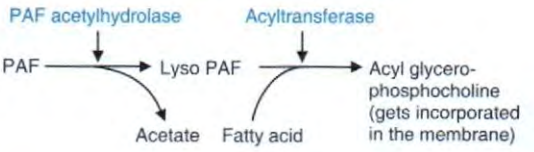
Like eicosanoids, platelet activating factor (PAF) is a cell membrane derived polar lipid with intense biological activity. Discovered in 1970s PAF is active at subnanomolar concentration and is now recognized to be an important signal molecule. PAF is acetyl-glyceryl ether-phosphoryl choline. The ether-linked alkyl chain in human PAF is mostly 16 or 18 C long.

Synthesis and degradation PAF is synthesized from precursor phospholipids present in cell membrane by the following reactions:



The second step is rate limiting. Antigen-antibody reaction and a variety of mediators stimulate PAF synthesis in a Ca^{2+} dependent manner on demand. There are no preformed stores of PAF. In contrast to eicosanoids, the types of cells which synthesize PAF is quite limited—mainly WBC, platelets, vascular endothelium and kidney cells.

PAF is degraded in the following manner:



Actions PAF has potent actions on many tissues/organs.

Platelets PAF induces aggregation and release reaction; also releases TXA_2; i.v. injection of PAF results in intravascular thrombosis.

WBC PAF is a potent chemotactic for neutrophils, eosinophils and monocytes. It stimulates neutrophils to aggregate, to stick to vascular endothelium and migrate across it to the site of infection. It also prompts release of lysosomal enzymes and LTs as well as generation of superoxide radical by the polymorphs. The chemotactic action may be mediated through release of LTB_4. It induces degranulation of eosinophils.

Blood vessels Vasodilatation mediated by release of EDRF occurs causing fall in BP on i.v. injection. Decreased coronary blood flow has been observed on intracoronary injection, probably due to formation of platelet aggregates and release of TXA_2.

PAF is the most potent agent known to increase vascular permeability. Wheal and flare occur at the site of intradermal injection.

Injected into the renal artery PAF reduces renal blood flow and Na^+ excretion by direct vasoconstrictor action, but this is partly counteracted by local PG release.

Visceral smooth muscle Contraction occurs by direct action as well as through release of LTC_4, TXA_2 and PGs. Aerosolized PAF is a potent bronchoconstrictor. In addition, it produces mucosal edema, secretion and a delayed and long-lasting bronchial hyper-responsiveness. It also stimulates intestinal and uterine smooth muscle.

Stomach PAF is highly ulcerogenic: erosions and mucosal bleeding occur shortly after i.v. injection of PAF. The gastric smooth muscle contracts.

Mechanism of action Membrane bound specific PAF receptors have been identified. The PAF receptor is a

G-protein coupled receptor which exerts most of the actions by coupling with Gq protein and generating intracellular messengers $IP_3/DAG \rightarrow Ca^{2+}$ release. It can also inhibit adenylyl cyclase by coupling with Gi protein.

As mentioned above, many actions of PAF are mediated/augmented by PGs, TXA_2 and LTs which may be considered its extracellular messengers. PAF also acts intracellularly, especially in the endothelial cells. Rise in PAF concentration within the endothelial cells is associated with exposure of neutrophil binding sites on their surface. Similarly, its proaggregatory action involves unmasking of fibrinogen binding sites on the surface of platelets.

PAF antagonists A number of natural and synthetic PAF receptor antagonists have been investigated. Important among these are ginkgolide B (from a Chinese plant), and some structural analogues of PAF. The PAF antagonists have manyfold therapeutic potentials like treatment of stroke, intermittent claudication, sepsis, myocardial infarction, shock, g.i. ulceration, asthma and as contraceptive. Some of them have been tried clinically but none has been found worth marketing. Alprazolam and triazolam antagonize some actions of PAF.

Pathophysiological roles PAF has been implicated in many pathological states and some physiological processes by mediating cell-to-cell interaction. These are:

1. *Inflammation:* Generated by leukocytes at the site of inflammation PAF appears to participate in the causation of vasodilatation, exudation, cellular infiltration and hyperalgesia.

2. *Bronchial asthma:* Along with LTC_4 and LTD_4, PAF appears to play a major role by causing bronchoconstriction, mucosal edema, recruiting eosinophils and provoking secretions. It is unique in producing prolonged airway hyper-reactivity, so typical of human bronchial asthma.

3. *Anaphylactic (and other) shock conditions:* are associated with high circulating PAF levels.

4. *Haemostasis and thrombosis:* PAF may participate by promoting platelet aggregation.

5. PAF may also play a role in implantation of fertilized ovum, ischaemic states of brain, heart and g.i.t., including g.i. ulceration.

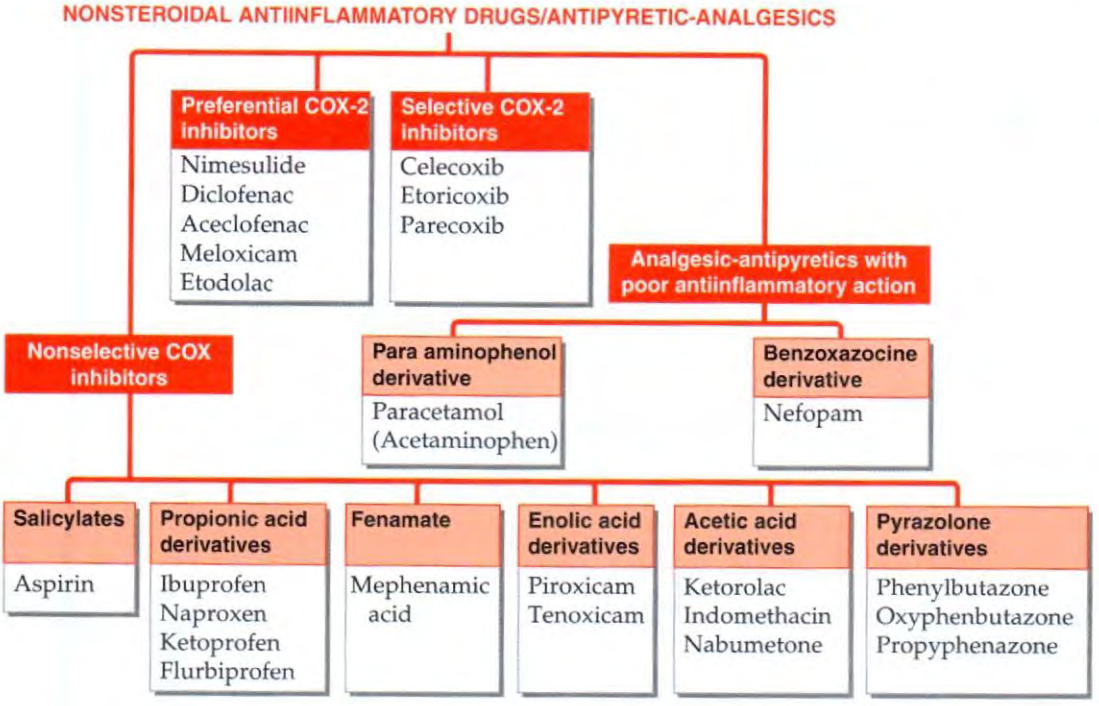
☞ PROBLEM DIRECTED STUDY

13.1 A full term primigravida presented with labour pains. On examination the BP was 110/70 mm Hg and she was not anaemic. The presentation was vertex, head was engaged, foetal heart sound was normal, there was no cephalopelvic disproportion, no placenta previa, membranes were intact and uterine contractions were adequate. The labour was allowed to progress under observation. After 8 hours the cervix was still firm and not adequately dilated.
(a) Can some medicaion be used to soften the cervix, help its ripening and facilitate delivery? If so, which drug and route of administration should be used?
(b) Given the above findings, is there any contraindication to the use of such medication?
(see Appendix-1 for solution)

Chapter 14 Nonsteroidal Antiinflammatory Drugs and Antipyretic-Analgesics

The nonsteroidal antiinflammatory drugs (NSAIDs) and antipyretic analgesics are a class of drugs that have analgesic, antipyretic and antiinflammatory actions in different measures. In contrast to morphine they do not depress CNS, do not produce physical dependence, have no abuse liability and are particularly effective in inflammatory pain. They are also called *nonnarcotic, nonopioid* or *aspirin-like* analgesics. They act primarily on peripheral pain mechanisms, but also in the CNS to raise pain threshold. They are more commonly employed and many are over-the-counter or nonprescription drugs.

Willow bark (*Salix alba*) had been used as a medicine for many centuries. Salicylic acid was prepared by hydrolysis of the bitter glycoside obtained from this plant. *Sodium salicylate* was used for fever and pain in 1875. Its great success led to the introduction of acetylsalicylic acid (aspirin) in 1899. *Phenacetin* and *antipyrine* were also produced at that time. The next major advance was the development of phenylbutazone in 1949 having antiinflammatory activity almost comparable to corticosteroids. The term Nonsteroidal Antiinflammatory Drugs (NSAIDs) was coined to designate such drugs. *Indomethacin* was introduced in 1963. A host



of compounds heralded by the propionic acid derivative *ibuprofen* have been added since then, and cyclooxygenase (COX) inhibition is recognised to be their most important mechanism of action. Subsequently some selective COX-2 inhibitors (celecoxib, etc.) have been added.

The NSAIDs are chemically diverse, but all are weak organic acids or their active metabolites are organic acids.

NSAIDs and prostaglandin (PG) synthesis inhibition

In 1971 Vane and coworkers made the landmark observation that aspirin and some NSAIDs blocked prostaglandin (PG) generation. This is now considered to be the major mechanism of action of NSAIDs. Prostaglandins, prostacyclin (PG I_2) and thromboxane A_2 (TXA_2) are produced from arachidonic acid by the enzyme cyclooxygenase (*see* p. 198) which exists in a constitutive (COX-1) and an inducible (COX-2) isoforms; the former serves physiological 'house keeping' functions, while the latter, normally present in minute quantities, is induced by cytokines and other signal molecules at the site of inflammation. This leads to generation of PGs locally which mediate many of the inflammatory changes. However, COX-2 is constitutively present at some sites in brain, in juxtaglomerular cells and in the foetus; it may serve physiological role at these sites. Most NSAIDs inhibit COX-1 and COX-2 nonselectively, but now some selective COX-2 inhibitors have been produced. Features of nonselective COX-1/COX-2 inhibitors (traditional NSAIDs) and selective COX-2 inhibitors are compared in Table 14.1

Aspirin inhibits COX irreversibly by acetylating one of its serine residues; return of COX activity depends on synthesis of fresh enzyme.

Beneficial actions due to PG synthesis inhibition

- Analgesia: prevention of pain nerve ending sensitization
- Antipyresis
- Antiinflammatory
- Antithrombotic
- Closure of ductus arteriosus in newborn

Other NSAIDs are competitive and reversible inhibitors of COX; return of activity depends on their dissociation from the enzyme which in turn is governed by the pharmacokinetic characteristics of the compound.

Analgesia PGs induce hyperalgesia (*see* p. 203) by affecting the transducing property of free nerve endings so that stimuli that normally do not elicit pain are able to do so. NSAIDs do not affect the tenderness induced by direct application of PGs, but block the pain sensitizing mechanism induced by bradykinin, TNFα, interleukins (ILs) and other algesic substances primarily by inhibiting COX-2. This constitutes the peripheral component of the analgesic action of NSAIDs. They are, therefore, more effective against inflammation associated pain.

Lately the central component of analgesic action of NSAIDs has also been shown to involve inhibition of PG synthesis in the spinal dorsal horn neurones as well as in brain, so that PG mediated amplification of pain impulses does not occur.

Antipyresis NSAIDs lower body temperature in fever, but do not cause hypothermia in normothermic individuals. Fever during infection and tissue injury is produced through the generation of pyrogens including, ILs, TNFα, interferons which induce PGE_2 production in hypothalamus—raise its temperature set point. NSAIDs block the action of pyrogens but not that of PGE_2 injected into the hypothalamus. The isoform dominant at this site appears to be COX-2 (possibly COX-3, a splice variant of COX-1 that is inhibited by paracetamol as well). However, fever can occur through non-PG mediated mechanisms as well.

Antiinflammatory The most important mechanism of antiinflammatory action of NSAIDs is considered to be inhibition of COX-2 mediated enhanced PG synthesis at the site of injury. However, there is some evidence that inhibition of the constitutive COX-1 also contributes to suppression of inflammation, especially in the initial stages. The antiinflammatory potency of different compounds roughly corresponds with their potency to inhibit COX. However, nimesulide is a potent antiinflammatory but relatively weak COX inhibitor. PGs are only one of the

Table 14.1: Features of nonselective COX inhibitors and selective COX-2 inhibitors

Action	COX-1/ COX-2 inhibitors	COX-2 inhibitors
1. Analgesic	+	+
2. Antipyretic	+	+
3. Antiinflammatory	+	+
4. Antiplatelet aggregatory	+	–
5. Gastric mucosal damage	+	–
6. Renal salt/water retention	+	+
7. Delay/prolongation of labour	+	+
8. Ductus arteriosus closure	+	?
9. Aspirin sensitive asthma precipitation	+	–

mediators of inflammation, and inhibition of COX does not depress the production of other mediators like LTs, PAF, cytokines, etc. Inflammation is the result of concerted participation of a large number of vasoactive, chemotactic and proliferative factors at different stages, and there are many targets for antiinflammatory action.

Activated endothelial cells express adhesion molecules (ELAM-1, ICAM-1) on their surface and play a key role in directing circulating leucocytes to the site of inflammation (chemotaxis). Similarly, inflammatory cells express *selectins* and *integrins*. Certain NSAIDs may act by additional mechanisms including inhibition of expression/activity of some of these molecules and generation of superoxide/other free radicals. Growth factors like GM-CSF, IL-6 as well as lymphocyte transformation factors and TNFα may also be affected. Stabilization of lysosomal membrane of leukocytes and antagonism of certain actions of kinins may be contributing to antiinflammatory action of NSAIDs.

Dysmenorrhoea Involvement of PGs in dysmenorrhoea has been clearly demonstrated: level of PGs in menstrual flow, endometrial biopsy and that of $PGF_{2\alpha}$ metabolite in circulation are raised in dysmenorrhoeic women. Intermittent ischaemia of the myometrium is probably responsible for menstrual cramps. NSAIDs lower uterine PG levels—afford excellent relief in 60–70% and partial relief in the remaining. Ancillary symptoms of headache, muscle ache and nausea are also relieved. Excess flow may be normalized.

Shared toxicities due to PG synthesis inhibition

- Gastric mucosal damage
- Bleeding: inhibition of platelet function
- Limitation of renal blood flow : Na^+ and water retention
- Delay/prolongation of labour
- Asthma and anaphylactoid reactions in susceptible individuals

Antiplatelet aggregatory NSAIDs inhibit synthesis of both proaggregatory (TXA_2) and antiaggregatory (PGI_2) prostanoids, but effect on platelet TXA_2 (COX-1 generated) predominates. Therapeutic doses of most NSAIDs inhibit platelet aggregation and prolong bleeding time. *Aspirin is highly active*, because it acetylates platelet COX irreversibly in the portal circulation before getting deacetylated by first pass metabolism in liver. Small doses of aspirin are therefore able to exert antithrombotic effect for several days. Risk of surgical and anticoagulant associated bleeding is enhanced.

Ductus arteriosus closure During foetal circulation ductus arteriosus is kept patent by local elaboration of PGE_2 by COX-2. Unknown mechanisms switch off this synthesis at birth and the ductus closes. When this fails to occur, small doses of indomethacin or aspirin bring about closure in majority of cases within a few hours by inhibiting PG production. Administration of NSAIDs in late pregnancy has been found to promote premature closure of ductus in some cases. Risk of post-partum haemorrhage is increased. Prescribing of NSAIDs near term should be avoided.

Parturition Sudden spurt of PG synthesis by uterus occurs just before labour begins. This is believed to trigger labour as well as facilitate its progression. Accordingly, NSAIDs have the potential to delay and retard labour. However, labour can occur in the absence of PGs.

Gastric mucosal damage Gastric pain, mucosal erosion/ulceration and blood loss are caused by all NSAIDs to varying extents: relative gastric toxicity is a major consideration in the choice of NSAIDs. Inhibition of COX-1 mediated synthesis of gastroprotective PGs (PGE_2, PGI_2) is clearly involved, though local action inducing back diffusion of H^+ ions in gastric mucosa also plays a role. Deficiency of PGs reduces mucus and HCO_3^- secretion, tends to enhance acid secretion and may promote mucosal ischaemia. Thus, NSAIDs enhance aggressive factors and contain defensive factors in gastric mucosa; are therefore ulcerogenic. Paracetamol, a very weak inhibitor of COX is practically free of gastric toxicity and selective COX-2 inhibitors are relatively safer. Stable PG analogues (misoprostol) administered concurrently with NSAIDs counteract their gastric toxicity.

Renal effects Conditions leading to hypovolaemia, decreased renal perfusion and Na^+ loss induce renal PG synthesis which brings about intrarenal adjustments by promoting vasodilatation, inhibiting tubular Cl^- reabsorption (Na^+ and water accompany) and opposing ADH action. NSAIDs produce renal effects by at least 3 mechanisms:

- COX-1 dependent impairment of renal blood flow and reduction of g.f.r., which can worsen renal insufficiency.
- Juxtaglomerular COX-2 (probably COX-1 also) inhibition dependent Na^+ and water retention.
- Ability to cause papillary necrosis on habitual intake.

Renal effects of NSAIDs are not marked in normal individuals, but become significant in those with CHF, hypovolaemia, hepatic cirrhosis, renal disease and in patients receiving diuretics or antihypertensives. In them Na^+ retention and edema can occur; diuretic and antihypertensive drug effects are blunted.

Involvement of PG synthesis inhibition in analgesic nephropathy is uncertain.

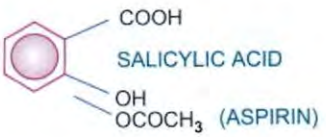
Analgesic nephropathy occurs after years of heavy ingestion of analgesics. Such individuals probably have some personality defect. Regular use of combinations of NSAIDs and chronic/repeated urinary tract infections increase the risk of analgesic nephropathy. Pathological lesions are papillary necrosis, tubular atrophy followed by renal fibrosis. Urine concentrating ability is lost and the kidneys shrink. Because phenacetin was first implicated, it went into disrepute, though other analgesics are also liable to produce similar effects.

Anaphylactoid reactions Aspirin precipitates asthma, angioneurotic swellings, urticaria or rhinitis in certain susceptible individuals. These subjects react similarly to chemically diverse NSAIDs, ruling out immunological basis for the reaction. Inhibition of COX with consequent diversion of arachidonic acid to LTs and other products of lipoxygenase pathway may be instrumental, but there is no proof.

SALICYLATES

Aspirin (prototype)

Aspirin is acetylsalicylic acid. It is rapidly converted in the body to salicylic acid which is responsible for most of the actions. Other actions are the result of acetylation of certain macromolecules including COX. It is one of the oldest analgesic-antiinflammatory drugs and has diverse uses.



Pharmacological Actions

1. *Analgesic, antipyretic, antiinflammatory actions* Aspirin is a weaker analgesic (has lower maximal efficacy) than morphine type drugs: aspirin 600 mg ≃ codeine 60 mg. However, it effectively relieves inflammatory, tissue injury related, connective tissue and integumental pain, but is relatively ineffective in severe visceral and ischaemic pain. The analgesic action is mainly due to obtunding of peripheral pain receptors and prevention of PG-mediated sensitization of nerve endings. A central subcortical action raising threshold to pain perception also contributes to analgesia, but the morphine-like action on psychic processing

or reaction component of the pain is missing. No sedation, subjective effects, tolerance or dependence is produced.

Aspirin resets the hypothalamic thermostat and rapidly reduces fever by promoting heat loss (sweating, cutaneous vasodilatation), but does not decrease heat production.

Antiinflammatory action is exerted at high doses (3–6 g/day or 100 mg/kg/ day). Signs of inflammation like pain, tenderness, swelling, vasodilatation and leucocyte infiltration are suppressed. In addition to COX inhibition, quenching of free radicals may contribute to its antiinflammatory action. However, progression of the underlying disease in rheumatoid arthritis, osteoarthritis and rheumatic fever, etc. is not affected.

2. *GIT* Aspirin, as well as salicylic acid released from it irritate gastric mucosa, cause epigastric distress, nausea and vomiting. At high doses, it stimulates CTZ. Vomiting caused by aspirin has a central component as well.

Aspirin (pKa 3.5) remains unionized and diffusible in the acid gastric juice, but on entering the mucosal cell (pH 7.1) it ionizes and becomes indiffusible. This 'ion trapping' (*see* p. 17) in the gastric mucosal cell enhances gastric toxicity. Further, aspirin particle coming in contact with gastric mucosa promotes local back diffusion of acid. This causes focal necrosis of mucosal cells and capillaries → acute ulcers, erosive gastritis, congestion and microscopic haemorrhages. The occult blood loss in stools is increased by even a single tablet of aspirin. Blood loss averages 5 ml/day at antiinflammatory doses. Haematemesis occurs occasionally: may be an idiosyncratic reaction.

Soluble aspirin tablets containing calcium carbonate + citric acid and other buffered preparations are less liable to cause gastric irritation, but incidence of ulceration and bleeding is not significantly lowered.

3. *Blood* Aspirin, even in small doses, irreversibly inhibits TXA_2 synthesis by platelets. Thus, it interferes with platelet aggregation and bleeding time is prolonged to nearly twice the normal value. This effect lasts for about a week (turnover time of platelets).

Long-term intake of large dose decreases synthesis of clotting factors in liver and predisposes to bleeding. This can be prevented by prophylactic vit K therapy.

4. *Metabolic and other effects of high (antiinflammatory/toxic) doses* Analgesic doses of aspirin (0.3–0.6 g 6–8 hourly) employed for headache, fever, etc. produce almost no other action. However, high doses (3–5 g/day or 100 mg/kg/day) needed for antiinflammatory action in rheumatoid arthritis/rheumatic fever produce several other effects.

- Cellular metabolism is enhanced, especially in skeletal muscles, due to uncoupling of oxidative phosphorylation. Glucose utilization is increased resulting in fall in blood glucose level (especially in diabetics); liver glycogen is depleted. However, toxic doses may cause central sympathetic stimulation and rise in blood sugar.
- Respiration is stimulated by direct action on respiratory centre as well as due to increased CO_2 production. Hyperventilation followed by respiratory depression occurs at toxic doses.
- Respiratory stimulation tends to washout CO_2 and produce respiratory alkalosis. This is compensated by enhanced HCO_3^- excretion by kidney. Most adults receiving 3–5 g/day stay in a state of *compensated respiratory alkalosis.* Still higher doses depress respiration while excess CO_2 production continues to cause *respiratory acidosis.* Increased production of metabolic acids (lactic, pyruvic, acetoacetic) and dissociated salicylic acid may contribute to uncompensated *metabolic acidosis,* since plasma HCO_3^- is already low. Dehydration occurs due to excess water loss in urine, sweating and hyperventilation. Most children menifest this phase during salicylate poisoning, while in adults it is seen only in late stages of poisoning.
- Aspirin has no direct effect on heart or circulation, but doses which enhance metabolic rate, increase cardiac output indirectly. Toxic doses depress vasomotor centre, so that blood pressure may fall. CHF may be precipitated if cardiac reserve is low.

- Aspirin interferes with urate excretion and antagonises the uricosuric effect of probenecid. However, at high doses (≥ 5 g/day) it may block urate reabsorption and increase its excretion, but aspirin is not a reliable uricosuric.

Pharmacokinetics

Aspirin is absorbed from the stomach and small intestines. Its poor water solubility is the limiting factor in absorption: microfining the drug-particles and inclusion of an alkali (solubility is more at higher pH) enhances absorption. However, higher pH also favours ionization, thus decreasing the diffusible form.

Aspirin is rapidly deacetylated in the gut wall, liver, plasma and other tissues to release salicylic acid which is the major circulating and active form. It is ~80% bound to plasma proteins and has a volume of distribution ~0.17 L/kg. Entry into brain is slow, but aspirin freely crosses placenta. Both aspirin and salicylic acid are conjugated in liver with glycine to form salicyluric acid (major pathway). They are conjugated with glucuronic acid as well. The metabolites are excreted by glomerular filtration and tubular secretion, only 1/10th is excreted as free salicylic acid.

The plasma t½ of aspirin as such is 15–20 min, but taken together with that of released salicylic acid, it is 3–5 hours. However, metabolic processes get saturated over the therapeutic range; t½ of antiinflammatory doses may be 8–12 hours while that during poisoning may be as long as 30 hours. Thus, elimination is dose dependent.

Adverse effects

(a) *Side effects* that occur at analgesic dose (0.5–2.0 g/day) are nausea, vomiting, epigastric distress, increased occult blood loss in stools. The most important adverse effect of aspirin is gastric mucosal damage and peptic ulceration.
(b) *Hypersensitivity and idiosyncrasy* Though infrequent, these can be serious. Reactions include rashes, fixed drug eruption, urticaria, rhinorrhoea, angioedema, asthma and anaphylactoid reaction. Profuse gastric bleeding occurs in rare instances.
(c) *Antiinflammatory doses* (3–5 g/day) produce the syndrome called 'salicylism'—dizziness, tinnitus, vertigo, reversible impairment of hearing and vision, excitement, hyperventilation and electrolyte imbalance.

Aspirin therapy in children with rheumatoid arthritis has been found to raise serum transaminases, indicating liver damage. Most cases are asymptomatic but it is potentially dangerous. An association has been noted between salicylate therapy and 'Reye's syndrome', a rare form of hepatic encephalopathy seen in children having viral (varicella, influenza) infection.

In adults also, long-term therapy with high dose aspirin can cause hepatic injury. Salt and water retention occurs in a dose related manner.
(d) *Acute salicylate poisoning* It is more common in children. Fatal dose in adults is estimated to be 15–30 g, but is considerably lower in children. Manifestations are:

Vomiting, dehydration, electrolyte imbalance, acidotic breathing, hyper/hypoglycaemia, petechial haemorrhages, restlessness, delirium, hallucinations, hyperpyrexia, convulsions, coma and death due to respiratory failure + cardiovascular collapse.

Treatment is symptomatic and supportive. Most important is external cooling and i.v. fluid with Na^+, K^+, HCO_3^- and glucose according to need determined by repeated monitoring. Blood transfusion and vit K should be given if bleeding occurs.

Precautions and contraindications

- Aspirin is contraindicated in patients who are sensitive to it and in those with peptic ulcer or bleeding tendencies; in children suffering from chicken pox or influenza. Due to risk of Reye's syndrome, pediatric formulations of aspirin are prohibited in India and the UK.
- In chronic liver disease aspirin can precipitate hepatic necrosis.
- Aspirin should be avoided in diabetics, in those with low cardiac reserve or frank CHF and in juvenile rheumatoid arthritis.
- Aspirin should be stopped 1 week before elective surgery.

- Given repeatedly during pregnancy it may be responsible for low birth weight babies. Delayed or prolonged labour, greater postpartum blood loss and premature closure of ductus arteriosus are possible if aspirin is taken at or near term.
- Aspirin should be avoided by breastfeeding mothers.
- Avoid high doses in G-6PD deficient individuals—haemolysis can occur.

Interactions

1. Aspirin displaces warfarin, sulfonylureas, phenytoin and methotrexate from binding sites on plasma proteins: overdose symptoms of these drugs may occur. Its antiplatelet action increases the risk of bleeding in patients on oral anticoagulants.
2. Aspirin at analgesic doses inhibits tubular secretion of uric acid and antagonizes uricosuric action of probenecid. Tubular secretion of methotrexate is also interfered.
3. Aspirin blunts diuretic action of furosemide and thiazides and reduces K^+ conserving action of spironolactone. Competition between canrenone (active metabolite of spironolactone) and aspirin for active transport in proximal tubules has been demonstrated.

Uses

1. *As analgesic* For headache (including mild migraine), backache, myalgia, joint pain, pulled muscle, toothache, neuralgias and dysmenorrhoea; it is effective in low doses (0.3–0.6 g 6–8 hourly). Analgesic effect is maximal at ~ 1000 mg (single dose).

2. *As antipyretic* Aspirin is effective in fever of any origin; dose is same as for analgesia. However, paracetamol, being safer, is generally preferred.

3. *Acute rheumatic fever* Aspirin is the first drug to be used in all cases; other drugs are added or substituted only when it fails or in severe cases (corticosteroids act faster). In a dose of 4–5 g or 75–100 mg/kg/day (in divided portions) it brings about marked symptomatic relief in 1–3 days. Dose reduction may be started after 4–7 days and maintenance doses (50 mg/kg/day) are continued for 2–3 weeks or till signs of active disease (raised ESR) persist. Withdrawal should be gradual over the next 2 weeks.

Granulomatous lesions, nodules, cardiac complications, valvular defects, chorea and duration of disease are not altered by salicylate therapy.

4. *Rheumatoid arthritis* Aspirin in a dose of 3–5 g/day produces relief of pain, swelling and morning stiffness, but progress of the disease process is not affected. Since large doses of aspirin are poorly tolerated for long periods, it is rarely used now; newer NSAIDs are preferred.

5. *Osteoarthritis* It affords symptomatic relief, but is infrequently used now; paracetamol is the first choice analgesic for most cases.

6. *Postmyocardial infarction and poststroke patients* By inhibiting platelet aggregation aspirin lowers the incidence of reinfarction. TXA_2 synthesis in platelets is inhibited at low doses. It has been argued that high doses can reverse the beneficial effects by concurrently inhibiting PGI_2 (antiaggregatory and vasodilatory) synthesis in vessel wall. Large studies have demonstrated that aspirin 75–150 mg/day reduces the incidence of myocardial infarction (MI): it is now routinely prescribed to post-infarct patients. 'New onset' or 'sudden worsening' angina is associated with high infarction rate. This can be reduced to half by 100–150 mg aspirin per day for 12 weeks.

Aspirin reduces 'transient ischaemic attacks' and lowers incidence of stroke in such patients. But the risk of stroke in post-MI patients is not reduced.

7. *Prevention of preeclampsia* Imbalance between synthesis of TXA_2 and PGI_2 is believed to be causative in pregnancy related hypertension and preeclampsia. Aspirin 80–100 mg/day administered from 12th week of gestation till child birth has been found to reduce the risk of

Adverse effects of NSAIDs

Gastrointestinal
Nausea, anorexia, gastric irritation, erosions, peptic ulceration, gastric bleeding/perforation, esophagitis

Renal
Na^+ and water retention, edema, chronic renal failure, nephropathy, papillary necrosis (rare)

CVS
Rise in BP, risk of myocardial infarction (especially with COX-2 inhibitors), CHF

Hepatic
Raised transaminases, hepatic failure (rare)

CNS
Headache, tinnitus, mental confusion, vertigo, seizure precipitation

Haematological
Bleeding, thrombocytopenia, haemolytic anaemia, neutropenia

Others
Asthma exacerbation, rhinitis, nasal polyposis, skin rashes, pruritus, angioedema

preeclampsia in pregnant women with diabetes, chronic kidney disease and other predisposing conditions.

8. Other conditions in which aspirin may be used are:
   - Familial colonic polyposis: aspirin and other NSAIDs suppress polyp formation and afford symptomatic relief in this rare disorder.
   - Prevention of colon cancer: incidence of colon cancer among regular aspirin users is much lower. Colonic tumours express large quantities of COX-2. However, the rofecoxib trial (APPROVE) was prematurely terminated and the drug withdrawn due to increased incidence of cardiovascular events. The Adenoma Prevention with Celecoxib (APC) trial has also been terminated due to 2.5 fold increase in risk of major fatal/nonfatal cardiovascular events.
   - To prevent flushing attending nicotinic acid ingestion, which is due to PGD_2 release in the skin.

ASPIRIN 350 mg tab, COLSPRIN 100, 325 mg tabs, ECOSPRIN 75, 150, 325 mg tabs, DISPRIN 350 mg tab (with cal. carbonate 105 mg + citric acid 35 mg), LOPRIN 75, 162.5 mg tabs.

An injectable preparation has also been made available; BIOSPIRIN: Lysine acetylsalicylate 900 mg + glycine 100 mg/vial for dissolving in 5 ml water and i.v. injection.

PROPIONIC ACID DERIVATIVES

Ibuprofen was the first member of this group to be introduced in 1969 as a better tolerated alternative to aspirin. Many others have followed. All have similar pharmacodynamic properties but differ considerably in potency and to some extent in duration of action (Table 14.2).

All members inhibit PG synthesis, naproxen being the most potent; but their *in vitro* potency to inhibit COX does not closely parallel *in vivo* antiinflammatory potency. Inhibition of platelet aggregation is short-lasting with ibuprofen, but longer lasting with naproxen.

Adverse effects Ibuprofen and all its congeners are better tolerated than aspirin. Side effects are milder and their incidence is lower. Gastric discomfort, nausea and vomiting, though less than aspirin or indomethacin, are still the most common side effects. Gastric erosion and occult blood loss are rare.

CNS side effects include headache, dizziness, blurring of vision and tinnitus.

Rashes, itching and other hypersensitivity phenomena are infrequent. However, these drugs precipitate aspirin-induced asthma.

Fluid retention is less marked.

They are not to be prescribed to pregnant women and should be avoided in peptic ulcer patient.

Pharmacokinetics and interactions All propionic acid derivative NSAIDs are well absorbed orally, highly bound to plasma proteins (90–99%), but displacement interactions are not clinically significant—dose of oral anticoagulants and oral hypoglycaemics need not be altered. Because they inhibit platelet function, use with anticoagulants should, nevertheless, be avoided. Similar to other NSAIDs, they are likely to decrease diuretic and antihypertensive action of thiazides, furosemide and β blockers.

All NSAIDs of this class enter brain, synovial fluid and cross placenta. They are largely metabolized in liver by hydroxylation and glucuronide conjugation and excreted in urine as well as in bile.

Drug interactions with NSAIDs

Pharmacodynamic		*Pharmacokinetic*	
Diuretics	: ↓ diuresis	Coumarin anticoagulants	Metabolism inhibited; competition for plasma protein binding
β blocker	: ↓ antihypertensive effect	Sulfonylureas	
ACE inhibitors	: ↓ antihypertensive effect	Phenytoin	
Anticoagulants	: ↑ risk of g.i. bleed	Valproate	
Sulfonylureas	: ↑ risk of hypoglycaemia		
Alcohol	: ↑ risk of g.i. bleed	Digoxin	↓ Renal excretion of interacting drug
Cyclosporine	: ↑ nephrotoxicity	Lithium	
Corticosteroids	: ↑ risk of g.i. bleed	Aminoglycosides	
Selective serotonin reuptake inhibitors	: ↑ risk of g.i. bleed	Methotrexate	

Uses

1. Ibuprofen is used as a simple analgesic and antipyretic in the same way as low dose of aspirin. It is particularly effective in dysmenorrhoea in which the action is clearly due to PG synthesis inhibition. It is available as an 'over-the-counter' drug.
2. Ibuprofen and its congeners are widely used in rheumatoid arthritis, osteoarthritis and other musculoskeletal disorders, especially where pain is more prominent than inflammation.
3. They are indicated in soft tissue injuries, fractures, vasectomy, tooth extraction, postpartum and postoperatively, wherein they suppress swelling and inflammation.

Ibuprofen It has been rated as the safest traditional NSAID by the spontaneous adverse drug reaction reporting system in U.K. Ibuprofen (400 mg) has been found equally or more efficacious than a combination of aspirin (650 mg) + codeine (60 mg) in relieving dental surgery pain, but is a weaker antiinflammatory; not suitable for acute gout and other similar conditions.

Concurrent treatment with ibuprofen has been found to prevent irreversible COX inhibition by low dose aspirin, because it reversibly occupies the active serine residue of COX-1 and protects it from irreversible acetylation by aspirin. Thus, the antiplatelet action of ibuprofen is short lasting, and it abolishes the antiplatelet and cardioprotective effect of low dose aspirin.

Naproxen The antiinflammatory activity is stronger and it is particularly potent in inhibiting leucocyte migration—may be more valuable in acute gout: dose 750 mg stat followed by 250 mg 8 hourly till attack subsides. It is also recommended for rheumatoid arthritis and ankylosing spondylitis. Because of longer t½, regular use can effectively suppress platelet function. Gastric bleeding is more common than with ibuprofen. Naproxen carries lower thrombotic risk than diclofenac, etoricoxib, etc. Dose should be reduced in the elderly.

Naproxen is marketed as active single S(–) enantiomer preparation, which poses less renal burden. However, some R(+) enantiomer is formed *in vivo* due to inversion.

Table 14.2: Dosage and preparations of propionic acid derivatives

Drug	*Plasma t½*	*Dosage*	*Preparations*
1. Ibuprofen	2–4 hr	400–600 mg (5–10 mg/kg) TDS	BRUFEN, EMFLAM, IBUSYNTH 200, 400, 600 mg tab, IBUGESIC also 100 mg/5 ml susp.
2. Naproxen	12–16 hr	250 mg BD–TDS	NAPROSYN, NAXID, ARTAGEN, XENOBID 250 mg tab., NAPROSYN also 500 mg tab.
3. Ketoprofen	2–3 hr	50–100 mg BD–TDS	KETOFEN 50, 100 mg tab; OSTOFEN 50 mg cap. RHOFENID 100 mg tab, 200 mg SR tab; 100 mg/2 ml amp.
4. Flurbiprofen	4–6 hr	50–100 mg BD–QID	ARFLUR 50, 100 mg tab, 200 mg SR tab, FLUROFEN 100 mg tab.

Ketoprofen An additional action to stabilize lysosomes and to inhibit LOX has been demonstrated with ketoprofen; though antiinflammatory efficacy is similar to ibuprofen, and side effects are more.

Flurbiprofen It may have some additional mechanisms of antiinflammatory action, and is more effective than ibuprofen, but gastric side effects are also more. It is used as an ocular antiinflammatory as well.

OCUFLUR, FLUR, FLURBIN, 0.03% eye drops, 1 drop 6 hourly.

Choice among different propionic acid derivatives is difficult; *naproxen* is probably more efficacious and better tolerated in antiinflammatory doses. It is longer acting and has the advantage of twice daily dosing. However, individuals vary in their preference for different members.

FENAMATE (Anthranilic acid derivative)

Mephenamic acid An analgesic, antipyretic and weaker antiinflammatory drug, which inhibits synthesis of PGs as well as antagonises some of their actions.

Adverse effects Diarrhoea is the most important dose-related side effect. Epigastric distress is complained, but gut bleeding is not significant. Skin rashes, dizziness and other CNS manifestations have occurred. Haemolytic anaemia is a rare but serious complication.

Pharmacokinetics Oral absorption is slow but almost complete. It is highly bound to plasma proteins, partly metabolized and excreted in urine as well as bile. Plasma t½ is 2–4 hours.

Uses Mephenamic acid is indicated primarily as analgesic in muscle, joint and soft tissue pain where strong antiinflammatory action is not needed. It is quite effective in dysmenorrhoea. It may be useful in some cases of rheumatoid and osteoarthritis but has no distinct advantage.

Dose: 250–500 mg TDS; MEDOL 250, 500 mg cap; MEFTAL 250, 500 mg tab, 100 mg/5 ml susp.

PONSTAN 125, 250, 500 mg tab, 50 mg/ml syrp.

Comorbid conditions aggravated by NSAIDs

- Peptic ulcer
- Hypertension
- Congestive heart failure
- Renal insufficiency
- Hemostatic disorders

ENOLIC ACID DERIVATIVES (Oxicams)

Piroxicam It is a long-acting potent NSAID with antiinflammatory potency similar to indomethacin and good analgesic-antipyretic action. It is a nonselective, reversible inhibitor of COX; lowers PG concentration in synovial fluid and inhibits platelet aggregation—prolonging bleeding time. In addition, it decreases the production of free radicals and IgM rheumatoid factor. Leucocyte chemotaxis is inhibited. Thus, it can inhibit inflammation in diverse ways.

Pharmacokinetics Piroxicam is rapidly and completely absorbed: 99% plasma protein bound; largely metabolized in liver by hydroxylation and glucuronide conjugation; excreted in urine and bile; enterohepatic cycling occurs. Plasma t½ is long—nearly 2 days. Single daily administration is sufficient, and steady-state concentrations are achieved in a week.

Adverse effects The g.i. side effects are more than ibuprofen, but low doses are better tolerated and less ulcerogenic than indomethacin. However, ulcer and g.i. bleeding are frequent with higher doses. Rashes and pruritus are seen in ~ 1% patients, and serious skin reactions are possible. Edema and reversible azotaemia have been observed.

Uses Due to slow onset of action piroxicam is suitable for use as long-term antiinflammatory drug in rheumatoid and osteoarthritis, ankylosing spondylitis, etc., but is not a first choice drug for any condition because of relatively higher toxicity. It has also been used for acute gout, musculoskeletal injuries and in dentistry.

Dose: 20 mg BD for two days followed by 20 mg OD:

DOLONEX, PIROX 10, 20 mg cap, 20 mg dispersible tab, 20 mg/ml inj in 1 and 2 ml amps; PIRICAM 10, 20 mg cap.

Tenoxicam A congener of piroxicam with similar properties and uses.

TOBITIL 20 mg tab; dose 20 mg OD.

ACETIC ACID DERIVATIVES

Ketorolac This arylacetic acid NSAID has potent analgesic but modest antiinflammatory activity. In postoperative pain it has equalled the efficacy of morphine, but does not interact with opioid receptors and is free of opioid side effects. Like other NSAIDs, it inhibits PG synthesis and relieves pain primarily by a peripheral mechanism. In short-lasting pain, it has compared favourably with aspirin.

Ketorolac is rapidly absorbed after oral and i.m. administration. It is highly plasma protein bound and 60% excreted unchanged in urine. Major metabolic pathway is glucuronidation; plasma t½ is 5–7 hours.

Adverse effects Nausea, abdominal pain, dyspepsia, ulceration, loose stools, drowsiness, headache, dizziness, nervousness, pruritus, pain at injection site, rise in serum transaminase and fluid retention have been noted.

Ketorolac has been used concurrently with morphine to keep its dose low. However, it should not be given to patients on anticoagulants.

Use Injected ketorolac is used in postoperative, dental and acute musculoskeletal pain: 15–30 mg i.m. or i.v. every 4–6 hours (max. 90 mg/day). It may also be used for renal colic, migraine and pain due to bony metastasis.

Orally it is used in a dose of 10–20 mg 6 hourly for short-term management of moderate pain, but not for osteo- or rheumatoid arthritis. Continuous use for more than 5 days is not recommended due to risk of g.i. and renal toxicity. It should not be used for preanaesthetic medication or for obstetric analgesia. Topical ketorolac is quite popular for noninfective ocular conditions.

KETOROL, ZOROVON, KETANOV, TOROLAC 10 mg tab, 30 mg in 1 ml amp.

KETLUR, ACULAR 0.5% eye drops; 1–2 drops 2–4 times a day for noninfective ocular inflammatory conditions.

Indomethacin This indole acetic acid derivative is a potent antiinflammatory drug with prompt antipyretic action. Indomethacin relieves only inflammatory or tissue injury related pain. It is a highly potent inhibitor of PG synthesis and suppresses neutrophil motility. In toxic doses it uncouples oxidative phosphorylation (like aspirin).

Pharmacokinetics Indomethacin is well absorbed orally, rectal absorption is slow but dependable. It is 90% bound to plasma proteins, partly metabolized in liver to inactive products and excreted by kidney. Plasma t½ is 2–5 hours.

Adverse effects A high incidence (up to 50%) of gastrointestinal and CNS side effects is produced.

Gastric irritation, nausea, anorexia, gastric bleeding and diarrhoea are prominent.

Frontal headache (very common), dizziness, ataxia, mental confusion, hallucination, depression and psychosis can occur.

Leukopenia, rashes and other hypersensitivity reactions are also reported.

Increased risk of bleeding due to decreased platelet aggregability.

Indomethacin is contraindicated in machinery operators, drivers, psychiatric patients, epileptics, kidney disease, pregnant women and in children.

Dose: 25–50 mg BD-QID. Those not tolerating the drug orally may be given nightly suppository.

IDICIN, INDOCAP 25 mg cap, 75 mg SR cap, ARTICID 25, 50 mg cap, INDOFLAM 25, 75 mg caps, 1% eye drop. RECTICIN 50 mg suppository.

Uses Because of prominent adverse effects, indomethacin is used as a reserve drug in conditions requiring potent antiinflammatory action like ankylosing spondylitis, acute exacerbations of destructive arthropathies, psoriatic arthritis and acute gout or rheumatoid arthritis that are not responding to better tolerated NSAIDs.

Malignancy associated fever refractory to other antipyretics may respond to indomethacin.

It has been the most common drug used for medical closure of patent ductus arteriosus: three 12 hourly i.v. injections of 0.1–0.2 mg/kg achieve closure in majority of cases.

Bartter's syndrome responds dramatically, as it does to other PG synthesis inhibitors.

Nabumetone It is a prodrug—generates an active metabolite 6-methoxy naphthyl acetic acid (6-MNA) which inhibits both COX-1 and COX-2. It possesses analgesic, antipyretic and antiinflammatory activities; effective in the treatment of rheumatoid and osteoarthritis as well as in soft tissue injury. Nabumetone has caused a lower incidence of gastric erosions, ulcers and bleeding, probably because the active COX inhibitor is produced in the tissues after absorption. However, abdominal cramps and diarrhoea can occur. Rashes and photosensitivity are reported. The plasma t½ is 24 hours.

NABUFLAM 500 mg tab; 1–2 tab OD.

PYRAZOLONES

Antipyrine (phenazone) and amidopyrine (aminopyrine) were introduced in 1884 as antipyretic and analgesic. Their use was associated with high incidence of agranulocytosis: are banned globally. *Phenylbutazone* was introduced in 1949 and soon its active metabolite *oxyphenbutazone* was also marketed. These two are potent antiinflammatory drugs, inhibit COX, but have slow onset. Their gastric toxicity is high; edema due to Na^+ and water retention is frequent and CNS side effects, hypersensitivity reactions, hypothyroidism are reported. They have gone out of use due to residual risk of bone marrow depression and other toxicity.

Propyphenazone This is the only pyrazolone still avilable in India, though prohibited in many countries for risks similar to other drugs in this group. It has fast onset short duration analgesic-antipyretic-antiinflammatory action. Marketed only as 'over-the-counter' analgesic-antipyretic FDCs, it is mostly used by people for self medication of headache, bodyache, toothache, fever, etc.

SARIDON: propyphenazone 150 mg + paracetamol 250 mg + caffeine 30 mg tab.

PREFERENTIAL COX-2 INHIBITORS

Nimesulide This NSAID is a relatively weak inhibitor of PG synthesis and moderately COX-2 selective. Antiinflammatory action may be exerted by other mechanisms as well, e.g. reduced generation of superoxide by neutrophils, inhibition of PAF synthesis and TNFα release, free radical scavenging, inhibition of metalloproteinase activity in cartilage. The analgesic, antipyretic and antiinflammatory activity of nimesulide has been rated comparable to other NSAIDs. It has been used primarily for short-lasting painful inflammatory conditions like sports injuries, sinusitis and other ear-nose-throat disorders, dental surgery, bursitis, low backache, dysmenorrhoea, postoperative pain, osteoarthritis and for fever.

Nimesulide is almost completely absorbed orally, 99% plasma protein bound, extensively metabolized and excreted mainly in urine with a t½ of 2–5 hours.

Adverse effects of nimesulide are gastrointestinal (epigastralgia, heart burn, nausea, loose motions), dermatological (rash, pruritus) and central (somnolence, dizziness). Gastric tolerability of nimesulide is better, though ulcer complications are as prevalent as with other NSAIDs.

Instances of *fulminant hepatic failure* have been associated with nimesulide and it has been withdrawn in Spain, Ireland, Singapore and Turkey; use in children is banned in Portugal, Israel and now in India as well. Considering that it has not been marketed in many countries like the UK, USA, Australia, Canada, the overall safety of this drug, especially in children, has been questioned. However, most asthmatics and those who develop bronchospasm or intolerance to aspirin and other NSAIDs do not cross react with nimesulide. Its specific usefulness appears to be only in such patients.

Dose: 100 mg BD; NIMULID, NIMEGESIC, NIMODOL 100 mg tab, 50 mg/5 ml susp.

Diclofenac sodium An analgesic-antipyretic-antiinflammatory drug, similar in efficacy to naproxen. It inhibits PG synthesis and is somewhat COX-2 selective. The antiplatelet action is not appreciable due to sparing of COX-1, and the cardioprotective effect of low dose aspirin is not blocked. Neutrophil chemotaxis and superoxide production at the inflammatory site are reduced.

Diclofenac is well absorbed orally, 99% protein bound, metabolized and excreted both

in urine and bile. The plasma t½ is ~2 hours. However, it has good tissue penetrability and concentration in synovial fluid is maintained for 3 times longer period than in plasma, exerting extended therapeutic action in joints.

Adverse effects of diclofenac are generally mild: epigastric pain, nausea, headache, dizziness, rashes. Gastric ulceration and bleeding are less common. Some comparative trials have found its gastric toxicity to be similar to celecoxib and etoricoxib. Like many NSAIDs, diclofenac can increase the risk of heart attack and stroke, probably reflecting lack of antiplatelet action. Reversible elevation of serum amino-transferases has been reported more commonly. Renal blood flow and g.f.r may be reduced, especially at higher doses.

Diclofenac is among the most extensively used NSAID; employed in rheumatoid and osteoarthritis, bursitis, ankylosing spondylitis, toothache, dysmenorrhoea, renal colic, post-traumatic and postoperative inflammatory conditions—affords quick relief of pain and wound edema.

Dose: 50–75 mg TDS, then BD oral, 75 mg deep i.m.
VOVERAN, DICLONAC, MOVONAC 50 mg enteric coated tab, 100 mg S.R. tab, 25 mg/ml in 3 ml amp. for i.m. inj. DICLOMAX 25, 50 mg tab, 75 mg/3 ml inj., DYNAPAR AQ, JUSTIN AQ: diclofenac sod. 75 mg in 1 ml for i.m./i.v. injection; This more concentrated parenteral formulation of diclofenac can be given i.m. (less painful, because propylene glycol is not used) as well as by bolus i.v. injection without dilution.
Diclofenac potassium: VOLTAFLAM 25, 50 mg tab, ULTRA-K 50 mg tab; VOVERAN 1% topical gel.
DICLONAC, VOVERAN OPHTHA 0.1% eye drops.

Aceclofenac A moderately COX-2 selective congener of diclofenac having similar properties. Enhancement of glycosaminoglycan synthesis may confer chondroprotective property to aceclofenac.

Dose: 100 mg BD;
ACECLO, DOLOKIND 100 mg tab, 200 mg SR tab.

Meloxicam This newer congener of piroxicam has a COX-2/COX-1 selectivity ratio of about 10. Since measurable inhibition of platelet TXA_2 production (a COX-1 function) occurs at therapeutic doses of meloxicam, it has been labelled 'preferential COX-2 inhibitor'. Efficacy of meloxicam in osteo- and rheumatoid arthritis is comparable to piroxicam. Plasma t½ is 15–20 hours permiting single daily dose. In short-term studies, gastric changes with the lower dose (7.5 mg/day) were found to be similar to placebo, but at the higher dose (15 mg/day) they were intermediate between placebo and piroxicam. Gastric side effects of meloxicam are milder, but ulcer complications (bleeding, perforation) have been reported on long-term use. There is no convincing evidence that meloxicam is safer than other NSAIDs.

Dose: 7.5–15 mg OD;
MELFLAM, MEL-OD, MUVIK, M-CAM 7.5 mg, 15 mg tabs.

Etodolac This newer indole-acetic acid NSAID is moderately COX-2 selective with properties similar to diclofenac. At lower doses, gastric tolerance is better than older NSAIDs. It is metabolized by hydroxylation and glucuronide conjugation, and excreted in urine with a t½ of 7 hours. Postoperative analgesia with etodolac lasts for 6–8 hours. Side effects are abdominal pain, rashes and dizziness. It is approved for use in osteo- and rheumatoid arthritis as well as in acute musculoskeletal pain.

Dose: 200–400 mg BD–TDS;
ETOVA 200, 300, 400 mg tabs, ETOGESIC 400 mg tab.

Etodolac 400 mg/2 ml for i.m. injection has been approved for postoperative orthopedic pain.

SELECTIVE COX-2 INHIBITORS (Coxibs)

Because of the theoretical advantage of inhibiting COX-2 which is induced at the sites of inflammation without affecting the 'house keeping' COX-1 function, some highly selective COX-2 inhibitors have been introduced over the past 3 decades. They cause less gastric mucosal damage; occurrence of peptic ulcer and ulcer bleeds is clearly lower than that with traditional NSAIDs. They do not depress TXA_2 production by platelets, because it is COX-1 dependent; do not inhibit platelet aggregation or prolong bleeding time, but reduce PGI_2 production by vascular endothelium. Thus, they lack the cardioprotective property of aspirin.

Currently, 3 selective COX-2 inhibitors (also called coxibs) *Celecoxib*, *Etoricoxib* and *Parecoxib* are available in India. *Rofecoxib* and

Selective COX-2 inhibitors and cardiovascular risk

COX-2 inhibitors reduce endothelial PGI_2 production without affecting platelet TXA_2 synthesis. This appears to exert prothrombotic influence and enhance CV risk.

- VIGOR (VIOXX gastrointestinal outcomes research) study in over 8000 patients found 4-fold higher incidence of myocardial infarction (MI) in rofecoxib (VIOXX) recipients compared to those on naproxen.
- APPROVE (adenomatous polyp prevention on VIOXX) a placebo controlled trial among subjects with history of colorectal adenomas was stopped prematurely at 3 years because it confirmed higher risk of heart attack and stroke: rofecoxib was withdrawn globally in 2004.
- A metaanalysis of 18 trials with rofecoxib for musculoskeletal disorders has also inferred that it increases incidence of MI.
- Valdecoxib increased occurrence of MI in patients undergoing coronary bypass surgery. There were reports of severe skin reactions as well. It was withdrawn in 2005.
- Though CLASS (celecoxib long-term safety study) did not find any increase in CV events, the APC (adenoma prevention with celecoxib) trial has been terminated prematurely due to 2.5 fold higher risk of the same.
- There is no clear evidence as yet that etoricoxib also increases CV risk.
- A joint committee in USA (2005) concluded that enough evidence to withdraw all selective COX-2 inhibitors is lacking, but that their labelling should include a warning of CV risk.

Valdecoxib were withdrawn within few years of marketing for increasing cardiovascular (CV) risk. *Lumiracoxib* marketed only in Europe has been suspended due to hepatotoxicity.

It has been concluded that *selective COX-2 inhibitors should be used only in patients at high risk of peptic ulcer, perforation or bleeds.* If selected, they should be administered in the lowest dose for the shortest period of time. Moreover, they should be avoided in patients with history of ischaemic heart disease/hypertension/cardiac failure/cerebrovascular disease, who are predisposed to CV events. Combination of low-dose aspirin with COX-2 inhibitors for reducing cardiovascular risk increases gastroduodenal injury, and is not advised.

Concerns, other than cardiovascular, have also been expressed about selective COX-2 inhibitors (*see* box).

Other concerns with selective COX-2 inhibitors

- COX-1 generated PGs may also play a role in inflammation: COX-2 inhibitors may not have as broad range of efficacy as traditional NSAIDs.
- Ulcer injury and *H. pylori* induce COX-2 in gastric mucosa, which may contribute to gastroprotective PG synthesis; COX-2 inhibition may delay ulcer healing. Moreover, part of gastric mucosal COX-2 activity may be constitutive.
- Juxtaglomerular COX-2 is constitutive; its inhibition can cause salt and water retention. Pedal edema, precipitation of CHF and rise in BP can occur with all coxibs.

Celecoxib The COX-2 selectivity of celecoxib is modest (about 10 times). It exerts antiinflammatory, analgesic and antipyretic actions with low ulcerogenic potential. Comparative trials in rheumatoid arthritis have found it to be as effective as naproxen or diclofenac, without affecting COX-1 activity in gastroduodenal mucosa. Platelet aggregation in response to collagen exposure remained intact in celecoxib recipients and serum TXB_2 levels were not reduced. Though tolerability of celecoxib is better than traditional NSAIDs, still abdominal pain, dyspepsia and mild diarrhoea are the usual side effects. Rashes, edema and a small rise in BP have also been noted.

Celecoxib is absorbed slowly, 97% plasma protein bound and metabolized primarily by CYP2C9 with a t½ of ~10 hours. It is approved for use in osteo- and rheumatoid arthritis in a dose of 100–200 mg BD.

CELACT, REVIBRA, COLCIBRA 100, 200 mg caps.

Etoricoxib This newer COX-2 inhibitor has the highest COX-2 selectivity. It is suitable for once-a-day treatment of osteo/rheumatoid/acute gouty arthritis, ankylosing spondylitis, dysmenorrhoea, acute dental surgery pain and similar conditions, without affecting platelet function or damaging gastric mucosa. The t½ is ~ 24 hours. The rate of thrombotic cardiovascular events with etoricoxib use has been found similar to that with diclofenac. However, it should be considered as a treatment option only as per conditions stated above for all

COX-2 inhibitors. Side effects are dyspepsia, abdominal pain, pedal edema, rise in BP, dry mouth, aphthous ulcers, taste disturbance and paresthesias.

Dose: 60–120 mg OD; ETOSHINE, TOROCOXIA, ETOXIB, NUCOXIA 60, 90, 120 mg tabs.

Parecoxib It is a prodrug of valdecoxib suitable for injection, and to be used in post-operative or similar short-term pain, with efficacy similar to ketorolac. It shares the same risk of serious cutaneous reactions as valdecoxib; should be stopped at the first appearance of a rash.

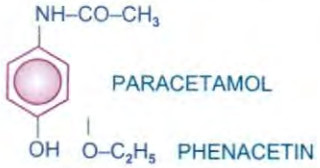
Dose: 40 mg oral/i.m./i.v., repeated after 6–12 hours.

REVALDO, VALTO-P 40 mg/vial inj, PAROXIB 40 mg tab.

PARA-AMINO PHENOL DERIVATIVES

Phenacetin introduced in 1887 was extensively used as analgesic-antipyretic, but was banned when it was implicated in analgesic abuse nephropathy (*see* p. 212)

Paracetamol (acetaminophen) It is the deethylated active metabolite of phenacetin that was also introduced in the last century, but has come into common use only since 1950.



Actions The central analgesic action of paracetamol is like aspirin, i.e. it raises pain threshold, but has weak peripheral antiinflammatory component. Analgesic action of aspirin and paracetamol is additive. Paracetamol is a good and promptly acting antipyretic.

Paracetamol has negligible antiinflammatory action. It is a poor inhibitor of PG synthesis in peripheral tissues, but more active on COX in the brain. One explanation offered for the discrepancy between its analgesic-antipyretic and antiinflammatory actions is its inability to inhibit COX in the presence of peroxides which are generated at sites of inflammation, but are not present in the brain. The ability of paracetamol to inhibit COX-3 (an isoenzyme so far located in dog brain) could also account for its analgesic-antipyretic action.

In contrast to aspirin, paracetamol does not stimulate respiration or affect acid-base balance; does not increase cellular metabolism. It has no effect on CVS. Gastric irritation is insignificant—mucosal erosion and bleeding occur rarely only in overdose. It does not affect platelet function or clotting factors and is not uricosuric.

Pharmacokinetics Paracetamol is well absorbed orally, only about 1/4th is protein bound in plasma and it is uniformly distributed in the body. Metabolism occurs mainly by conjugation with glucuronic acid and sulfate: conjugates are excreted rapidly in urine. Plasma $t_{1/2}$ is 2–3 hours. Effects after an oral dose last for 3–5 hours.

Adverse effects In isolated antipyretic doses paracetamol is safe and well tolerated. Nausea and rashes occur occasionally, leukopenia is rare.

Acute paracetamol poisoning It occurs especially in small children who have low hepatic glucuronide conjugating ability. If a large dose (> 150 mg/kg or > 10 g in an adult) is taken, serious toxicity can occur. Fatality is common with > 250 mg/kg.

Early manifestations are just nausea, vomiting, abdominal pain and liver tenderness with no impairment of consciousness. After 12–18 hours centrilobular hepatic necrosis occurs which may be accompanied by renal tubular necrosis and hypoglycaemia that may progress to coma. Jaundice starts after 2 days. Further course depends on the dose taken. Fulminating hepatic failure and death are likely if the plasma levels are high. If the levels are lower —recovery with supportive treatment is the rule.

Mechanism of toxicity N-acetyl-p-benzoquinoneimine (NABQI) is a highly reactive arylating minor metabolite of paracetamol which is detoxified by conjugation with glutathione. When a very large dose of paracetamol is taken, glucuronidation capacity is saturated, more of the minor metabolite is formed—hepatic glutathione is depleted and this metabolite binds covalently to proteins in liver cells (and renal tubules) causing necrosis. Toxicity thus shows

a threshold effect manifesting only when glutathione is depleted to a critical point.

In chronic alcoholics even 5 g taken in one day can result in hepatotoxicity because alcoholism induces CYP2E1 that metabolises paracetamol to NABQI.

Paracetamol is not recommended in premature infants (< 2 kg) for fear of hepatotoxicity.

Note: Exercising abundant caution, because paracetamol is an over-the-counter drug, the US-FDA (2009) has recommended to reduce the amount of this drug in any single dosage form (tab./cap.) to 650 mg (in place of 1000 mg earlier limit), and the total daily dose for an adult to 2600 mg (in place of 4000 mg earlier).

Treatment If the patient is brought early, vomiting should be induced or gastric lavage done. Activated charcoal is given orally or through the tube to prevent further absorption. Other supportive measures, as needed, should be taken.

Specific antidote: N-acetylcysteine (MUCOMIX, MUCARE 200 mg/ml inj in 2, 5 ml amps, ACETINE 1 g/5 ml inj.) MUCOMYKS 1 g/5 ml inj, 600 mg tab.) 150 mg/kg should be infused i.v. in 200 ml 5% glucose solution over 15 min, followed by the same dose given i.v. over the next 20 hours. Alternatively, 75 mg/kg may be given orally every 4–6 hours for 2–3 days. It replenishes the glutathione stores of liver and prevents binding of the toxic metabolite to other cellular constituents.

Ingestion-treatment interval is critical; earlier the better. It is practically ineffective if started 16 hours or more after paracetamol ingestion.

Uses Paracetamol is one of the most commonly used 'over-the-counter' analgesic for headache, mild migraine, musculoskeletal pain, dysmenorrhoea, etc. but is relatively ineffective when inflammation is prominent as in rheumatoid arthritis. Paracetamol is recommended as first choice analgesic for osteoarthritis by many professional bodies. It is one of the best drugs to be used as antipyretic for fever due to any cause, especially in children (no risk of Reye's syndrome). However, antipyretics are not useful in fever due to *heat stroke*, in which only external cooling lowers body temperature.

Dose to dose paracetamol is equally efficacious to aspirin for noninflammatory conditions. It is much safer than aspirin in terms of gastric irritation, ulceration and bleeding (can be given to ulcer patients), does not prolong bleeding time. Hypersensitivity reactions are rare; no metabolic effects or acid-base disturbances. Paracetamol can be used in all age groups (infants to elderly), pregnant/lactating women, in presence of other disease states and in patients in whom aspirin is contraindicated. It does not have significant drug interactions. Thus, it may be preferred over aspirin for most minor conditions.

Dose: 325–650 mg (children 10–15 mg/kg) 3–4 times a day.

CROCIN 0.5 g tab, 120 mg/5 ml oral susp., 100 mg/ml oral drops; METACIN, PARACIN 500 mg tab, 125 mg/5 ml syrup, 150 mg/ml paed. drops, ULTRAGIN, PYRIGESIC, CALPOL 500 mg tab, 125 mg/5 ml syrup, NEOMOL, FEVASTIN, FEBRINIL 300 mg/2 ml inj., CROCIN PAIN RELIEF: 650 mg + Caffeine 50 mg tab.

KABIPARA: paracetamol 1g/100 ml for slow i.v. injection; AEKNIL: 150 mg/ml inj in 2,3,15 ml amps, for slow i.v. inj. JUNIMOL-RDS 80, 170, 250 mg suppository (for children), PARACETAMOL RECTAL SUPPOSITORY 80, 170 mg.

BENZOXAZOCINE DERIVATIVE

Nefopam It is a nonopioid analgesic which does not inhibit PG synthesis but relieves traumatic, postoperative and short-lasting musculoskeletal pain. It may be used if pain is persistent and is not adequately relieved by other analgesics.

Nefopam produces anticholinergic (dry mouth, urinary retention, blurred vision) and sympathomimetic (tachycardia, nervousness) side effects, and nausea is often dose limiting. It is contraindicated in epileptics.

Dose: 30–60 mg TDS oral, 20 mg i.m. 6 hourly.

NEFOMAX 30 mg tab, 20 mg in 1 ml amp.

Topical NSAIDs

Many NSAIDs have been marketed in topical formulations (mostly as gels) for application over painful muscles or joints. These preparations are being used for osteoarthritis, sprains, sports injuries, tenosinovitis, backache, spondylitis and other forms of soft tissue rheumatism. It is presumed that the drug would penetrate to the subjacent tissues attaining high concentrations in the affected muscles/joints, while maintaining low blood levels. Consequently, the g.i. and other systemic adverse effects would be

minimised and first pass hepatic metabolism would also be avoided.

While there is no doubt about their safety, doubt has been raised about their actual efficacy over and above a strong placebo effect of local application, massaging and that due to presence of counter irritants like menthol, methyl salicylate, etc. in most of them. Often they are used in addition to oral NSAID medication. Guidelines of several professional bodies recommend topical NSAIDs in mild-to-moderate osteoarthritis of knee and hand as initial or adjunctive therapy.

Measurement of drug concentration attained in tissues underlying the site of application, as well as concurrent blood levels has shown that systemic absorption from topical NSAID preparations is slow taking ~10 times longer time to attain peak concentration compared to oral dosing. Highest blood levels remain below 15% of that attained after the same dose given orally. This is consistent with their lack of systemic toxicity. Local concentrations are high upto a depth of 4–6 mm, i.e. in dermis, but at 25 mm depth in muscles, the concentration is low and nearly the same as in blood. Marked variation has been noted in the concentration attained in muscles and joints depending on the type of formulation, depth and distance from site of application as well as among different individuals. Reports on the clinical efficacy of topical NSAIDs are also variable. Better responses have generally been obtained in short lasting musculoskeletal pain. Clinical trials in osteoarthritis of knee have generally rated topical formulations of NSAIDs, notably those of diclofenac and ketoprofen to be superior to placebo. Though overall efficacy of topical NSAIDs in musculoskeletal pain is low, it appears to be clinically valuable.

Preparations

Diclofenac 1% gel : VOLINI GEL, RELAXYL GEL, DICLONAC GEL
Ibuprofen 10% gel : RIBUFEN GEL
Naproxen 10% gel : NAPROSYN GEL
Ketoprofen 2.5% gel : RHOFENID GEL
Flurbiprofen 5% gel : FROBEN GEL
Nimesulide 1% gel : NIMULID TRANS GEL, ZOLANDIN GEL, NIMEGESIC-T-GEL
Piroxicam 0.5% gel : DOLONEX GEL, MOVON GEL, PIROX GEL, MINICAM GEL

Choice of nonsteroidal antiinflammatory drug

Efficacy differences among different NSAIDs are minor, but they have their own spectrum of adverse effects. They differ quantitatively among themselves in producing different side effects and there are large inter-individual differences. At present NSAIDs are a bewildering array of strongly promoted drugs. No single drug is superior to all others for every patient. Choice of drug is inescapably empirical.

The cause and nature of pain (mild, moderate or severe; acute or chronic; ratio of pain: inflammation) along with consideration of risk factors in the given patient (age, concurrent disease and drug therapy, history of allergy) govern selection of the analgesic. Also to be considered are the past response of the patient, acceptability and individual preference. Patients differ in their analgesic response to different NSAIDs. If one NSAID is unsatisfactory in a patient, it does not mean that other NSAIDs will also be unsatisfactory. Some subjects 'feel better' on a particular drug, but not on a closely related one. It is inthis context that availability of such a wide range of NSAIDs may be welcome. Some guidelines are:

1. Mild-to-moderate pain with little inflammation: paracetamol or low-dose ibuprofen.
2. Postoperative or similar acute but short- lasting pain: injectable ketorolac, or diclofenac or oral propionic acid derivative/nimesulide.
3. A parenteral NSAID may be employed for renal colic, acute gout, acute back pain, dental pain, fractures and other grievous trauma. Three NSAIDs, *viz.* Ketorolac, diclofenac and parecoxib are available for i.m./i.v. use. Paracetamol can be given by slow i.v. infusion.
4. Exacerbation of rheumatoid arthritis, ankylosing spondylitis, acute gout, acute rheumatic fever: naproxen, piroxicam, indomethacin, high dose aspirin.

5. Gastric intolerance to traditional NSAIDs or predisposed patients: a selective COX-2 inhibitor or paracetamol. Arthritis patients who are dependent on NSAIDs and have developed peptic ulcer must receive concurrent proton pump inhibitor as gastroprotective.
6. Patients with history of asthma or anaphylactoid reaction to aspirin/other NSAIDs: nimesulide, COX-2 inhibitor.
7. Patients with hypertension or other risk factor for heart attack/stroke: avoid selective COX-2 inhibitor; a propionic acid derivative or aspirin may be used at the lowest dose for the shortest period.
8. Paediatric patients: Only paracetamol, aspirin, ibuprofen and naproxen have been adequately evaluated in children.One of these should be preferred in children. Due to risk of Reye's syndrome, aspirin should be avoided.
9. Elderly patients: use lower dose of the chosen NSAID.
10. Fast acting drug formulation is suitable for fever, headache and other short lasting pain, while longer acting drugs/sustained release formulations are appropriate for chronic arthritic pain.
11. Pregnancy: paracetamol is the safest; low-dose aspirin is probably the second best.
12. Hypertensive, diabetic, ischaemic heart disease, epileptic and other patients receiving long-term regular medication: possibility of drug interaction with NSAIDs should be considered.

Analgesic combinations

Combination of aspirin and paracetamol is additive (not supra-additive) and a ceiling analgesic effect is obtained when the total amount of aspirin + paracetamol is ~ 1000 mg. The same is true of combinations of paracetamol with other NSAIDs like ibuprofen, diclofenac, etc. There is no convincing evidence that such combinations are superior to single agents, either in efficacy or in safety. If at all used, such combinations should be limited to short periods.

Combination of codeine (an opioid analgesic) with aspirin or paracetamol is also additive, but in this case combination provides additional analgesia beyond the ceiling effect of aspirin/paracetamol. However, this is true only when each is given in full dose which will produce opioid side effects (nausea, vomiting, constipation, drowsiness, risk of dependence) as well. The mechanisms of pain relief by these two classes of drugs are different. Such combination should be considered only for pain refractory to single agent.

To obviate inadvertent misuse and chance of producing dependence, the fixed dose combinations of analgesics with hypnotics/sedatives/anxiolytics is banned in India.

☞ PROBLEM DIRECTED STUDY

14.1 A 65-year-old lady presented with pain in both knees, more on the left side. The pain is worsened by walking or standing for some time. X-ray of knee shows narrowing of joint space, mild effusion and osteophytic projections. A diagnosis of osteoarthritis of knee is made. She gave history of suffering a heart attack one year back which was treated by angioplasty and a stent was placed. She regularly takes aspirin 75 mg daily for prophylaxis of further myocardial infarction.

(a) Which analgesic/NSAID will be suitable for relieving her knee pain?

(b) Which analgesic/NSAIDs should not be prescribed for her?

(c) Whether any locally applied medication can be helpful in relieving her knee pain?

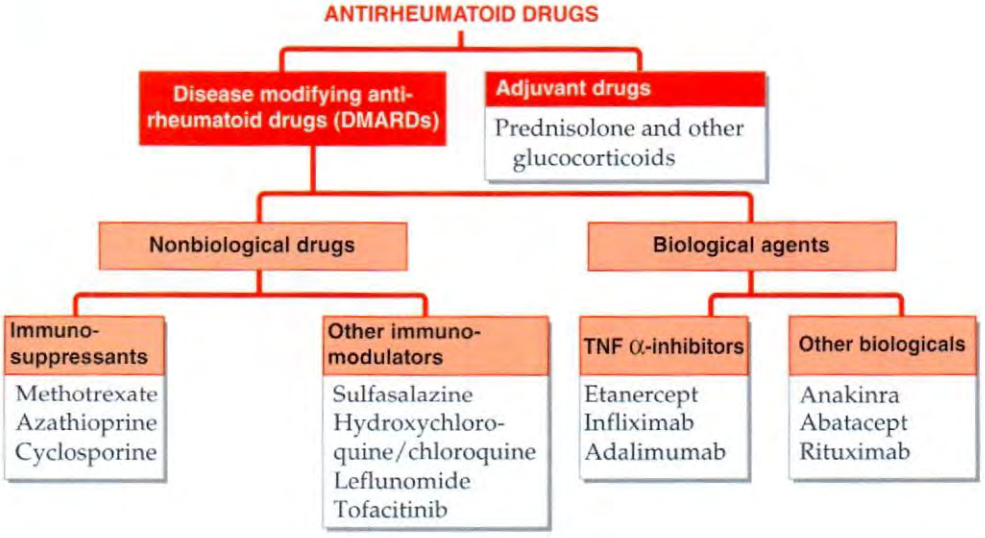
(see Appendix-1 for solution)

Chapter 15 Antirheumatoid and Antigout Drugs

ANTIRHEUMATOID DRUGS

These are drugs which (except corticosteroids), can suppress the rheumatoid process, bring about a remission and retard disease progression, but do not have nonspecific antiinflammatory or analgesic action. They are used in rheumatoid arthritis (RA) in addition to NSAIDs, and are also referred to as *disease modifying antirheumatic drugs* (DMARDs) or *slow acting antirheumatic drugs* (SAARDs). The onset of benefit with DMARDs takes a few months of regular treatment, and relapses occur at least a few months after cessation of therapy. Recently, some biological agents (antibodies and other proteins) have been added for resistant cases.

Rheumatoid arthritis (RA) is an autoimmune disease in which there is joint inflammation, synovial proliferation and destruction of articular cartilage. Immune complexes composed of IgM activate complement and release cytokines (mainly TNFα and IL-1) which are chemotactic for neutrophils. These inflammatory cells secrete lysosomal enzymes which damage cartilage and erode bone, while PGs produced in the process cause vasodilatation and pain. RA is a chronic progressive, crippling disorder with a waxing and waning course. Multiple small joints of hands and feet are preferentially affected; deformities are produced as the disease progresses. NSAIDs are the first line drugs which afford symptomatic relief in pain, swelling, morning



stiffness, immobility, but do not arrest the disease process.

The goals of drug therapy in RA are:

- Ameliorate pain, swelling and joint stiffness
- Prevent articular cartilage damage and bony erosions
- Preserve joint function and prevent deformity.

Though mild/early cases are still mostly treated with NSAIDs alone, the current recommendation is to add DMARDs as soon as the diagnosis of RA is confirmed. However, use of DMARDs in early/mild RA should be weighed against their potential adverse effects, which may be serious. More than one DMARD may be used concurrently; advanced cases may require 2 or 3 drugs together, because all DMARDs tend to lose effectiveness with time.

Nonbiological drugs

1. Immunosuppressants (see Ch. 65)

Methotrexate (Mtx) This dihydrofolate reductase inhibitor has prominent immunosuppressant and antiinflammatory property. Beneficial effects in RA are probably related to inhibition of cytokine production, chemotaxis and cell-mediated immune reaction. Proliferation of immune-inflammatory cells is inhibited. Induction of oral low-dose (7.5–15 mg) weekly Mtx regimen has improved acceptability of this drug in RA. Onset of symptom relief is relatively rapid (3–6 weeks), therefore Mtx is preferred for initial treatment. Mtx is now the DMARD of first choice and the standard treatment for most patients, including cases of juvenile RA. Response is more predictable and sustained over long-term. Combination regimens of 2 or 3 DMARDs mostly include Mtx.

Oral bioavailability of Mtx is variable and may be affected by food. Its excretion is hindered in renal disease; therefore, not recommended for such patients. Probenecid and aspirin increase Mtx levels and toxicity. Trimethoprim can add to inhibition of dihydrofolate reductase and depress bone marrow. Oral ulceration and g.i. upset are the major side effects of low dose Mtx regimen. With prolonged therapy, dose dependent progressive liver damage leading to cirrhosis occurs in some patients, while this is not seen with short courses used for cancer. Incidence of chest infection is increased. Mtx is contraindicated in pregnancy, breast-feeding, liver disease, active infection, leucopenia and peptic ulcer.

NEOTREXATE, BIOTREXATE 2.5 mg tab.

Azathioprine This purine synthase inhibitor acts after getting converted to 6-mercaptopurine by the enzyme thiopurine methyl transferase (TPMT). It is a potent suppressant of cell-mediated immunity; appears to selectively affect differentiation and function of T-cells and natural killer cells. It also suppresses inflammation. However, remission is induced in smaller percentage of RA patients and it is less commonly used. Given along with corticosteroids, it has a steroid sparing effect, for which it is primarily used now, especially in cases with systemic manifestations. It is not combined with Mtx.

Dose: 50–150 mg/day; IMURAN; AZORAN, AZOPRINE 50 mg tab.

Immunosuppressants like cyclosporine, chlorambucil, cyclophosphamide are rarely used in RA. These drugs are reserved for cases not responding to other DMARDs.

2. Other immunomodulators

Sulfasalazine (*see* Ch. 49) It is a compound of sulfapyridine and 5-amino salicylic acid (5-ASA); exerts antiinflammatory activity in the bowel and is useful in ulcerative colitis. In addition, it suppresses the disease in a significant number of RA patients. The mechanism of action is not known. Sulfapyridine split off in the colon by bacterial action and absorbed systemically appears to be the active moiety (contrast ulcerative colitis, in which 5-ASA acting locally in the colon is the active component). Generation of superoxide radicals and cytokine elaboration by inflammatory cells may be suppressed. Efficacy of sulfasalazine in RA is modest and side effects may be unpleasant. Neutropenia/thrombocytopenia occurs in about 5–10% patients; regular blood count monitoring is needed. Hepatitis is possible. Sulfasalazine

is used as a second line drug for milder cases or is combined wih Mtx.

Dose: 1–3 g/day in 2–3 divided doses.

SALAZOPYRIN, SAZO-EN 0.5 g tab.

Hydroxychloroquine/Chloroquine (*see* Ch. 61) These are antimalarial drugs found to induce remission in upto 50% patients of RA, but take 3–6 months. Their advantage is relatively low toxicity, but efficacy is also low; bony erosions are not prevented. Their mechanism of action is not known, however, they have been found to reduce monocyte IL–I, consequently inhibiting B lymphocytes. Antigen processing may be interfered with. Lysosomal stabilization and free radical scavenging are the other proposed mechanisms.

For RA, these drugs have to be given for long periods: accumulate in tissues (especially melanin containing tissue) and produce toxicity, most disturbing of which is retinal damage and corneal opacity. This is less common and reversible in case of hydroxychloroquine, which is preferred over chloroquine. Other adverse effects are rashes, graying of hair, irritable bowel syndrome, myopathy and neuropathy.

Hydroxychloroquine/Chloroquine are employed in milder nonerosive disease, especially when only one or a few joints are involved, or they are combined with Mtx/sulfasalazine.

Hydroxychloroquine 400 mg/day for 4–6 weeks, followed by 200 mg/day for maintenance.

ZHQUINE, ZYQ, HCQS 200, 400 mg tab.

Chloroquine 150 mg (base) per day.

In patients of vitiligo, improvement in skin pigmentation has been noted after few months therapy with hydroxychloroquine, but vitiligo is not an approved use of this drug.

Leflunomide This immunomodulator inhibits proliferation of stimulated lymphocytes in patients with active RA. Arthritic symptoms are suppressed and radiological progression of disease is retarded. In clinical trials its efficacy has been rated comparable to Mtx and onset of benefit is as fast (4 weeks).

Leflunomide is rapidly converted in the body to an active metabolite which inhibits *dihydro-orotate dehydrogenase* and pyrimidine synthesis in actively dividing cells. Antibody production by B-cells may be depressed. The active metabolite has a long t½ of 2–3 weeks; leflunomide, therefore, is given in a loading dose of 100 mg daily for 3 days followed by 20 mg OD.

Adverse effects of leflunomide are diarrhoea, headache, nausea, rashes, loss of hair, thrombocytopenia, leucopenia, increased chances of chest infection and raised hepatic transaminases. It is not to be used in children and pregnant/lactating women. Leflunomide is an alternative to Mtx or can be added to it, but the combination is more hepatotoxic. Combination with sulfasalazine improves benefit.

LEFRA 10 mg, 20 mg tabs.

Tofacitinib It is a new synthetic drug approved for severe cases of RA that are not responding to Mtx. Tofacitinib can be used alone or concurrently with Mtx, but should not be combined with azathioprine, cyclosporine or biological DMARDs. It is a JAK-3 and JAK-1 kinase inhibitor, interferes with the JAK-STAT signaling pathway and DNA transcription. Production of inflammatory mediators and release of cytokines is inhibited. Adverse effects are headache, insomnia, diarrhoea, hypertension, anaemia, susceptibility to respiratory infections, flaring of tuberculosis and liver damage.

Dose: 5 mg BD (XELJANZ 5 mg tab).

Biological agents

Lately, several recombinant proteins/monoclonal antibodies that bind to and inhibit cytokines, especially TNFα or IL-1 have been produced and found to afford substantial benefit in autoimmune diseases like RA, inflammatory bowel diseases, psoriasis, scleroderma, etc. All of them produce prominent adverse effects, are expensive, and are used only as reserve drugs for severe refractory disease.

TNFα inhibitors

Because the cytokine TNFα plays a key role in the inflammatory cascade of RA by activating membrane bound receptors ($TNFR_1$ and $TNFR_2$) on the surface of T-cells, macrophages, etc., exogenously administered soluble TNF-receptor protein or antibody can neutralize it and interrupt the reaction. TNF inhibitors mainly suppress macrophage and T-cell function; inflammatory changes in the joint regress and new erosions are slowed. Quicker response than nonbiologic

DMARDs has been obtained. Though effective as monotherapy, they are generally added to Mtx when response to the latter is not adequate or in rapidly progressing cases. Susceptibility to opportunistic infections, including tuberculosis and pneumocystis pneumonia is increased, because TNFα plays important role in combating bacterial infection, especially granulomatous infections.

Etanercept: It is a recombinant fusion protein of TNF-receptor with Fc portion of human IgG_1; and is administered by s.c. injection 50 mg weekly. It binds to and prevents TNFα from activating TNF receptors on the membrane of T-cells/macrophages. Pain, redness, itching and swelling occur at injection site and chest infections may be increased, but immunogenicity is not a clinical problem.

Dose: 25–50 mg s.c. once or twice weekly;
ENBREL, ENBROL 25 mg in 0.5 ml, 50 mg in 1 ml inj.

Infliximab: It is a chimeral monoclonal antibody which binds and neutralizes TNFα; 3–5 mg/kg is infused i.v. every 4–8 weeks. An acute reaction comprising of fever, chills, urticaria, bronchospasm, rarely anaphylaxis may follow the infusion. Susceptibility to respiratory infections is increased and worsening of CHF has been noted. It is usually combined with Mtx which improves the response and decreases antibody formation against infliximab.

Adalimumab: This recombinant human monoclonal anti-TNF antibody is administered s.c. 40 mg every 2 weeks. Injection site reaction and respiratory infections are the common adverse effects. Combination with Mtx is advised to improve the response and decrease antibody formation.

Certolizumab and *Golimumab* are the other TNFα inhibitors.

Other biological agents

Anakinra: It is a recombinant human IL-1 receptor antagonist. Due to lower clinical efficacy it is rarely used now for RA. However, it is indicated in cases who have failed on one or more DMARDs.

Dose: 100 mg s.c. daily.

Local reaction and chest infections are the main adverse effects.

Several other IL-1 inhibitors like *Rilonacept* and *Canakinumab* have also been introduced.

Abatacept It is a recombinant fusion protein which combines part of Fc domain of human IgG with extracellular domain of T-cell inhibitory receptor CTLA4. By binding to CD80 and CD86 molecules, it prevents the 2nd signal for costimulation of T-cells. Beneficial response occurs in many RA patients who are refractory to a combination of Mtx + a TNFα antagonist. Abatacept is approved for use in moderate-severe active RA not responding to Mtx. It can be combined with Mtx and other DMARDs, but not with TNFα antagonists due to greatly increased risk of infections. It can be given by i.v. infusion as well as by s.c. injection.

Abatacept: (ORENCIA 250 mg powder for inj.)

Rituximab (*see* Ch. 64) This chimerized monoclonal antibody depletes B-lymphocytes and is indicated in B-cell lymphomas, as well as some autoimmune diseases. It has been combined with Mtx for treating active RA not responding to Mtx + a TNFα inhibitor.

Corticosteroids (*see* Ch. 20)

Glucocorticoids have potent immunosuppressant and antiinflammatory activity. They can be inducted almost at any stage in RA along with first or second line drugs, if potent antiinflammatory action is required while continuing the NSAID ± DMARD. Symptomatic relief is prompt and marked, but they do not arrest the rheumatoid process, though joint destruction may be slowed and bony erosions delayed.

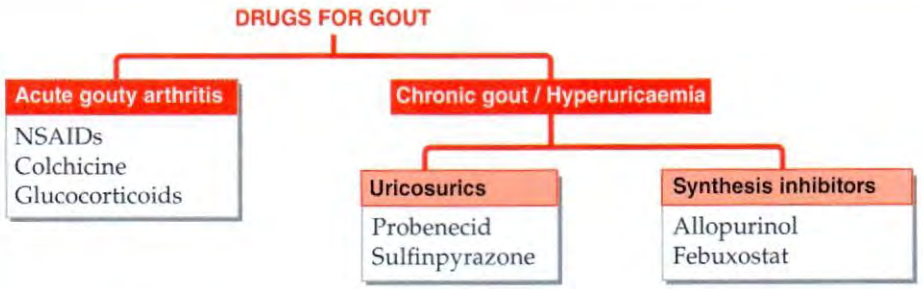
Long-term use of corticosteroids carries serious disadvantages. Therefore,

- Either low doses (5–7.5 mg prednisolone or equivalent) are used to supplement NSAIDs. Once used in this manner, it is difficult to withdraw the steroid—exacerbation is mostly precipitated and the patient becomes steroid dependent.
- Or high doses are employed over short periods in cases with severe systemic manifestations (organ-threatening disease, vasculitis) while the patient awaits response from a remission inducing drug.

In cases with single or a few joint involvement with severe symptoms, intraarticular injection of a soluble glucocorticoid affords relief for several weeks; joint damage may be slowed. This procedure should not be repeated before 3–4 months.

DRUGS USED IN GOUT

Gout It is a metabolic disorder characterized by hyperuricaemia (normal plasma urate 2–6 mg/dl). Uric acid, a product of purine metabolism, has low water solubility, especially at low pH. When blood urate levels are high,



it precipitates and deposits in joints, kidney and subcutaneous tissue (tophi).

Secondary hyperuricaemia occurs in:

(a) Leukaemias, lymphomas, polycythaemia—especially when treated with chemotherapy or radiation. This is due to enhanced nucleic acid metabolism and uric acid production.

(b) Drug induced—thiazides, furosemide, pyrazinamide, ethambutol, levodopa reduce uric acid excretion by kidney.

ACUTE GOUTY ARTHRITIS

Acute gout manifests as sudden onset of severe inflammation in a small joint (commonest is metatarso-phalangeal joint of great toe) due to precipitation of urate crystals in the joint space. The joint becomes red, swollen and extremely painful and requires immediate treatment with strong antiinflammatory drugs, without attempting to lower blood urate level. When the attack subsides, urate lowering therapy is instituted, and antiinflammatory cover is continued for several weeks. If hyperuricaemia is not controlled, the attacks recur, involve many joints, and result in chronic deforming arthritis.

1. NSAIDs

One of the strong antiinflammatory drugs, e.g. *naproxen, piroxicam, diclofenac, indomethacin* or *etoricoxib* is given in relatively high and quickly repeated doses. They are quite effective in terminating the attack, but may take 12–24 hours, while complete resolution takes 5–10 days. Response is somewhat slower than with colchicine, but they are generally better tolerated. Majority of patients prefer NSAIDs over colchicine. Their strong antiinflammatory (not uricosuric) action is responsible for the benefit. Naproxen and piroxicam specifically inhibit chemotactic migration of leucocytes into the inflamed joint. After the attack is over, NSAIDs should be continued at lower doses for 3–4 weeks while drugs to control hyperuricaemia take effect.

2. Colchicine

It is an alkaloid from *Colchicum autumnale* which has been used in gout since 1763. The pure alkaloid was isolated in 1820. Colchicine is neither analgesic nor antiinflammatory, but it specifically suppresses gouty inflammation. It does not inhibit the synthesis or promote the excretion of uric acid.

An acute attack of gout is started by the precipitation of urate crystals in the synovial fluid. On being engulfed by the synovial cells, they release mediators and start an inflammatory response. Chemotactic factors are produced → granulocytes migrate into the joint; they phagocytose urate crystals and release a glycoprotein which aggravates the inflammation by:

- Increasing lactic acid production from inflammatory cells → local pH is reduced → more urate crystals are precipitated.
- Releasing lysosomal enzymes which cause joint destruction.

Colchicine does not affect phagocytosis of urate crystals, but inhibits release of chemotactic factors and of the glycoprotein, thus suppressing the subsequent events. By binding to fibrillar protein tubulin, it inhibits granulocyte migration into the inflamed joint and thus interrupts the vicious cycle. Other actions of colchicine are:

(a) Antimitotic: causes metaphase arrest by binding to microtubules of mitotic spindle.
(b) Increases gut motility through neural mechanisms.

Colchicine is rapidly absorbed orally, partly metabolized in liver and excreted in bile—undergoes enterohepatic circulation; ultimate disposal occurs in urine and faeces over many days. Inhibitors of CYP3A4 retard colchicine metabolism and enhance its toxicity.

Toxicity of colchicine is high and dose related. Nausea, vomiting, watery or bloody diarrhoea and abdominal cramps occur as dose limiting adverse effects. Accumulation of the drug in intestine and inhibition of mitosis in its rapid turnover mucosa is responsible for the toxicity. In overdose, colchicine produces kidney damage, CNS depression, intestinal bleeding; death is due to muscular paralysis and respiratory failure.

Use Colchicine is the fastest acting drug to control an acute attack of gout; 0.5 mg 1–3 hourly with a total of 4 doses in a day; maximum 6.0 mg in a course spread over 3–4 days. Control of attack is usually achieved in 6–12 hours, but complete resolution may take 3–5 days. A second course should not be started before 3–7 days. The response is dramatic, so much so that it may be considered diagnostic. However, because of higher toxicity, it is a second line option to NSAIDs. Maintenance doses (0.5–1 mg/day) may be given for 4–8 weeks in which time control of hyperuricaemia is achieved with other drugs.

Taken at the first symptom of an attack, small doses (0.5–1.5 mg) of colchicine abort it.
ZYCOLCHIN, GOUTNIL 0.5 mg tab.

3. Corticosteroids

Intraarticular injection of a soluble steroid (e.g. triamcinolone acetonide 10 mg in small finger/toe joints, 30 mg in wrist) suppresses symptoms of acute gout. Crystalline preparations should not be used. It is indicated when only one or few joints are involved, and in those not tolerating NSAIDs/colchicine.

Systemic steroids are rarely needed. They are highly effective and produce nearly as rapid a response as colchicine, but are reserved for patients with renal failure/history of peptic ulcer bleed in whom NSAIDs are contraindicated or for cases not responding to or not tolerating NSAIDs. Prednisolone 40–60 mg may be given in one day, followed by tapering doses over 1–2 weeks.

CHRONIC GOUT/HYPERURICAEMIA

When pain and stiffness persist in a joint between attacks, gout has become chronic. Other cardinal features are hyperuricaemia, tophi (chalk-like stones under the skin in pinna, eyelids, nose, around joints and other places) and urate stones in the kidney. In majority of patients, hyperuricaemia is due to undersecretion of uric acid, while in few it is due to over production. Chronic gouty arthritis may cause progressive disability and permanent deformities.

A. Uricosuric drugs

Probenecid

It is a highly lipid-soluble organic acid developed in 1951 to inhibit renal tubular secretion of penicillin so that its duration of action could be prolonged. Probenecid competitively blocks active transport of organic acids by OATP at all sites; that in renal tubules being the most prominent. This transport is bidirectional: net effect of probenecid on excretion depends on whether secretion or reabsorption of the particular organic acid is quantitatively more important, e.g.:

- Penicillin is predominantly secreted by the proximal tubules, its reabsorption is minimal. Net effect of probenecid is inhibition of penicillin excretion; more sustained blood levels are achieved.
- Uric acid is largely reabsorbed by active transport, while less of it is secreted; only 1/10th of the filtered load is excreted in urine. The major transporter involved is URAT-1, which is a member of the OATP family. Probenecid, therefore, inhibits reabsorption

and promotes excretion of uric acid, and lowers its blood level.

Probenecid does not have any other significant pharmacological action; it is neither analgesic nor antiinflammatory.

Interactions

1. In addition to penicillins, probenecid inhibits the urinary excretion of cephalosporins, sulfonamides, Mtx and indomethacin.
2. It inhibits biliary excretion of rifampicin. Pyrazinamide and ethambutol may interfere with uricosuric action of probenecid.
3. Probenecid inhibits tubular secretion of nitrofurantoin which may not attain antibacterial concentration in urine.
4. Aspirin blocks uricosuric action of probenecid.

Pharmacokinetics Probenecid is completely absorbed orally; 90% plasma protein bound: partly conjugated in liver and excreted by the kidney; plasma t½ is 6–8 hours.

Adverse effects Probenecid is generally well tolerated. Dispepsia is the most common side effect (upto 25% incidence with high doses). It should be used cautiously in peptic ulcer patients. Rashes and other hypersensitivity phenomena are rare.

Uses

1. Chronic gout and hyperuricaemia: Probenecid is a second line/adjuvant drug to allopurinol. Started at 0.25 g BD and increased to 0.5 g BD, it gradually depletes the urate pool in the body and lowers blood urate level. Arthritis, tophi and other lesions may take months to resolve. Colchicine/NSAID cover is advised during the initial 1–2 months to avoid precipitation of acute gout.

Probenecid and other uricosurics are ineffective in the presence of renal insufficiency. It should be used only when creatinine clearance is > 50 ml/min or serum creatinine is < 2 mg/dl. Patients with renal stones should not be given probenecid. Plenty of fluids should be given with probenecid to avoid urate crystallization in urinary tract.

2. Probenecid is also used to prolong penicillin or ampicillin action by enhancing and sustaining their blood levels, e.g. in gonorrhoea, SABE.
3. Probenecid is given along with cidofovir, a drug for CMV retinitis in AIDS patients, to prevent its nephrotoxicity.

BENEMID, BENCID 0.5 g tab.

Sulfinpyrazone It is a pyrazolone derivative, related to phenylbutazone, having uricosuric action, but is neither analgesic nor anti-inflammatory. It inhibits tubular reabsorption of uric acid. Though equally efficacious as probenecid, sulfinpyrazone has gone into disuse because of more gastric irritation and other side effects. It inhibits platelet aggregation as well.

Lesinurad It is a new uricosuric drug, approved recently by US-FDA as a treatment option for hyperuricaemia, either alone or in combination with a xanthine oxidase inhibitor. Its mechanism of action is similar to that of probenecid.

B. Uric acid synthesis inhibitors

Allopurinol

This hypoxanthine analogue was synthesized as a purine antimetabolite for cancer chemotherapy. However, it had no antineoplastic activity but was a substrate as well as inhibitor of *xanthine oxidase*, the enzyme responsible for uric acid synthesis (Fig. 15.1).

Allopurinol itself is a short-acting (t½ 2 hrs) competitive inhibitor of xanthine oxidase, but its major metabolite *alloxanthine (oxypurine)* is a long-acting (t½ 24 hrs) and noncompetitive inhibitor. Alloxanthine is thus primarily responsible for uric acid synthesis inhibition *in vivo*. During allopurinol administration, plasma concentration of uric acid is reduced and that of hypoxanthine and xanthine is somewhat increased. In place of uric acid alone, all 3 oxipurines are excreted in urine. Since xanthine and hypoxanthine are more soluble, have a higher renal clearance than that of uric acid and each has its individual solubility, precipitation and crystallization in tissues and urine does not occur.

Because of raised levels of xanthine and hypoxanthine, some feedback inhibition of *de novo* purine synthesis and reutilization of metabolically derived purine also occurs.

Pharmacokinetics About 80% of orally administered allopurinol is absorbed. It is not

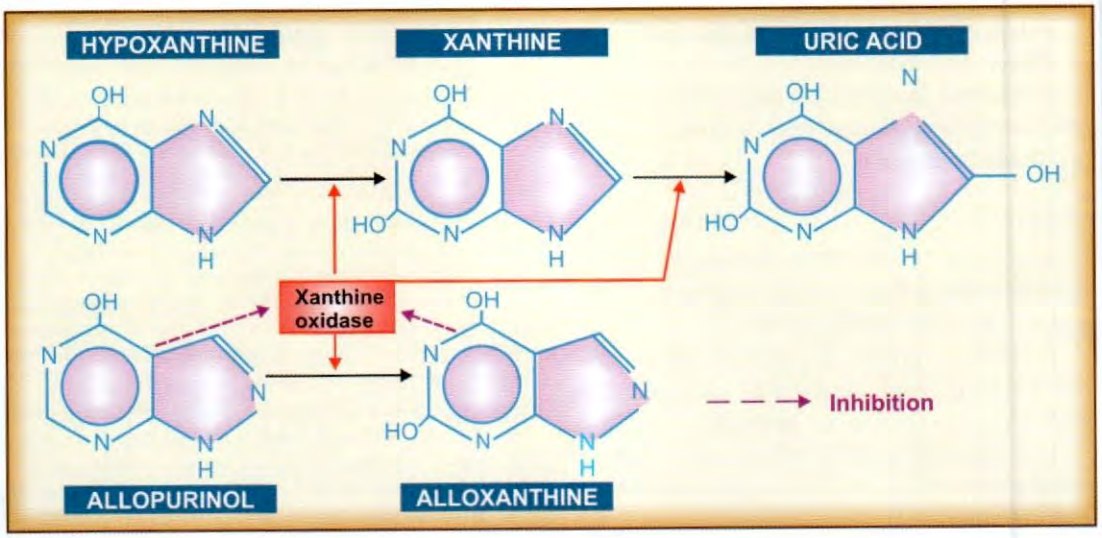


Fig. 15.1: Uric acid synthesis and the action of allopurinol

bound to plasma proteins; metabolized largely to alloxanthine. During chronic medication, it inhibits its own metabolism and about 1/3rd is excreted unchanged, the rest as alloxanthine.

Interactions

1. Allopurinol inhibits the degradation of 6-mercaptopurine and azathioprine: their doses should be reduced to 1/3rd, but not that of thioguanine, because it follows a different metabolic path (S-methylation).
2. Probenecid given with allopurinol has complex interaction; while probenecid shortens t½ of alloxanthine, allopurinol prolongs t½ of probenecid.
3. Allopurinol can potentiate warfarin and theophylline by inhibiting their metabolism.
4. A higher incidence of skin rashes has been reported when ampicillin is given to patients on allopurinol.

Adverse effects These are uncommon. Hypersensitivity reaction consisting of rashes, fever, malaise and muscle pain is the most frequent. It subsides on stopping the drug. Allopurinol should not be restarted in these patients, because serious reactions may follow. Renal impairment increases the incidence of rashes and other reactions to allopurinol. Stevens-Johnson syndrome is a rare but serious risk. Gastric irritation, headache, nausea and dizziness are infrequent; do not need withdrawal. Liver damage is rare.

Precautions and contraindications Liberal fluid intake is advocated during allopurinol therapy. It is contraindicated in hypersensitive patients, during pregnancy and lactation.
It should be cautiously used in the elderly, children and in patients with kidney or liver disease.

Uses Allopurinol is the first choice drug in *chronic gout*. It can be used in both *over producers* and *under excretors* of uric acid. The more severe cases with tophi or nephropathy also respond well. Uricosurics are infrequently used in India; they are less effective when g.f.r. is low and are inappropriate in stone formers. The two classes of drugs, *viz.* uricosurics and synthesis inhibitors, can be used together when the body load of urate is large.

Allopurinol therapy is generally long term (years, or even life long). During prolonged allopurinol therapy, tophi disappear gradually and nephropathy is halted, even reversed.

- *Secondary hyperuricaemia* due to cancer chemotherapy/radiation/thiazides or other drugs: can be controlled by allopurinol. It can even be used prophylactically in these situations.

- Allopurinol can also be used to *potentiate 6-mercaptopurine or azathioprine* in cancer chemotherapy and immunosuppressant therapy.

Dose: Start with 100 mg OD, gradually increase as needed to 300 mg/day; maximum 600 mg/day.

ZYLORIC 100, 300 mg tabs., ZYLOPRIM, CIPLORIC 100 mg cap.

Caution Allopurinol as well as uricosurics should not be started during acute attack of gout. During the initial 1–2 months of treatment with these drugs, attacks of acute gout are more common—probably due to fluctuating plasma urate levels favouring intermittent solubilization and recrystallization in joints. This period should be covered by NSAIDs or colchicine.

Febuxostat

It is a newer nonpurine xanthine oxidase inhibitor, equally or more effective than allopurinol in lowering blood uric acid level in patients with hyperuricaemia and gout. It is rapidly absorbed orally, highly plasma protein bound, oxidized as well as glucuronide conjugated in the liver and excreted by kidney; the plasma t½ is ~ 6 hours.

Hypersensitivity reactions are rare with febuxostat, but it should be stopped if they occur. The most important adverse effect is liver damage; liver function needs to be monitored during febuxostat therapy. Diarrhoea, nausea and headache are the usual side effects. By inhibiting xanthine oxidase, febuxostat has the potential to interact with mercaptopurine, azathioprine and theophylline. It should not be given to patients receiving these drugs.

Febuxostat is an alternative drug to allopurinol, but should not be combined with it. However, the two can be given sequentially in case of intolerance/nonresponsiveness to one. It is not indicated in malignancy associated hyperuricaemia. Like other drugs used to treat hyperuricaemia, NSAID/colchicine cover should be provided for 1–2 months while initiating febuxostat therapy.

Dose: Start with 40 mg OD, increase to 80 mg OD if target uric acid level is not achieved; Maximum dose 120 mg/day.

FABULAS, FABUSTAT, ZURIG 40,80,120 mg tabs.

Pegloticase It is recombinant uricase, an enzyme which oxidizes uric acid to highly soluble allantoin, that is easily excreted by kidney. Humans lack this enzyme. In this preparation, the enzyme has been coupled with methoxy polyethylene glycol (mPEG) which serves to prolong its sojourn in the body, permitting i.v. infusion of the drug to be given every 2 weeks. It is indicated only in rare cases of refractory symptomatic gout. Pegloticase is immunogenic and carries high risk of infusion reactions, including anaphylaxis. It should be administered only by professionals in a setting where facilities for managing anaphylaxis are available. Due to formation of antibodies, the response is gradually lost in many patients.

☞ PROBLEM DIRECTED STUDY

15.1 A 44-year-old lady presents with complaints of pain, swelling and stiffness of the interphalangeal and metacarpophalangeal joints of both hands for the last 8 months. Initially the symptoms were mild, but are increasing progressively despite treatment by her neighbourhood doctor. Her prescription reveals that she is taking Diclofenac sod. 75 mg SR tab twice daily and Pantoprazole 40 mg tab once daily in the morning. Though, initially she was getting good relief, but now the relief is incomplete, and she is disabled for 2–3 hours in the morning. Physical examination confirmed the swelling, tenderness and stiffness of hand and finger joints. Investigations were ordered. The significant findings of the test reports are: mild normocytic anaemia (Hb–10.2 g/dl), ESR-54 mm at 1 hour, TLC-6,800/mm^3, rheumatoid factor and Anti-CCP antibodies positive, C-reactive protein 2.2 mg/L (raised). X-ray of hand revealed mild soft tissue swelling around the affected joints, but no joint and bone abnormality. She was diagnosed as a case of active rheumatoid arthritis.

(a) Should the diclofenac dose be increased, or should it be substituted by another NSAID? Will these measures treat her adequately?

(b) Should any drug, other than an NSAID, be prescribed for this patient? If so, which one, and why?

(c) What needs to be done before prescribing this drug? When and what benefits are expected to be obtained from this drug?

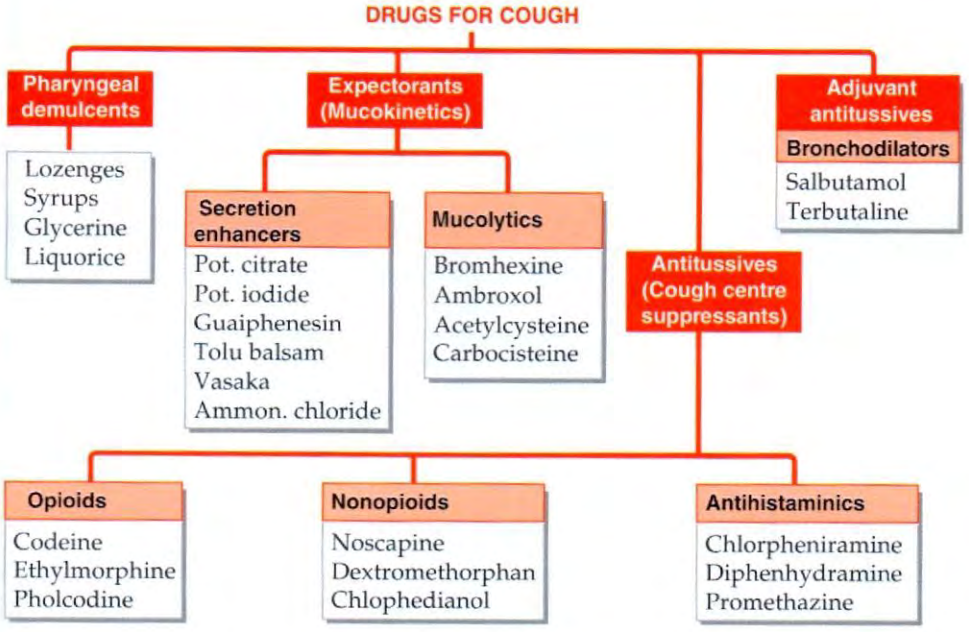
(d) Why pantoprazole has been prescribed to this patient? Should it be continued or stopped?

RESPIRATORY SYSTEM DRUGS

Chapter 16 Drugs for Cough and Bronchial Asthma

DRUGS FOR COUGH

Cough is a protective reflex, its purpose being expulsion of respiratory secretions and foreign particles from air passages. It occurs due to stimulation of mechano- or chemoreceptors in throat and respiratory passages or stretch receptors in the lungs. Cough may be useful or useless. Useless (nonproductive) cough should be suppressed. Useful (productive) cough serves to drain the airway; its suppression is not desirable; may even be harmful, except when the amount of expectoration achieved is small compared to the effort of continuous coughing. The commonest cause of acute cough (lasting < 3 weeks) is respiratory viral infections. Apart from specific remedies (antibiotics, etc. *see* box on p. 238), cough may be treated as a symptom (nonspecific therapy) with:



DEMULCENTS AND EXPECTORANTS

Pharyngeal demulcents soothe the throat and reduce afferent impulses from the inflamed/irritated pharyngeal mucosa, thus provide symptomatic relief in dry cough arising from throat.

Expectorants (Mucokinetics) are drugs believed to increase bronchial secretion or reduce its viscosity, facilitating its removal by coughing.

Sodium and potassium citrate are considered to increase bronchial secretion by salt action. Potassium iodide is secreted by bronchial glands and can irritate the airway mucosa. Prolonged use can affect thyroid function and produce iodism. It is not used now. Guaiphenesin, vasaka, tolu balsam are plant products which are supposed to enhance bronchial secretion and mucociliary function while being secreted by tracheobronchial glands. Ammonium salts are nauseating—reflexly increase respiratory secretions.

A variety of expectorant formulations containing an assortment of the above ingredients, often in combination with antitussives/antihistaminics are marketed and briskly promoted, but objective evidence of efficacy of expectorants is nonconclusive. The US-FDA has stopped marketing of all expectorants, except guaiphenesin. Steam inhalation and proper hydration may be more helpful in clearing airway mucus.

Mucolytics

Bromhexine A derivative of the alkaloid *vasicine* obtained from *Adhatoda vasica* (Vasaka), is a mucolytic and mucokinetic, capable of inducing thin copious bronchial secretion. It depolymerises mucopolysaccharides directly as well as by liberating lysosomal enzymes—network of fibres in tenacious sputum is broken. It is particularly useful if mucus plugs are present. *Side effects* are rhinorrhoea and lacrimation, nausea, gastric irritation, hypersensitivity.

Dose: adults 8 mg TDS, children 1–5 years 4 mg BD, 5–10 years 4 mg TDS.

BROMHEXINE 8 mg tablet, 4 mg/5 ml elixir.

Ambroxol A metabolite of bromhexine having similar mucolytic action, uses and side effects.

Dose: 15–30 mg TDS.

AMBRIL, AMBROLITE, AMBRODIL, MUCOLITE 30 mg tab, 30 mg/5 ml liquid, 7.5 mg/ml drops, ACOCONTIN 75 mg CR tab.

Acetylcysteine It opens disulfide bonds in mucoproteins present in sputum and makes it less viscid. It can be administered orally (200–600 mg TDS) as well as by inhalation of 10–20% nebulized solution. In intubated patients, the thick sticky secretion can be liquefied by instillation of 10–20% acetylcysteine solution directly into the respiratory tract.

MUCOTAB 600 mg tab, FLUIMUCIL 200 mg, 600 mg effervescent tab; MUCOMIX 200 mg/ml inj in 1,2,5 ml amps. The injectable solution can be nebulized/instilled through tracheostomy tube.

Specific treatment approaches to cough

Etiology of cough	*Treatment approach*
• Upper/lower respiratory tract infection	• Appropriate antibiotics
• Smoking/chronic bronchitis/bronchiectasis	• Cessation of smoking/avoidance of pollutants, steam inhalation, postural drainage
• Pulmonary tuberculosis	• Antitubercular drugs
• Asthmatic cough	• Inhaled β_2 agonists/corticosteroids/ipratropium
• Cough in pulmonary eosinophilia	• Diethyl carbamazine citrate, inhaled corticosteroids
• Postnasal drip due to sinusitis	• Antibiotic, nasal decongestant, H_1 antihistaminic
• Postnasal drip due to allergic/perennial rhinitis	• Avoidance of precipitating factor(s), corticosteroid nasal spray, H_1 antihistaminic
• Gastroesophageal reflux	• Bed head elevation, light dinner, diet modification, H_2 blocker, proton pump inhibitor, mosapride
• ACE inhibitor associated cough	• Substitute ACE inhibitor by angiotensin receptor blocker, NSAIDs may reduce cough
• Post-viral cough	• No specific treatment, subsides by itself.

The gastric mucus barrier may be breached by orally administered acetylcysteine.

Carbocisteine It liquefies viscid sputum in the same way as acetylcysteine and is administered orally (250–750 mg TDS). Some patients of chronic bronchitis have been shown to benefit. It may break the gastric mucus barrier; therefore is contraindicated in peptic ulcer patients. Side effects are gastric discomfort and rashes.
MUCODYNE 375 mg cap, 250 mg/5 ml syr.
It is available in combination with amoxicillin or cephalexin for treatment of bronchitis, bronchiectasis, sinusitis, etc.
CARBOMOX: Carbocisteine 150 mg + amoxicillin 250 or 500 mg caps. CARBICEF: Carbocisteine 150 mg + cephalexin 250 or 500 mg caps.

Mucolytics are specifically useful in patients with tracheostomy, asthmatic bronchitis, cystic fibrosis, etc. who have thick tenacious sputum or mucus plugs.

ANTITUSSIVES

These are drugs that act in the CNS to raise the threshold of cough centre or act peripherally in the respiratory tract to reduce tussal impulses, or both these actions. Because they aim to control rather than eliminate cough, antitussive drugs should be used only for dry nonproductive cough or if it is unduly tiring, disturbs sleep or is hazardous (hernia, piles, cardiac disease, ocular surgery).

Opioid antitussives

Morphine and its congeners are the most effective antitussives, but morphine is not suitable for treating cough, because of its strong addicting and respiratory depressant property.

Codeine (*see* Ch. 34) An opium alkaloid, qualitatively similar to and less potent than morphine, but is more selective for cough centre. Codeine is regarded as the standard antitussive; suppresses cough for about 6 hours. The antitussive action is blocked by naloxone indicating that it is exerted through opioid receptors in the brain. That in certain opioid congeners, antitussive action can be dissociated from the analgesic-addicting action, indicates that the receptors mediating the two actions are not identical. Abuse liability is low, but present; constipation is the chief drawback. At higher doses respiratory depression and drowsiness can occur, especially in children. Driving may be impaired. Like morphine, it is contraindicated in asthmatics and in patients with diminished respiratory reserve; should be avoided in children.
Dose: Antitussive dose is lesser than analgesic dose. 10–30 mg; children 2–6 years 2.5–5 mg, 6–12 years 5–10 mg, frequently used as syrup codeine phos. 4–8 ml.
CODINE 15 mg tab, 15 mg/5 ml linctus.

Ethylmorphine It is closely related to codeine which is methylmorphine, and has antitussive, respiratory depressant properties like it, but is believed to be less constipating.
Dose: 10–30 mg TDS; DIONINDON 16 mg tab.

Pholcodine It has practically no analgesic or addicting property, but is similar in efficacy as antitussive to codeine and is longer acting—acts for 12 hours; dose: 10–15 mg.

Nonopioid antitussives

Noscapine (Narcotine) An opium alkaloid of the benzoisoquinoline series (*see* Ch. 34), which depresses cough but has no narcotic, analgesic or dependence inducing properties. It is nearly equipotent antitussive as codeine, especially useful in spasmodic cough. Headache and nausea occur occasionally as side effect. It can release histamine and produce bronchoconstriction in asthmatics.
Dose: 15–30 mg, children 2–6 years 7.5 mg, 6–12 years 15 mg.
COSCOPIN 7 mg/5 ml syrup, COSCOTABS 25 mg tab.

Dextromethorphan A synthetic central NMDA (N-methyl D-aspartate) receptor antagonist; the *d*-isomer has antitussive action while *l*-isomer is analgesic. Dextromethorphan does not depress mucociliary function of the airway mucosa and is practically devoid of constipating action. Though considered nonaddicting, some drug abusers indulge in it.

Side effect: Dizziness, nausea, drowsiness; at high doses hallucinations and ataxia may occur.
Dose: 10–20 mg, children, 6–12 years 5–10 mg. It is a common ingredient of many proprietary cough formulations (*see* antitussive combinations below), but not advocated for children < 6 years.

Chlophedianol It is a centrally acting antitussive with weak antihistaminic, anticholinergic and local anaesthetic properties. Onset of action is slow and duration longer.

Side effect: Dryness of mouth, vertigo, irritability.
Dose: 20–40 mg.

Prenoxdiazine A drug developed in Hungary which acts as antitussive by desensitizing the pulmonary stretch receptors. Tussal impulses originating in the lungs are suppressed. Efficacy, however, is not impressive.
Dose: 100–200 mg TDS; PRENOXID 100, 200 mg tab.

Antihistamines

Many H_1 antihistamines have been conventionally added to antitussive/expectorant formulations (*see* below). They afford relief in cough due to their sedative and anticholinergic actions, but lack selectivity for the cough centre. They have no expectorant property, may even reduce secretions by anticholinergic action. They have been specially promoted for cough in respiratory allergic states, though their lack of efficacy in asthma is legendary.

Chlorpheniramine (2–5 mg), Diphenhydramine (15–25 mg) and Promethazine (15–25 mg; PHENERGAN 5 mg/5 ml elixir) are commonly used. Second generation antihistamines like fexofenadine, loratadine, etc. are ineffective.

Bronchodilators Bronchospasm can induce or aggravate cough. Stimulation of pulmonary receptors can trigger both cough and bronchoconstriction, especially in individuals with bronchial hyperreactivity. Bronchodilators relieve cough in such individuals and improve the effectiveness of cough in clearing secretions by increasing surface velocity of airflow during the act of coughing. They should be used only when an element of bronchoconstriction is present and not routinely. Their fixed dose combinations with antitussives are not satisfactory because of differences in time course of action of the components and liability for indiscriminate use.

Fixed dose combinations of a centrally acting antitussive with a bronchodilator or with an antihistaminic having high atropinic activity have been banned in India, but many are still marketed.

Majority of the FDC cough formulations that are marketed and briskly advertized are irrational and have only placebo effect.

Aeromatic chest rub is widely advertized as a cough remedy. Though it has been shown to reduce experimentally induced cough in healthy volunteers, there is no evidence of benefit in pathological cough.

SOME ANTITUSSIVE-EXPECTORANT COMBINATIONS

ASTHALIN EXPECTORANT: Salbutamol 2 mg, guaiphenesin 100 mg per 10 ml syr; dose 10–20 ml.

ASCORIL-C: Codeine 10 mg, chlorpheniramine 4 mg per 5 ml syr.

AXALIN: Ambroxol 15 mg, guaiphenesin 50 mg, salbutamol 1 mg, menthol 1 mg per 5 ml syr.

BRONCHOSOLVIN: Guaiphenesin 100 mg, terbutalin 2.5 mg, bromhexine 8 mg per 10 ml susp.

CADICOFF, GRILINCTUS: Dextromethorphan 5 mg, chlorpheniramine 2.5 mg, guaiphenesin 50 mg, Amm. chloride 60 mg per 5 ml syr.

BENADRYL COUGH FORMULA: Diphenhydramine 14 mg, amm. chlor. 138 mg, sod. citrate 57 mg, menthol 1.1 mg per 5 ml syrup; dose 5–10 ml, children 2.5–5 ml.

BRO-ZEDEX: Bromhexine 8 mg, guaiphenesin 100 mg, terbutaline 2.5 mg, menthol 5 mg per 10 ml syrup; dose 10 ml.

CADISTIN EXPECTORANT: Chlorpheniramine 2 mg, glyceryl guaiacolate 80 mg, amm. chlor. 100 mg, sod. citrate 44 mg, menthol 0.8 mg, terpin hydrate 4 mg, tolu balsam 6 mg, Vasaka syrup 0.13 ml per 5 ml syrup; dose 10 ml.

CHERICOF: Dextromethorphan 10 mg, chlorpheniramine 2 mg, phenylpropanolamine 12.5 mg per 5 ml liq.

CLISTIN: Carbinoxamine 4 mg, amm. chlor. 240 mg, sod. citrate 240 mg per 10 ml syrup.

COREX: Chlorpheniramine 4 mg, codeine phos. 10 mg, menthol 0.1 mg per 5 ml syrup; dose 5 ml, children 1.25–2.5 ml.

COSCOPIN LINCTUS: Noscapine 7 mg, chlorpheniramine 2 mg, citric acid 29 mg, sod. citrate 3 mg, amm. chlor. 28 mg, per 5 ml syrup; dose 10–20 ml.

COSOME: Dextromethorphan 10 mg, phenylpropanolamine 25 mg, chlorpheniramine 4 mg per 10 ml syr; dose 10 ml.

GRILINCTUS: Dextromethorphan 5 mg, chlorpheniramine 2.5 mg, guaiphenesin 50 mg, ammon. chlor. 60 mg/5 ml syr; dose 5–10 ml.

GRILINCTUS SOFTCAPS: Dextromethorphan 10 mg, chlorpheniramine 2 mg, phenylpropanolamine 12.5 mg softcaps.

SOLVIN EXPECTORANT: Bromhexine 4 mg, pseudoephedrine 30 mg tablet and in 10 ml liquid; dose 1 tablet/5 ml liquid.

TOSSEX: Codeine phos 10 mg, chlorpheniramine 4 mg. menthol 1.5 mg, sod. citrate 75 mg per 5 ml liquid; dose 5 ml.

VENTORLIN EXPECTORANT: Salbutamol 2 mg, guaiphenesin 100 mg per 10 ml syrup; dose 10 ml, children 2.5–7.5 ml.

ZEET LINCTUS: Dextromethorphan 10 mg, guaiphenesin 50 mg, phenylpropanolamine 25 mg per 5 ml syr; dose 5 ml.

DRUGS FOR BRONCHIAL ASTHMA

Bronchial asthma is characterised by hyperresponsiveness of tracheobronchial smooth muscle to a variety of stimuli, resulting in narrowing of air tubes, often accompanied by increased secretion, mucosal edema and mucus plugging. Symptoms include dyspnoea, wheezing, cough and may be limitation of activity.

Asthma is now recognized to be a primarily inflammatory condition: inflammation underlying hyperreactivity. An allergic basis can be demonstrated in many adult, and higher percentage of pediatric patients. In others, a variety of trigger factors (infection, irritants, pollution, exercise, exposure to cold air, psychogenic) may be involved. Two principal varieties are recognised:
Extrinsic asthma: It is mostly episodic, less prone to status asthmaticus.
Intrinsic asthma: It tends to be perennial, status asthmaticus is more common.

The inflammation in bronchial asthma is initiated by mast cells (present in lungs), and the infiltrate is dominated by eosinophils, lymphocytes and mast cells. The initial inflammatory reaction produces a multitude of mediators by the following processes:

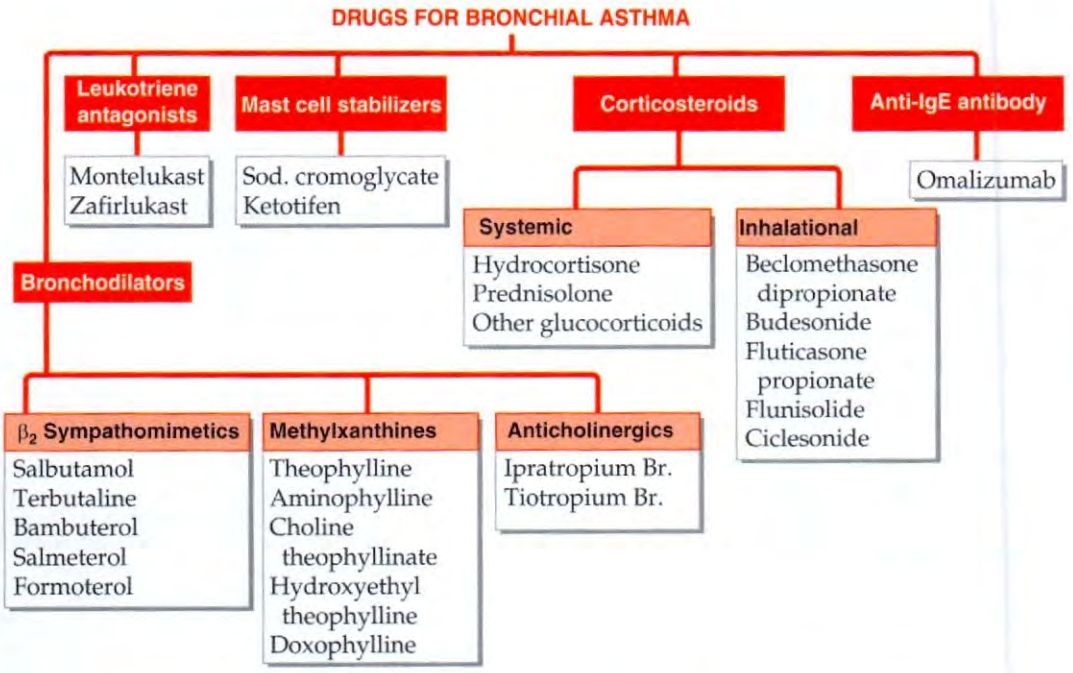
- Release of mediators stored in intracellular granules *(immediate):* histamine, protease enzymes, TNFα.
- Release of phospholipids from cell membrane followed by mediator synthesis *(within minutes):* PGs, LTs, PAF.
- Activation of genes followed by protein synthesis *(over hours):* Interleukins, TNFα.

These mediators together constrict bronchial smooth muscle, cause mucosal edema, hyperemia and produce viscid secretions, all resulting in reversible airway obstruction. The inflammation perpetuates itself by cell-to-cell communication and recruitment of more and more lymphocytes, eosinophils and neutrophils. Bronchial smooth muscle hypertrophy, increase in the population of mucus secreting cells and blood vessels occurs over time and damage to bronchial epithelium accentuates the hyperreactivity. Vagal discharge to bronchial muscle is enhanced reflexly. Airway remodeling progressively worsens the disease.

Chronic obstructive pulmonary disease (COPD) is also an inflammatory disease of the airways and lungs where inflammation is dominated by neutrophils, macrophages and cytotoxic lymphocytes. It is characterized by progressive emphysema (alveolar destruction) and bronchiolar fibrosis in variable proportions. Loss of bronchiolar elasticity leads to closure of smaller air tubes during expiration. The airway obstruction is accentuated during exercise causing shortness of breath. The expiratory airflow limitation does not fluctuate markedly over long periods of time, but there are exacerbations precipitated by respiratory infections, pollutants, etc. COPD is clearly related to smoking and characteristically starts after the age of 40. Quiting smoking reduces the rate of decline in lung function. Bronchodilators prevent closure of peripheral air tubes during expiration and afford symptomatic relief in COPD patients, but improvement in forced expiratory volume in 1st second (FEV_1) following inhalation of a shortacting β_2 agonist is generally <15%. An increasing part of airway obstruction is irreversible.

Approaches to Treatment

1. *Prevention of AG:AB reaction*—avoidance of antigen, hyposensitization—possible in extrinsic asthma and if antigen can be identified.
2. *Neutralization of IgE (reaginic antibody)*—Omalizumab.
3. *Suppression of inflammation and bronchial hyperreactivity*—corticosteroids.
4. *Prevention of release of mediators*—mast cell stabilizers.
5. *Antagonism of released mediators*—leukotriene antagonists, antihistamines, PAF antagonists.
6. *Blockade of constrictor neurotransmitter*—anticholinergics.
7. *Mimicking dilator neurotransmitter*—sympathomimetics.



8. *Directly acting bronchodilators*—methylxanthines.

SYMPATHOMIMETIC DRUGS (*see* Ch. 9)

Adrenergic drugs cause bronchodilatation through β_2 receptor stimulation → increased cAMP formation in bronchial muscle cell → relaxation. In addition, increased cAMP in mast cells and other inflammatory cells decreases mediator release. Since β_2 receptors on inflammatory cells desensitize quickly, the contribution of the latter action to the beneficial effect of β_2 agonists in asthma where airway inflammmation is chronic, is uncertain, and at best minimal. Adrenergic drugs are the mainstay of treatment of reversible airway obstruction, but should be used cautiously in hypertensives, ischaemic heart disease patients and in those receiving digitalis. The β_2 agonists are the most effective and fastest acting bronchodilators when inhaled.

Though adrenaline (β_1+β_2+α receptor agonist) and isoprenaline (β_1+β_2 agonist) are effective bronchodilators, it is the selective β_2 agonists that are now used in asthma to minimize cardiac side effects.

Salbutamol (Albuterol) A highly selective β_2 agonist; cardiac side effects are less prominent. Selectivity is further increased by inhaling the drug. Inhaled salbutamol delivered mostly from pressurized metered dose inhaler (pMDI) produces bronchodilatation within 5 min and the action lasts for 2–4 hours. It is, therefore, used to abort and terminate attacks of asthma, but is not suitable for round-the-clock prophylaxis. Muscle tremors are the dose related side effect. Palpitation, restlessness, nervousness, throat irritation and ankle edema can also occur. Hypokalaemia is a possible complication. Oral salbutamol undergoes presystemic metabolism in the gut wall, bioavailability is 50%. Oral salbutamol acts for 4–6 hours, is longer acting and safer than isoprenaline, but not superior in bronchodilator efficacy. Muscle tremor is the principal side effect.

Because of more frequent side effects, oral β_2 agonist therapy is reserved for patients who cannot correctly use inhalers or as alternative/adjuvant medication in severe asthma.

Dose: 2–4 mg oral, 0.25–0.5 mg i.m./s.c., 100–200 µg by inhalation.

ASTHALIN 2, 4 mg tab., 8 mg SR tab., 2 mg/5 ml syrup, 100 µg/metered dose inhaler; 5 mg/ml respirator

soln., 200 µg rota caps; CROYSAL 0.5 mg/ml inj, SALOL 2.5 mg/3 ml inj; VENTORLIN 2 mg/5 ml syr, 4 mg, 8 mg CR caps; DERIHALER 100 µg metered dose inhaler.

Single enantiomer preparation of R(–) salbutamol has also been marketed, because it is the active β_2 agonist and more potent bronchodilator which may produce fewer side effects than the racemate.

Terbutaline It is similar to salbutamol in properties and use.

Dose: 5 mg oral, 0.25 mg s.c., 250 µg by inhalation.

TERBUTALINE, BRICAREX 2.5, 5 mg tab., 3 mg/5 ml syrup, 0.5 mg/ml inj; MISTHALER 250 µg/metered dose, 10 mg/ml nebulizing soln.; BRICANYL 0.5 mg/ml inj, 2.5 mg, 5 mg tabs, 1.5 mg/5 ml syr.

Inhaled salbutamol and terbutaline are currently the most popular drugs for quick reversal of bronchospasm, but should not be used on a regular schedule. Regular use does not reduce bronchial hyperreactivity: may even worsen it. This may be responsible for the diminished responsiveness that occurs after long-term use of these drugs. Regular use also down regulates bronchial β_2 receptors. It is advised that patients requiring regular medication should be treated with inhaled steroids, with or without inhaled long acting β_2 agonists (e.g. salmeterol), while short acting β_2 agonist inhalers should be restricted to symptomatic relief of wheezing.

Bambuterol This biscarbamate ester prodrug of terbutaline is slowly hydrolysed in plasma and lungs by pseudocholinesterase to release the active drug over 24 hours. Reversible inhibition of pseudocholinesterase occurs in a dose dependent manner. It is indicated in nocturnal and chronic asthma as a single evening dose of 10–20 mg oral.

BAMBUDIL 10 mg, 20 mg tabs, 5 mg/5 ml oral soln; BETADAY 10, 20 mg tabs.

Salmeterol It is the first long acting selective β_2 agonist with a slow onset of action which is used by inhalation on a twice daily schedule for maintenance therapy, as well as for nocturnal asthma, but not for acute symptoms. It is more β_2 selective than salbutamol, as well as more lipophilic which probably accounts for its longer duration of action. Concern of asthma worsening due to regular use of inhaled β_2 agonists applies to salmeterol as well. Epidemiological studies indicate that risk of life-threatening asthma attacks may be increased by regular use of long acting β_2 agonists. Concurrent inhaled steroid appears to limit this risk. Excess mortality among asthmatics treated continuously with long acting β_2 agonist inhalations has been reported. Combined use of inhaled salmeterol with inhaled glucocorticoid produces effects equivalent to double dose of the corticoid alone. It is now advocated that long-acting β_2 agonists should be used only in combination with an inhaled steroid; combined formulations are available.

COPD: Long-acting β_2 agonists are superior to short-acting ones, and equivalent to inhaled anticholinergics in COPD. They reduce breathlessness by preventing expiratory closure of peripheral airways and abolishing the reversible component of airway obstruction.

SALMETER, SEROBID: Salmeterol 25 µg per metered dose inhaler; 2 puffs BD; severe cases 4 puffs BD; also SEROBID ROTACAPS 50 µg; 1–2 caps BD by inhalation.

SEROFLO—125/250/500 ROTACAPS: Salmeterol 50 µg + fluticasone 125 µg/250 µg/500 µg per rotacap

SEROFLO—125/250 INHALERS, COMBITIDE INHALER: Salmeterol 25 µg + fluticasone 125 µg/250 µg per puff MDI.

Indacaterol, Olodaterol and *Vilanterol* are new ultra long-acting selective β_2 agonists that have been approved for maintenance treatment of COPD. They are administered by inhalation in the powder form (indacaterol, vilanterol) or solution form (olodaterol) once a day. Cough, nasopharyngitis and dizziness are the side effects. Their efficacy and safety in the treatment of asthma has not been established.

Formoterol Another long-acting selective β_2 agonist which acts for 12 hrs when inhaled. In comparison to salmeterol, it has a faster onset of action. It is used on a regular morning-evening schedule for round-the-clock bronchodilatation.

Dose: 12–24 µg by inhalation twice daily.

FORATEC 12 µg rotacaps.

DERIFORM: 12 µg/puff MDI,

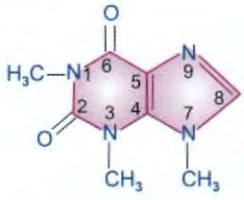
AIRTEC-FF, FORMOSONE: Formoterol 6 µg + fluticasone 125 µg or 250 µg/puff MDI

Ephedrine This oral sympathomimetic has $\alpha + \beta_1 + \beta_2$ actions which causes mild slowly developing bronchodilatation lasting for 3–5 hours. It is a constituent of older combination formulations and is used for mild to moderate chronic asthma. Because of low efficacy and frequent side effects, it is not preferred now.

METHYL XANTHINES

Theophylline and its compounds have been extensively used in asthma, but are now restricted to COPD and selected cases of asthma as adjuvant medication. Theophylline is one of

the three naturally occurring methylated xanthine alkaloids *caffeine, theophylline* and *theobromine*. The chemical relation between the three is depicted below:



THEOPHYLLINE
(1,3, Dimethylxanthine)

THEOBROMINE
(3,7, Dimethylxanthine)

CAFFEINE
(1,3,7, Trimethylxanthine)

All three are consumed as beverages. The sources and average alkaloid contents of the beverages, as they are usually prepared are given below.

Source	Alkaloid content in beverage		
1. *Thea sinensis* (Tea leaves)	Caffeine Theophylline	50 mg 1 mg	in an average cup of tea
2. *Coffea arabica* (Coffee seeds)	Caffeine	75 mg	in an average cup of coffee
3. *Theobroma cacao* (Cocoa, chocolate)	Theobromine Caffeine	200 mg 4 mg	in an average cup of cocoa
4. *Cola acuminata* (Guru nuts)	Caffeine	30 mg	in 200 ml bottle of cola drink

All three alkaloids have qualitatively similar actions, but there are marked quantitative (Table 16.1) and pharmacokinetic differences.

Table 16.1 : Comparative pharmacological actions of caffeine and theophylline

ACTION	*CAFF.*	*THEO.*
1. CNS—stimulation (low dose)	+++	++
—toxicity	++	+++
2. Heart—stimulation	++	+++
3. Blood vessel—relaxation	+	++
4. Bronchi—dilatation	+	+++
5. Kidney—diuresis	+	++
6. Sk. muscle—increased contractility	+++	++
7. Gastric mucosa—irritation	+	++
8. Phosphodiesterase inhibition	++	+++
9. Adenosine antagonism	++	+++

CAFF—Caffeine; THEO—Theophylline
Theobromine is of no therapeutic importance.

Pharmacological actions

1. *CNS* Caffeine and theophylline are CNS stimulants, primarily affect the higher centres. Caffeine 150–250 mg produces a sense of well-being, alertness, beats boredom, allays fatigue, thinking becomes clearer even when dullness has tended to prevail after a sustained intellectual effort. It tends to improve performance and increase motor activity. Caffeine is more active than theophylline in producing these effects. Higher doses cause nervousness, restlessness, panic, insomnia and excitement. Still higher doses produce tremors, delirium and convulsions. Theophylline has greater propensity to produce these adverse effects at higher doses and is definitely more toxic than caffeine.

These alkaloids also stimulate medullary vagal, respiratory and vasomotor centres. Vomiting at high doses is due to both gastric irritation and CTZ stimulation.

2. *CVS* Methylxanthines directly stimulate the heart and increase force of myocardial contractions. They tend to increase heart rate by cardiac action, but decrease it by causing vagal stimulation—net effect is variable. Tachycardia is more common with theophylline, but caffeine generally lowers heart rate. Cardiac output and cardiac work are increased. At high doses cardiac arrhythmias may be produced.

While consumption of > 9 cups of coffee per day has been found to be associated with increased incidence of arrhythmias, moderate ingestion of caffeine (upto 500 mg/day) does not increase frequency or severity of cardiac arrhythmias even in patients with ischaemic heart disease or preexisting ventricular extrasystoles.

Methylxanthines, especially theophylline, dilate systemic blood vessels, including coronaries, by direct action: peripheral resistance is reduced. However, cranial vessels are constricted, especially by caffeine; this is one of the basis of its use in migraine.

Effect of methylxanthines on BP is variable and unpredictable—

- Vasomotor centre and direct cardiac stimulation—tends to raise BP.
- Vagal stimulation and direct vasodilatation—tends to lower BP.

Usually a rise in systolic and fall in diastolic BP is observed.

3. *Smooth muscles* All smooth muscles are relaxed; most prominent effect is exerted on bronchi, especially in asthmatics. Theophylline is more potent bronchodilator than caffeine. Slow and sustained dose-related bronchodilatation is produced, but the effect is much less marked compared to that of inhaled β_2 agonists. Vital capacity is increased. Biliary spasm is relieved, but effect on intestines and urinary tract is negligible.

4. *Kidney* Methylxanthines are mild diuretics. They act by inhibiting tubular reabsorption of Na^+ and water as well as increased renal blood flow and g.f.r. However, the action is brief.

5. *Skeletal muscles* Caffeine enhances contractile power of skeletal muscles. At high concentrations it increases release of Ca^{2+} from sarcoplasmic reticulum by direct action. At low doses, twitch response to nerve stimulation is augmented, while at toxic doses contracture is produced.

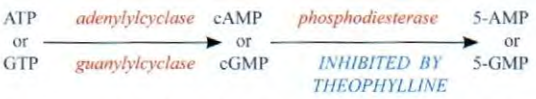
In addition, caffeine facilitates neuromuscular transmission by increasing ACh release. The central action of caffeine relieves fatigue and increases muscular work. Enhanced diaphragmatic contractility noted with theophylline in the therapeutic concentration range probably contributes to its beneficial effects in dyspnoea and COPD.

6. *Stomach* Methylxanthines enhance secretion of acid and pepsin in stomach, even on parenteral injection. They are also gastric irritants—theophylline more than caffeine.

7. *Metabolism* Caffeine and to a smaller extent theophylline increase BMR. Plasma free fatty acid levels are raised. They induce release of endogenous catecholamines, which appears to be partly responsible for these effects.

8. *Mast cells and inflammatory cells* Theophylline decreases release of histamine, other mediators and cytokines from mast cells and activated inflammatory cells. This may contribute to its therapeutic effect in bronchial asthma and COPD.

Mechanism of action Three distinct cellular actions of methylxanthines have been defined—**(a)** Release of Ca^{2+} from sarcoplasmic reticulum, especially in skeletal and cardiac muscle. **(b)** Inhibition of phosphodiesterase (PDE) which degrades cyclic nucleotides intracellularly.



Consequently the concentration of cyclic nucleotides is increased. Bronchodilatation, cardiac stimulation and vasodilatation occur and mediator release is inhibited when cAMP level rises in the bronchial/cardiac/vascular smooth muscle and in inflammatory cells, respectively. Several isoenzymes of the PDE superfamily exist in different tissues of which PDE3 and PDE4 appear to be involved in causing bronchodilatation and in inhibiting cytokine/inflammatory mediator release.

Some selective PDE4 inhibitors have been produced in the hope of finding an effective drug for asthma/COPD without the attendant toxicity as in theophylline. However, majority were clinically disappointing, but one of them *Roflumilast* has been approved by US-FDA for symptomatic treatment of COPD (but not bronchial asthma). It exerts antiinflammatory action, primarily in the lungs. Lung function is improved and risk of exacerbations is reduced. Most common adverse effect is diarrhoea. Psychiatric disturbances and weight loss are reported. Roflumilast appears to be a promising treatment option for moderate-to-severe cases of COPD. Theophylline is a subtype nonselective and weak PDE inhibitor.

(c) Blockade of adenosine receptors: adenosine acts as a local mediator in CNS, CVS and other organs. Adenosine contracts smooth muscles, especially bronchial; dilates cerebral blood vessels, depresses cardiac pacemaker and inhibits gastric secretion. Methylxanthines produce opposite effects.

Action (a) is exerted only at concentrations much higher than therapeutic plasma concentrations (range 5–20 µg/ml) of caffeine and theophylline. Action (b) and action (c) are exerted at concentrations in the therapeutic range and appear to contribute to bronchodilatation. Raised cAMP levels in inflammatory cells may

attenuate mediator release and promote eosinophil apoptosis, adding to the therapeutic effect of theophylline in asthma. Adenosine A_1 receptor antagonism is considered responsible for cardiac arrhythmias and seizures occurring in theophylline toxicity.

Recent evidence suggests that low concentrations of theophylline enhance histone deacetylation in airway inflammatory cells, suppressing proinflammatory gene transcription. Thus, even sub-bronchodilator doses of theophylline may exert some beneficial effect in asthma.

(Pharmacokinetics, adverse effects and uses of caffeine are described in Ch. 35)

Theophylline

Pharmacokinetics Theophylline is well absorbed orally; rectal absorption from suppositories is erratic. It is distributed in all tissues—crosses placenta and is secreted in milk (V 0.5 l/kg), 50% plasma protein bound and extensively metabolized in liver by demethylation and oxidation primarily by CYP1A2. Only 10% is excreted unchanged in urine. Elimination rate of theophylline varies considerably with age. At therapeutic concentrations, the t½ in adults is 7–12 hours. Children eliminate it much faster (t½ 3–5 hours) and elderly more slowly. In premature infants the t½ is markedly prolonged (24–36 hours). There are pronounced interindividual variations in plasma concentrations attained with the same dose.

Theophylline metabolizing enzymes are saturable, t½ is prolonged with higher doses (to as much as 60 hours) as kinetics changes from first to zero order. Plasma concentrations, therefore, increase disproportionately with dose.

Factors which need dose reduction are— age > 60 yr (× 0.6), CHF (× 0.6), pneumonia (× 0.4), liver failure (× 0.2–0.4).

Adverse effects Theophylline has a narrow margin of safety. Dose-dependent toxicity starts from the upper part of therapeutic concentration range (Fig. 16.1). Adverse effects are primarily referable to the g.i.t., CNS and CVS. Headache, nervousness and nausea are early symptoms. Children are more liable to develop CNS toxicity.

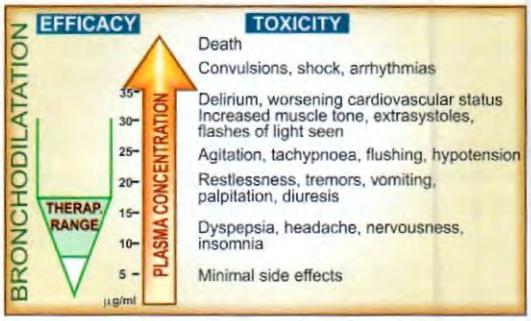


Fig. 16.1: Relationship between efficacy and toxicity of theophylline with its plasma concentration. The depicted concentration ranges are approximate

The irritant property of theophylline is reflected in gastric pain (with oral), rectal inflammation (with suppositories) and pain at site of i.m. injection. Rapid i.v. injection causes precordial pain, syncope and even sudden death—due to marked fall in BP, ventricular arrhythmias or asystole.

Interactions

1. Agents which enhance theophylline metabolism primarily by inducing CYP1A2 lower its plasma level: dose has to be increased by the factor given in parenthesis.

Smoking (1.6), phenytoin (1.5), rifampicin (1.5), phenobarbitone (1.2), charcoal broiled meat meal (1.3).

2. Drugs which inhibit theophylline metabolism and increase its plasma level are—erythromycin, ciprofloxacin, cimetidine, oral contraceptives, allopurinol; dose should be reduced to 2/3.

3. Theophylline enhances the effects of—furosemide, sympathomimetics, digitalis, oral anticoagulants, hypoglycaemics.

4. Theophylline decreases the effects of—phenytoin, lithium.

5. Aminophylline injection should not be mixed in the same infusion bottle/syringe with—ascorbic acid, chlorpromazine, promethazine, morphine, pethidine, phenytoin, phenobarbitone, insulin, penicillin G, tetracyclines, erythromycin.

Preparations and dose

(i) *Theophylline (Anhydrous)* 100–300 mg TDS (15 mg/kg/day) oral, THEOLONG 100, 200 mg SR cap., DURALYN-CR 400 mg continuous release cap, UNICONTIN 400 mg, 600 mg CR tabs, THEOBID 200 mg, 300 mg SR tabs. Only sustained release (SR) tab./caps. which produce effective blood levels for ~ 12 hours are used, because fast release tabs. produce high peak and low trough plasma concentrations.

Because solubility of theophylline is low, a number of soluble complexes and salts have been produced for oral and for parenteral use.

(ii) *Aminophylline (Theophylline-ethylenediamine; 85% theophylline)* water soluble, can be injected i.v. but not i.m. or s.c.—highly irritating. 250–500 mg oral or slow i.v. injection; children 7.5 mg/kg i.v.;
AMINOPHYLLINE 100 mg tab, 250 mg/10 ml inj.

(iii) *Hydroxyethyl theophylline (Etophylline, 80% theophylline)* water soluble; can be injected i.v. and i.m. (but not s.c.), less irritating; 250 mg oral/i.m./i.v.; DERIPHYLLIN 100 mg tab., 300 mg SR tab., 220 mg/2 ml inj.

(iv) *Theophylline ethanolate of piperazine* 250–500 mg oral or i.v.; CADIPHYLLATE 80 mg/5 ml elixir, ETOPHYLATE 125 mg/5 ml syrup.

Doxophylline A long-acting oral methylxanthine that is claimed not to interfere with sleep or stimulate gastric secretion.

Dose: 400 mg OD or BD, children 12 mg/kg/day; DOXOBID, DOXOVENT, DOXORIL 400 mg tab, 100 mg/5 ml syr.

The double salts/derivatives of theophylline are claimed to be less gastric irritant and better absorbed. However, anhydrous theophylline is completely absorbed and gastric irritancy of the salts is the same in terms of theophylline content.

Uses

1. *Bronchial asthma and COPD*: Theophylline may benefit by causing bronchodilatation as well as by decreasing release of inflammatory mediators, improving mucociliary clearance, stimulating respiratory drive and by augmenting diaphragmatic contractility. However, it has several limitations, *viz,* poor tolerability, narrow safety margin, lower efficacy and wide individual variability, because of which its use has declined. Sustained release theophylline is occasionally employed in mild-to-moderately severe asthma as an adjuvant drug, especially in patients with nocturnal asthma. It is more useful in COPD, and often added to other drugs.

Use of intravenous aminophylline in status asthmaticus is outmoded.

2. *Apnoea in premature infant*: Theophylline reduces the frequency and duration of episodes of apnoea that occur in some preterm infants in the first few weeks of life. Closely monitored oral or i.v. treatment is employed for 1–3 weeks. Caffeine is equally effective.

ANTICHOLINERGIC DRUGS (*see* Ch. 8)

Atropinic drugs cause bronchodilatation by blocking M_3 receptor mediated cholinergic constrictor tone. They act primarily in the larger airways (Fig. 16.2) which receive vagal innervation. However, some recent evidence points to presence of M_3 receptors on peripheral bronchiolar muscles as well, though these are not vagally innervated.

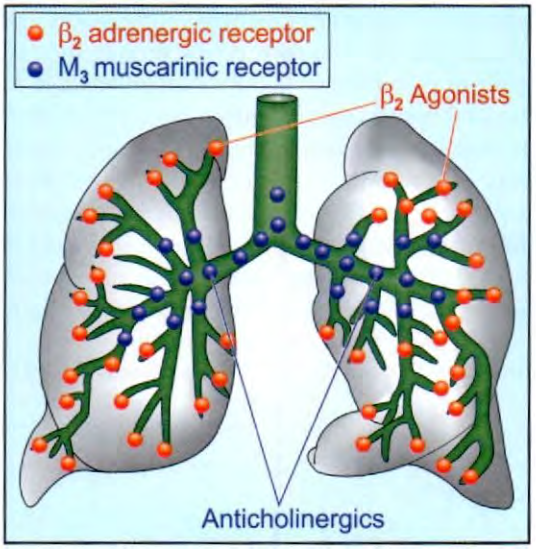


Fig. 16.2: Primary sites of bronchodilator action of inhaled adrenergic β_2 agonists and inhaled anticholinergics. Salbutamol mainly relaxes bronchiolar smooth muscle; Ipratropium blocks bronchoconstriction mainly in the larger airways

Ipratropium bromide is a short acting (duration 4–6 hours) inhaled anticholinergic bronchodilator, while *tiotropium bromide* is long acting (duration 24 hours). Administered as aerosol, they produce minimal antimuscarinic side effects due to poor systemic absorption. Anticholinergics are less efficacious than inhaled β_2 sympathomimetics in bronchial asthma. However, patients of asthmatic bronchitis, COPD and psychogenic asthma respond better to anticholinergics. Reflex cholinergic tone appears to be the major reversible component of airway obstruction in COPD. Inhaled anticholinergics are the bronchodilators of choice in COPD. Tiotropium is rated more effective than ipratropium in COPD; more suitable for severe cases (FEV_1<50% of predicted). No decline in its clinical efficacy has been noted over a period of 4 years. Regular maintenance therapy with long acting anticholinergic inhalations can also reduce episodes of COPD exacerbations.

The inhaled anticholinergics produce slower response than inhaled β_2 sympathomimetics and are better suited for regular prophylactic use (ipratropium 2–4 puffs 6 hourly or tiotropium 1 rotacap OD) than for quick relief of breathlessness. Combination of inhaled ipratropium with β_2 agonist produces more marked and longer lasting bronchodilatation; since their effects are additive. This synergism can be utilized for terminating severe exacerbations of asthma or COPD. Nebulized ipratropium mixed with salbutamol is employed in refractory asthma. Combined formulations are available.

Salbutamol + Ipratropium

DUOLIN INHALER, COMBIMIST INHALER 100 µg + 20 µg per metered dose
DUOLIN ROTACAP: 200 µg + 40 µg per rotacap
DUOLIN RESPULES, COMBIMIST RESPULES 2.5 mg + 500 µg in 2.5 ml solution

Glycopyrronium Br., another long acting quaternary anticholinergic, has been recently approved (50 µg inhalation powder per cap) as once a day maintenance treatment of COPD.

LEUKOTRIENE ANTAGONISTS

Since it was realized that cysteinyl leukotrienes (LT-C_4/D_4) produced by macrophages, eosinophils and other inflammatory cells in the lungs are important mediators of bronchial asthma, efforts were made to develop their antagonists and synthesis inhibitors. Two *cys*LT_1 receptor antagonists *montelukast* and *zafirlukast* are now established drugs for asthma.

Montelukast and Zafirlukast Both have similar actions and clinical utility. They competitively antagonize *cys*LT_1 receptor (*see* p. 205) mediated bronchoconstriction, airway mucus secretion, increased vascular permeability and recruitment of eosinophils. Bronchodilatation, reduced sputum eosinophil count, suppression of bronchial inflammation, mucus and hyperreactivity are noted in asthma patients. Parameters of lung function show improvement to variable degree. Episodes of asthma exacerbations are reduced. Some studies have found that certain patients are 'responders' while others are 'nonresponders' to anti-LT therapy. This may reflect differing extent of involvement of LTs as asthma mediators.

Montelukast and zafirlukast are indicated for prophylactic therapy of mild-to-moderate asthma as alternatives to inhaled glucocorticoids. Though efficacy is low, they may obviate need for inhaled steroids, and may be more acceptable in children. In severe asthma, they have additive effect with inhaled steroids, may permit reduction in steroid dose and need for rescue β_2 agonist inhalations. However, the additive effect of long-acting β_2 agonists is greater. Montelukast/zafirlukast are not to be used for terminating asthma episodes. The *cys*LT_1 antagonists are effective in aspirin-induced asthma and exercise induced asthma, but are of no value in COPD. They afford relief in perennial allergic rhinitis as well.

Both montelukast and zafirlukast are very safe drugs; produce few side effects like abdominal pain, headache and rashes. Eosinophilia and neuropathy are infrequent. Few cases of Churg-Strauss syndrome (vasculitis with eosinophilia) have been reported.

Montelukast and zafirlukast are well absorbed orally, highly plasma protein bound and

metabolized by CYP2C9 (montelukast by CYP3A4 as well). The plasma t½ of montelukast is 3–6 hours, while that of zafirlukast is 8–12 hours.

Montelukast: 10 mg OD; children 2–5 yr 4 mg OD, 6–14 yr 5 mg OD to be taken in the evening.

EMLUKAST, MONTAIR, VENTAIR 4 mg, 5 mg, 10 mg tabs

Orally disintegrating strips (ODS) of montelukast 4 mg, 5 mg and 10 mg have also been approved for marketing.

Zafirlukast: 20 mg BD; children 5–11 yr 10 mg BD;

ZUVAIR 10 mg, 20 mg tabs.

Zileuton It is a 5-LOX inhibitor, blocks LTC_4/D_4 as well as LTB_4 synthesis. It therefore has the potential to prevent all LT induced responses including those exerted by activation of *cys*LT_1 receptor. However, clinical efficacy in asthma is similar to that of montelukast. The duration of action of zileuton is short and it has hepatotoxic potential. These limitations have restricted its use.

MAST CELL STABILIZERS

Sodium cromoglycate (Cromolyn sod.)

It is a synthetic chromone derivative which inhibits degranulation of mast cells (as well as other inflammatory cells) by trigger stimuli. Release of mediators of asthma like histamine, LTs, PAF, interleukins, etc. is restricted. The basis of this effect is not well understood, but may involve a delayed Cl^- channel in the membrane of these cells inhibiting activation. Long-term treatment decreases the cellular inflammatory response; bronchial hyperreactivity is reduced to variable extents. Bronchospasm induced by allergens, irritants, cold air and exercise may be attenuated. Cromoglycate is not a bronchodilator and does not antagonize constrictor action of histamine, ACh, LTs, etc. Therefore, it is ineffective if given during an asthmatic attack.

Sod. cromoglycate is not absorbed orally. For asthma it is administered as an aerosol through metered dose inhaler. Only a small fraction of the inhaled drug is absorbed systemically; this is rapidly excreted unchanged in urine and bile.

Uses

1. *Bronchial asthma:* Sod. cromoglycate is rarely used now as a prophylactic in mild-to-moderate asthma. Decrease in the frequency and severity of attacks is more likely in extrinsic (atopic) and exercise-induced asthma, especially in younger patients. Therapeutic benefit (when it occurs) develops slowly over 2–4 weeks and lasts 1–2 weeks after discontinuing.
2. *Allergic rhinitis:* Cromoglycate is not a nasal decongestant, but regular 4 times daily use as a nasal spray produces some symptomatic improvement in many patients after 4–6 weeks.
3. *Allergic conjunctivitis:* Regular use as eye drops is beneficial in some chronic cases.

FINTAL inhaler: 1 mg and CROMAL 5 mg/puff metered dose inhaler; 2 puffs 4 times daily.
FINTAL nasal spray: 2% CROMAL AQ 2.8 mg/dose; 2 squeezes in each nostril QID.
FINTAL eye drops: 2% CROMAL 2% and 4% eye drops; 1 drop in each eye QID.

Adverse effects Because of poor aqueous solubility, absorption of cromoglycate is negligible; systemic toxicity is minimal. Bronchospasm, throat irritation and cough occurs in some patients, especially with fine powder inhalation.

Ketotifen It is an antihistaminic (H_1) with some cromoglycate like action. Stimulation of immunogenic and inflammatory cells (mast cells, macrophages, eosinophils, lymphocytes, neutrophils) and mediator release are reduced. Ketotifen is not a bronchodilator. It is infrequently used now; may be tried in patients with multiple allergic disorders.

Ketotifen is generally well tolerated. Sedation and dry mouth are common. Other side effects are dizziness, nausea, weight gain.

Dose: 1–2 mg BD; children 0.5 mg BD.

ASTHAFEN, 1 mg tab, 1 mg/5 ml syrup; KETOVENT 1 mg tab, KETORID 0.25% eye drops.

CORTICOSTEROIDS

Glucocorticoids are not bronchodilators. They benefit by inhibiting inflammatory cytokine production and eosinophilic, lymphocytic infiltration of lungs. They also reduce bronchial hyperreactivity, mucosal edema and suppress inflammatory response to AG:AB reaction or to other trigger stimuli. Their mechanism of action is detailed in Ch. 20.

The realization that asthma is primarily an inflammatory disorder which, if not controlled, accentuates with time; as well as the availability of inhaled corticosteroids (ICS) that produce few adverse effects, has led to early introduction and more extensive use of glucocorticoids in asthma. Corticosteroids afford more complete and sustained symptomatic relief than bronchodilators and other drugs. They improve airflow, reduce asthma exacerbations and may influence airway remodeling, retarding disease progression. They also increase airway smooth muscle responsiveness to β_2 agonists and reverse refractoriness to these drugs. However, long-term systemic steroid therapy has its own adverse effects which may be worse than asthma itself.

Systemic corticosteroid therapy

Systemic steroid therapy is resorted to in asthma under the following two situations:

(i) *Severe chronic asthma:* not controlled by bronchodilators and ICS, or when there are frequent recurrences of increasing severity; start with prednisolone 20–60 mg (or equivalent) daily; attempt dose reduction after 1–2 weeks of good control and finally try shifting the patient onto an ICS. Only few patients require long term oral steroids—in them dose should be kept at minimum.

In patients requiring long-term glucocorticoid therapy, alternative treatment with immunosuppressants like methotrexate (low dose) or cyclosporine has been tried.

(ii) *Status asthmaticus/acute asthma exacerbation:* asthma attack not responding to intensive bronchodilator therapy: start with high dose of a rapidly acting i.v. glucocorticoid which generally acts in 6–24 hours—shift to oral therapy for 5–7 days and then discontinue abruptly or taper rapidly.

COPD A short course (1–3 week) of oral glucocorticoid may benefit some patients of COPD during an exacerbation.

Inhaled corticosteroids

These are glucocorticoids with high topical and low systemic activity (due to poor absorption and/or marked first pass metabolism). *Beclomethasone dipropionate*, *Budesonide*, *Fluticasone* and *Ciclesonide* are the commonly used ICS. Because airway inflammation is present in early mild disease as well, and bronchial remodeling starts developing from the beginning, it has been advocated that ICS should be the 'step one' for all asthma patients. However, currently ICS are not considered necessary for patients with mild and episodic asthma. They are indicated in all cases of persistent asthma when inhaled β_2 agonists are required almost daily or the disease is not only episodic. Start with 100–200 µg BD, titrate dose upward every 3–5 days; max. 400 µg QID, beyond which no further benefit generally occurs.

Inhaled corticosteroids suppress bronchial inflammation, increase peak expiratory flow rate, reduce need for rescue β_2-agonist inhalations and prevent episodes of acute asthma. However, they have no role during an acute attack or in status asthmaticus. Peak effect is seen after 4–7 days of instituting ICS and benefit persists for a few weeks after discontinuation. They can be started in patients who in the past have required oral corticosteroids as well as in those with no such history. Patients who are to be switched over from oral steroid should receive ICS in addition for 1–2 weeks before oral steroid is tapered, otherwise steroid withdrawal may manifest (precipitation of asthma, muscular pain, lassitude, depression, hypotension). This confirms lack of systemic activity of ICS (at doses < 600 µg/day). Long-term experience has shown that efficacy of ICS is maintained and reinstitution of oral steroids is seldom needed. Short courses of oral steroids may be added during periods of exacerbation. Some patients who remain well controlled for long periods can even stop ICS without worsening of asthma.

COPD: The airway inflammation in COPD is not very responsive to corticosteroids. As such, only high dose ICS are beneficial in advanced COPD with frequent exacerbations. They should not be used in early/mild cases. There is no proof that they retard progression of COPD.

Adverse effects Hoarseness of voice, dysphonia, sore throat, asymptomatic or symptomatic oropharyngeal candidiasis are the most common side effects. These can be minimized by the use of a spacer, and by gargling after every dose (to wash off the drug deposited on oral and pharyngeal mucosa). Oral candidiasis can be prevented as well as treated by topical nystatin/clotrimazole. There is no evidence of mucosal damage or increased incidence of chest infections, even on prolonged use of ICS.

Systemic effects of long-term ICS are clinically relevant only at doses > 600 µg/day. The significant ones are—mood changes, osteoporosis, growth retardation in children, early cataract,

bruising, petechiae, hyperglycaemia and pituitary-adrenal suppression. Several reports of adrenal crisis have appeared, especially in children, during stress (of an infection, etc).

Inhaled steroids are safe during pregnancy.

Beclomethasone dipropionate

BECORIDE 50, 100, 250 µg per puff inhaler.
AEROCORT INHALER 50 µg/metered dose inhaler with salbutamol 100 µg.
ECONASE 0.05% nasal spray.

Intranasal spray (50 µg in each nostril BD–TDS) is effective in perennial rhinitis.

Budesonide It is a nonhalogenated glucocorticoid with high topical: systemic activity ratio (greater first pass metabolism than beclomethasone). Small fraction that is absorbed is rapidly metabolized; less systemic effects are noted. It may be preferred in more severe cases.

PULMICORT 100, 200, 400 µg/metered dose inhaler, 0.25 mg/ml and 0.5 mg/ml respules.
FORACORT: Formoterol 6 µg + Budesonide 100 µg/200 µg rotacaps.
RHINOCORT 50 µg per metered dose nasal spray;
BUDENASE AQ 100 µg metered dose aqueous nasal spray;
200–400 µg/day by intranasal spray for prophylaxis and treatment of seasonal and perennial allergic or vasomotor rhinitis, nasal polyposis; initially 2 puffs in each nostril every morning, maintenance 1 puff in each nostril in the morning.

Nasal irritation, sneezing, crusting, itching of throat and dryness may occur, especially in the beginning. It is contraindicated in presence of infection or nasal ulcers.

Fluticasone propionate This inhaled glucocorticoid has high potency (about double of beclomethasone); longer duration and negligible oral bioavailability. The dose swallowed after inhalation has little propensity to produce systemic effects. At high doses, systemic effects may be due to absorption from the lungs. It may be preferred in patients requiring higher doses.

FLOHALE INHALER 25 µg, 50 µg, 125 µg per actuation.
FLOHALE ROTACAPS 50 µg, 100 µg, 250 µg rotacaps.
FLOMIST 50 µg per actuation nasal spray.

Flunisolide This topical steroid is available for prophylaxis and treatment of seasonal and perennial rhinitis.

SYNTARIS 25 µg per actuation nasal spray; one spray in each nostril 2–3 times daily.

Ciclesonide This ICS utilizes a novel approach to improve topical: systemic activity ratio. It is a prodrug that is cleaved by esterases in the bronchial epithelium to release the active moiety. Though it is absorbed from the lungs, oral bioavailability is <1%. In the circulation it is extensively bound to plasma proteins, further minimizing exposure of tissue cells to the free and active drug.

CICLEZ 80 µg and 160 µg per metered dose inhaler with HFA propellant for once daily use, preferably in the evening.

The dose of the ICS depends upon the particular compound, its formulation, *viz.* metered dose inhaler (MDI) or dry powder inhaler (DPI), and the severity of asthma. The daily doses for each preparation can be categorized into low dose, medium dose or high dose, as presented in Table 16.2.

ANTI-IgE ANTIBODY

Omalizumab It is a humanized monoclonal antibody against IgE. Administered s.c., it neutralizes free IgE in circulation without activating mast cells and other inflammatory cells. On antigen challenge, little IgE is available bound to the mast cell surface receptors ($F_{\varepsilon}R1$) to trigger mediator release (*see* Fig. 11.2) and cause bronchoconstriction. In severe extrinsic asthma, omalizumab has been found to reduce exacerbations and steroid requirement. No benefit has been noted in nonallergic asthma. It is very expensive;

Table 16.2: Low, medium and high doses of inhaled corticosteroids for adults and adolescents (> 11 years age)

Inhaled corticosteroid	*Daily doses (µg/day)*			
	Low	*Medium*	*High*	*Maximum*
1. Beclomethasone dipropionate—MDI	200–400	400–800	> 800	1600
2. Budesonide—MDI	200–400	400–800	> 800	1600
3. Fluticasone propionate—MDI —DPI	100–250 200–400	250–500 400–800	> 500 > 800	1000 2000
4. Ciclesonide—MDI	80–160	160–320	> 320	640

MDI—Metered dose inhaler; DPI—Dry powder inhaler

use is reserved for resistant asthma patients with positive skin tests or raised IgE levels who require frequent hospitalization. It is being tried in other allergic diseases as well.

INHALED ASTHMA MEDICATION

Four classes of antiasthma drugs, *viz.* β_2 agonists, anticholinergics, cromoglycate and glucocorticoids are available for inhalational use. They are aimed at delivering the drug to the site of action so that lower dose is needed and systemic side effects are minimized. Faster action of bronchodilators can be achieved compared to oral administration. Most asthma patients are now maintained on inhaled medication only. Aerosols are of two types:

(i) use drug in solution: pressurized metered dose inhaler (MDI), nebulizers.

(ii) use drug as dry powder (DPI) spinhaler, rotahaler.

Pressurized metered dose inhalers use hydrofluroalkane (HFA) propellants and deliver a specified dose of the drug in spray form per actuation. Use of chlorofluorocarbon (CFC) propellants is now banned due to their effect on ozone layer. Device actuation has to be properly coordinated with deep inspiration, which many patients are unable to learn. A large volume 'spacer' (chamber interposed between the inhaler and the patient's mouth) can be used to improve drug delivery by obviating the need for precise coordination. Moreover, larger particles settle on the walls of the spacer reducing the fraction that deposits in the throat and is later swallowed. Local complications (candidiasis with inhaled steroids) as well as systemic exposure are reduced. Jet nebulizers produce a mist of the drug solution generated by pressurized air or oxygen which can be inhaled through a mouth piece, face mask or in a tent. Ultrasonic nebulizers use electrically vibrated crystals; pressurized air/oxygen is not needed. Metered dose inhalers are convenient handheld devices which can be carried along, while nebulizers are used at patient's bed side. Nebulizers are preferred for severe episodes of asthma as well as for children and elderly. More than one drug can be nebulized simultaneously.

Dry powder inhalers (DPIs) are also portable devices in which the capsule (rotacap) containing the drug is punctured/cut across and the powder is aerosolized by the inspiratory air flow of the patient. It requires high velocity inspiration which children, elderly and the very sick may not be capable of. The dry powder is also more likely to irritate the air passage—producing cough and bronchoconstriction.

Efficacy of aerosolized drug depends on the particle size: 1–5 μm diameter particles deposit on the bronchioles and effectively deliver the drug. Larger particles settle on the oropharynx, while very fine particles do not settle anywhere and are exhaled out. On an average only ~10% of the inhaled drug reaches the site of action. A considerable fraction is swallowed. Therefore, to minimize systemic action, the drug should have low oral bioavailability. Spacer devices improve inhaled to swallowed drug ratio. Slow and deep inbreathing after device actuation and holding the breath after inhalation also enhances efficacy of the inhaler. Greater proportion of smaller particles in a relatively narrow band width of 1–2 μM can be generated using the newer HFA propellant based MDIs. This improves delivery of the drug to the smaller bronchioles. However, systemic absorption from the peripheral lungs is also more.

CHOICE OF TREATMENT

The severity of asthma symptoms ranges from transient respiratory difficulty to incapacitating breathlessness, and characteristically fluctuates over time. The goals of drug therapy in asthma are to relieve the symptoms of breathlessness and wheezing, prevent recurrent exacerbations and to minimise need for emergency hospitalizations. A stepwise approach to assist the clinical decision-making in the treatment of asthma as per needs of the patient has been advocated.The following guidelines summarise the recommendations of the British Thoracic Society (2012)* as well as that of the National Asthma Education and Prevention Programme. Expert Panel Report (2007).[£] After the asthma is under control for 3–6 months, an attempt to reduce medication should be made in a stepwise manner.

1. *Mild episodic asthma* (symptoms less than once daily, normal in between attacks): Inhaled short-acting β_2 agonist at onset of each episode. Since asthma is intermittent, it does not require continuous prophylactic therapy (Step-1).

2. *Seasonal asthma* Start regular low-dose ICS 3–4 weeks before anticipated seasonal attacks and continue till 3–4 weeks after the season is over. Alternatively oral montelukast/zafirlukast may be tried, especially in children. Treat asthma episodes with inhaled short-acting β_2 agonist.

3. *Mild chronic (persistent) asthma with occasional exacerbations* (symptoms once

*British Thoracic Society and Scottish Intercollegiate Guidelines Network (Jan 2012; www.brit.thoracic.org.uk)

[£]National Asthma Education and Prevention Programme. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Institute of Health Pub No. 08-4051 (2007).

daily or so, subnormal ventilatory performance). Regular low-dose ICS (Step-2). Alternatively, montelukast/zafirlukast as above; but they may not be effective in some patients, or may afford less complete relief. Oral theophylline is a less satisfactory option. Episode treatment with inhaled short-acting β_2 agonist.

4. Moderate asthma with frequent exacerbations (attacks affect activity, occur > 1 per day or mild baseline symptoms persist). Low doses of ICS + inhaled long-acting β_2 agonist (Step-3), or medium dose ICS alone. In view of the potential risk of prolonged treatment with long-acting β_2 agonists, attempt should be made to discontinue it after maintaining asthma control over few months. Leukotriene antagonists may be tried in place of long-acting β_2 agonists, but their additive effect is less marked. Sustained release theophylline may be used as alternative additional drug to long-acting β_2 agonists, especially in nocturnal asthma.

5. Severe asthma (continuous symptoms; activity limitation; frequent exacerbations/ hospitalization) Regular high dose ICS through a large volume spacer device + inhaled long-acting β_2 agonist (salmeterol) twice daily. Additional treatment with one or more of the following (Step-4):

Leukotriene antagonist/sustained release oral theophylline/sustained release oral β_2 agonist.

Rescue treatment with short-acting inhaled β_2 agonist.

In patients not adequately controlled or those needing frequent emergency care—institute oral steroid therapy (Step-5) while continuing long acting β_2 inhalations and ICS. Efficacy of oral steroids is proven, but should be the last resort. Attempt to withdraw it should be made periodically. The British guidelines recommend continuing high dose ICS along with oral steroids.

6. Status asthmaticus/Refractory asthma

Any patient of asthma has the potential to develop acute severe asthma which may be life-threatening. Upper respiratory tract infection is the most common precipitant.

- Hydrocortisone hemisuccinate 100 mg (or equivalent dose of another glucocorticoid) i.v. *stat,* followed by 100–200 mg 4–8 hourly infusion; may take upto 6 hours to act.
- Nebulized salbutamol (2.5–5 mg) + ipratropium bromide (0.5 mg) intermittent inhalations driven by O_2.
- High flow humidified oxygen inhalation.
- Salbutamol/terbutaline 0.4 mg i.m./s.c. may be added, since inhaled drug may not reach smaller bronchi due to severe narrowing/ plugging with secretions.
- Intubation and mechanical ventilation, if needed.
- Treat chest infection with intensive antibiotic therapy.
- Correct dehydration and acidosis with saline + sod. bicarbonate/lactate infusion.

Aminophylline 250–500 mg diluted in 20–50 ml glucose (5%) solution injected i.v. over 20–30 min had been routinely used, but recent evidence shows that it does not afford additional benefit; may even produce more adverse effects; use is restricted to resistant cases.

Some antiasthma combinations

BRONKOPLUS: Salbutamol 2 mg, anhydrous theophylline 100 mg tab., also per 5 ml syrup.

BRONKOTUS: Bromhexine 8 mg, salbutamol 2 mg tab., also syrup—bromhexine 4 mg, salbutamol 2 mg per 5 ml.

TERPHYLIN: Terbutaline 2.5 mg, etophylline 100 mg tab, and per 10 ml syr.

THEO ASTHALIN: Salbutamol 2 mg, theophylline anhydrous 100 mg tab, and per 10 ml syr.

THEO ASTHALIN-SR: Salbutamol 4 mg, theophylline 300 mg SR tab.

THEO BRIC: Terbutaline 2.5 mg, theophylline 100 mg tab.

THEOBRIC SR: Terbutaline 5 mg, theophylline 300 mg SR tab.

DURASALYN-CR: Salbutamol 4 mg, theophylline 200 mg CR cap.

☞ PROBLEM DIRECTED STUDY

16.1 A 30-year-old man presents with complaints of episodic breathlessness, often following exertion. One to three episodes occur daily and are accompanied by wheezing. Every 2–3 days, he wakes up at night with breathlessness. The episodes subside on taking 2 puffs of the inhaler prescribed by his family doctor (salbutamol 100 μg/puff). Lately, the episodes have become more frequent and are limiting his activities to some extent. Spirometry revealed FEV_1 to be 70% of predicted value at baseline, and 88% after 2 puffs of salbutamol (100 μg/puff) inhalation. He is diagnosed to be a case of moderate bronchial asthma.

(a) Is this patient receiving adequate treatment for his condition, or some other drug/drugs need to be used? If so, what should be the first line treatment for this patient?

(b) In case another drug is prescribed, should this patient continue to use salbutamol inhalations to relieve episodes of breathlessness, when they occur?

(c) Which alternative drugs can be used in this patient.

16.2 A 60-year-old male patient of moderately severe chronic obstructive pulmonary disease (COPD) with FEV_1 45% of predicted, who has quit smoking for the last 5 years, and is maintained on—Ipratropium br. 20 μg/puff metered dose inhaler, 2 puffs 3 times a day, and Theophylline 400 mg SR tab. twice a day, developed sore throat and fever. He was prescribed—

Tab Erythromycin 250 mg, one tab 4 times a day for 5 days

Tab Paracetamol 500 mg 3 times a day till fever persists.

After 3 days he presented with pain in epigastrium, restlessness, irritability, inability to sleep, palpitation, tremor of fingers and hand, and had vomited twice. His fever had subsided and throat was better.

(a) What could be the reason for his recent illness?

(b) Could this illness be prevented, if so, how?

(see Appendix-1 for solution)

SECTION 5

HORMONES AND RELATED DRUGS

Introduction

Hormone (Greek *hormaein*—to stir up) is a substance of intense biological activity that is produced by *specific cells* in the body and is transported *through circulation* to act on its target cells.

Hormones regulate body functions to bring about a programmed pattern of life events (growth, development, metabolism, reproduction, ageing, etc.) and maintain homeostasis in the face of markedly variable external and internal environment.

Body function		Major regulator hormone(s)
1. Availability of fuel	:	Insulin, Glucagon, Growth hormone
2. Metabolic rate	:	Triiodothyronine, Thyroxine
3. Somatic growth	:	Growth hormone, Insulin-like growth factors
4. Sex and reproduction	:	Gonadotropins, Androgens, Estrogens, Progestins
5. Circulating volume	:	Aldosterone, Antidiuretic hormone
6. Adaptation to stress	:	Glucocorticoids, Adrenaline
7. Calcium balance	:	Parathormone, Calcitonin, Vitamin D

Hormones are secreted by the *endocrine* or *ductless* glands. These are:

1. *Pituitary*

(a) *Anterior* Growth hormone (GH), Prolactin (Prl), Adrenocorticotropic hormone (ACTH) or Corticotropin. Thyroid stimulating hormone (TSH) or Thyrotropin.
Gonadotropins—Follicle stimulating hormone (FSH) and Luteinizing hormone (LH).

(b) *Posterior*—Oxytocin, Antidiuretic hormone (ADH) or Vasopressin.

2. *Thyroid* Thyroxine (T_4), Triiodothyronine (T_3), Calcitonin.

3. *Parathyroid* Parathyroid hormone (PTH) or Parathormone.

4. *Pancreas* (*Islets of Langerhans*) Insulin, Glucagon.

5. *Adrenals*

(a) *Cortex* Glucocorticoids (hydrocortisone)
Mineralocorticoids (aldosterone)
Sex steroids (dehydroepiandrosterone)

(b) *Medulla* Adrenaline, Noradrenaline

6. *Gonads* Androgens (testosterone)
Estrogens (estradiol)
Progestins (progesterone)

In addition, hypothalamus, which is a part of the CNS and not a gland, produces many releasing and release inhibitory hormones which control the secretion of anterior pituitary hormones. Some important ones of these are given in the box.

Placenta also secretes many hormones:

Chorionic gonadotropin	Prolactin
Estrogens	Progesterone
Placental lactogen	Chorionic thyrotropin

Hypothalamic hormone/factor	Chemical nature
1. Thyrotropin releasing hormone (TRH)	Tripeptide
2. Corticotropin releasing hormone (CRH)	Peptide (41 AAs)
3. Gonadotropin releasing hormone (GnRH, LH-RH/ FSH-RH) or Gonadorelin	Decapeptide
4. Prolactin release inhibitory hormone (PRIH)	Dopamine
5. Growth hormone releasing hormone (GHRH)	Peptide (40, 44 AAs)
6. Somatostatin (Growth hormone release inhibitory hormone)	Peptide (14 AA)

The natural hormones and in many cases their synthetic analogues, which may be more suitable therapeutically, are used as drugs for substitution therapy as well as for pharmacotherapy. In addition, hormone antagonists and synthesis/ release inhibitors are of therapeutic importance.

Sites and mechanisms of hormone action

The hormones act on their specific receptors located on or within their target cells. Receptor activation by the hormones is translated into response in a variety of ways.

1. *At cell membrane receptors*

a. Through alteration of intracellular cAMP concentration → alteration of protein kinase A→ regulation of cell function: Ca^{2+} acting as third messenger in some situations.	Adrenaline, Glucagon, TSH, FSH, LH, PTH, Calcitonin, ACTH, some hypothalamic releasing hormones, Vasopressin (V_2 receptor)
b. Through IP_3/DAG generation: release of intracellular Ca^{2+} and protein kinase C activation.	Vasopressin (V_1 receptor), Oxytocin
c. Direct transmembrane activation of tyrosine protein kinase → phosphorylation cascade → regulation of various enzymes.	Insulin, Growth hormone Prolactin

2. *At cytoplasmic receptors*

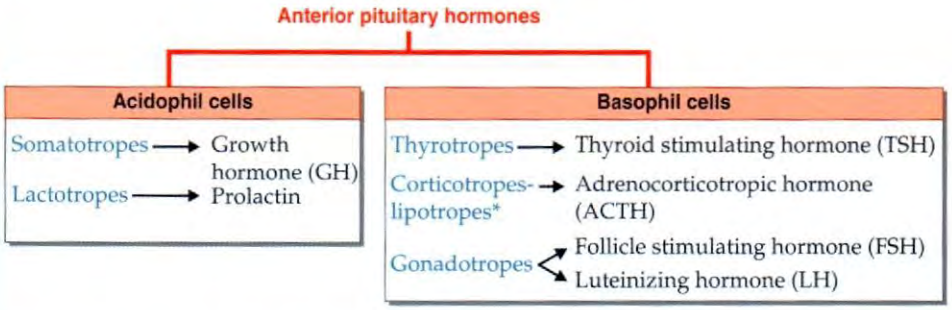
Penetrating cell membrane, hormone combines with a cytoplasmic receptor → exposes its DNA binding domain → migrates to nucleus and binds to specific genes → DNA mediated mRNA synthesis → synthesis of functional proteins.	Steroidal hormones: Glucocorticoids Mineralocorticoid Androgens Estrogens Progestins; Calcitriol

3. *At nuclear receptor*

The hormone penetrates the nucleus → combines with its receptor → alters DNA–RNA mediated protein synthesis.	Thyroid hormones: Thyroxine, Triiodothyronine

Chapter 17 Anterior Pituitary Hormones

Anterior pituitary (adenohypophysis), the master endocrine gland, elaborates a number of important regulatory hormones. All of these are peptide in nature and act at extracellular receptors located on their target cells. Secretion of pituitary hormones is controlled by the hypothalamus through *releasing* and *release-inhibitory* hormones that are transported *via* hypothalamohypophyseal portal system, and is subjected to feedback inhibition by the hormones of their target glands. Each anterior pituitary hormone is produced by a separate group of cells, which according to their staining characteristic are either acidophilic or basophilic. The pituitary cells and the hormone they secrete are:



*These cells also produce two lipotropins and two melanocyte stimulating hormones (MSHs)

Out of the above hormones only GH and gonadotropins (Gns) are used therapeutically, while TSH and ACTH have only diagnostic application in rare instances. Of greater clinical interest are the drugs which either inhibit or stimulate the secretion of a specific anterior pituitary hormone. These are presented in the chart below.

DRUGS ALTERING ANTERIOR PITUITARY HORMONE SECRETION

Inhibit GH release	Inhibit prolactin release	Enhance prolactin release	Inhibit gonadotropin (Gn) release
Somatostatin Octreotide Lanreotide	Bromocriptine Cabergoline Apomorphine	Chlorpromazine (other neuroleptics) Metoclopramide Reserpine	

Superactive GnRH agonists		GnRH antagonists
(Initially enhance Gn release)		Ganirelix
Nafarelin	Goserelin	Cetrorelix
Triptorelin	Leuprolide	

SECTION 5

GROWTH HORMONE (GH)

It is a 191 amino acid, single chain peptide of MW 22000.

Physiological functions During childhood and adolescence GH is required for normal growth and attainment of adult stature. It promotes growth of bones and all other organs by inducing hyperplasia. In general, there is a proportionate increase in the size and mass of all parts, but in the absence of gonadotropins, sexual maturation does not take place. The growth of brain and eye is independent of GH. It promotes retention of nitrogen, calcium and other tissue constituents: more protoplasm is formed. The positive nitrogen balance results from increased uptake of amino acids by tissues and their synthesis into proteins. In addition to protein metabolism, GH affects carbohydrate and fat metabolism throughout life. It promotes utilization of fat and spares carbohydrates. Uptake of glucose by muscles is reduced while its output from liver is enhanced; blood glucose level tends to rise.

GH acts on cell surface JAK-STAT binding protein kinase receptors (*see* p. 59) which are present on practically all types of cells. Binding of one GH molecule to the extracellular domain of a GH-receptor diamer results in the formation of a ternary complex which undergoes a conformational change and activates the intracellular domain to associate with cytoplasmic JAK-STAT tyrosine-protein kinase resulting in metabolic effects as well as regulation of gene expression.

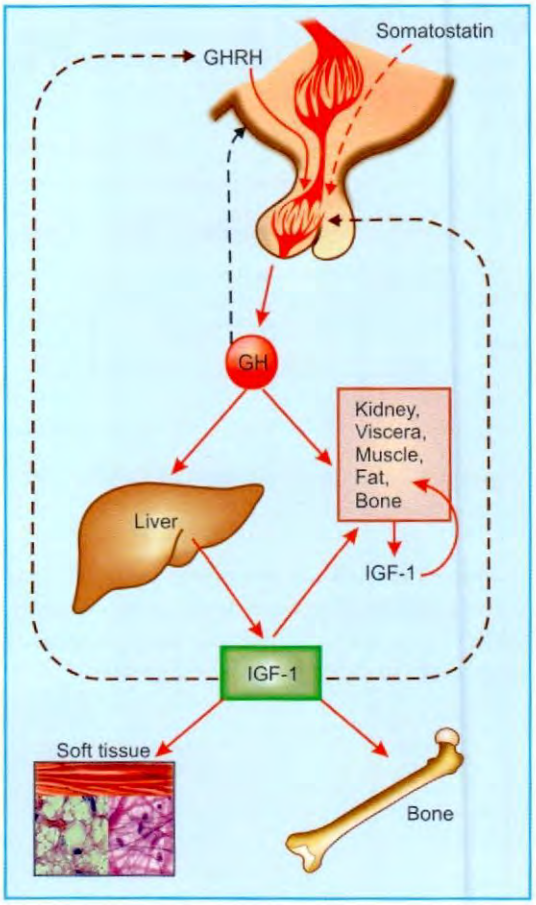


Fig. 17.1: Action of growth hormone (GH) and regulation of its secretion
GHRH—Growth hormone releasing hormone;
IGF-1: Insulin-like growth factor-1;
Stimulation (⟶); Inhibition (- - - ⟶)

The growth promoting, nitrogen retaining and certain metabolic actions of GH are exerted *indirectly* through the elaboration of peptides called *Somatomedins* or *Insulin-like growth factors (*mainly *IGF-1,* also *IGF-2)* which are extracellular mediators of GH response (Fig. 17.1). Liver is the major source of circulating IGF-1, while IGF-1 produced by other target cells acts locally in a paracrine manner. Like insulin, IGF-1 promotes lipogenesis and glucose uptake by muscles. Moreover, the IGF-1 receptor is structurally and functionally analogous to the insulin receptor (*see* p. 284).

GH acts directly as well, but induces lipolysis in adipose tissue, gluconeogenesis and glycogenolysis in liver and decreased glucose utilization by muscles. These effects are opposite to those of IGF-1 and insulin. As such, GH accentuates the metabolic derangement in diabetes.

Regulation of secretion The hypothalamus produces GH releasing (GHRH) as well as release inhibitory (*somatostatin*) hormones. Both are peptides. Receptors for GHRH and somatostatin are G protein coupled receptors (GPCRs) which enhance or inhibit GH secretion by increasing or decreasing cAMP formation respectively in pituitary somatotropes. IGF-1 causes feedback inhibition of GH secretion. Short-loop feedback inhibition of secretion by GH itself has also been described.

Pathological involvements Excess production of GH is responsible for *gigantism* in childhood and *acromegaly* in adults. Hyposecretion of GH in children results in *pituitary dwarfism*. Normal adult height is not attained, muscle mass is low and body fat is increased. Adult GH deficiency is rare, but when it occurs, it results in low muscle and bone mass, lethargy, decreased work capacity, hyperlipidaemia and increased cardiovascular risk.

Uses

Availability of *Somatropin*, the recombinant human GH (rhGH) has considerably widened the clinical application of GH. However, it should be used only by specialists.

1. *Pituitary dwarfism:* It is due to GH deficiency which is noticed in early childhood as subnormal height gain. Daily s.c. injection of somatropin (30–60 μg/kg), preferably in the evening, produces highly gratifying results. Growth is accelerated and near normal adult stature may be attained if therapy is instituted early and continued till the age of 20.
2. *Turner syndrome:* The short stature of girls can be largely corrected by rhGH treatment combined with properly timed androgen and estrogen therapy.
3. *Chronic renal insufficiency* in children causing suboptimal growth: rhGH is approved for restoring growth.
4. *Constitutional (idiopathic) short stature children:* Somatropin treatment has yielded encouraging results, but entails longterm costly medication. Ethical, social and medical objections have been raised.
5. *GH deficiency in adults:* rhGH treatment increases lean body mass, decreases body fat, improves energy and metabolism.
6. *AIDS related wasting:* Somatropin improves physical and mental health of affected patients. It has also been used in other catabolic states like severe burns, bedridden patients, chronic renal failure, etc.[8]

Somatropin is also being promoted for ageing, but benefits are uncertain. Its use by athletes is banned, and it is one of the drugs included in 'dope testing'.

Somatropin: NORDITROPIN, NORDILET 5, 10, 15 mg prefilled pen injector, HUMATROPE 6 mg, 12 mg cartridges, 1.33 and 5.33 mg vials.

Adverse effects Somatropin has low immunogenicity; allergic reactions or resistance to treatment are not a problem. Pain at injection site, lipodystrophy, glucose intolerance, hypothyroidism (due to unmasking of TSH deficiency), salt and water retention, hand stiffness, myalgia, headache are the possible adverse effects. Rise in intracranial tension occurs in few cases.

Mecasermin This is recently produced recombinant human IGF-1 (rhIGF-1), which is useful in children with retardation unresponsive to rhGH and is due to GH receptor/GH signaling pathway abnormality.

GH Inhibitors

Somatostatin

This 14 amino acid peptide inhibits the secretion of GH, prolactin, and TSH by pituitary; insulin and glucagon by pancreas, and of almost all gastrointestinal secretions including that of gastrin and HCl. The g.i. action produces steatorrhoea, diarrhoea, hypochlorhydria, dyspepsia and nausea as side effect. Somatostatin constricts splanchnic, hepatic and renal blood vessels. The decreased g.i. mucosal

blood flow can be utilized for controlling bleeding esophageal varices and bleeding peptic ulcer, but its analogue octreotide is preferred now due to longer duration of action. The antisecretory action of somatostatin is beneficial in pancreatic, biliary or intestinal fistulae; can also be used to reduce complications after pancreatic surgery. It has adjuvant value in diabetic ketoacidosis (by inhibiting glucagon and GH secretion).

Use of somatostatin in acromegaly is limited by its short duration of action (t½ 2–3 min), lack of specificity for inhibiting only GH secretion and GH rebound on discontinuation. Surgical removal of pituitary adenomas is the preferred treatment modality, but somatostatin analogues are being increasingly used.

Dose: (for upper g.i.bleeding) 250 µg slow i.v. injection over 3 min followed by 3 mg i.v. infusion over 12 hours.

STILMEN, SOMATOSAN, SOMASTAT 250 µg and 3 mg amps.

Octreotide This synthetic octapeptide surrogate of somatostatin is 40 times more potent in suppressing GH secretion and longer acting (t½ ~90 min), but only a weak inhibitor of insulin secretion. It is preferred over somatostatin for acromegaly and secretory diarrhoeas associated with carcinoid, AIDS, cancer chemotherapy or diabetes. Control of diarrhoea is due to suppression of hormones which enhance intestinal mucosal secretion.

Dose: Initially 50–100 µg s.c. twice daily, increased upto 200 µg TDS; for acromegaly maintain with 10–30 mg i.m. of microsphere formulation every 4 weeks.

Adverse effects are abdominal pain, nausea, steatorrhoea, diarrhoea, and gall stones (due to biliary stasis). Hyperglycaemia is infrequent.

Octreotide injected i.v. (100 µg followed by 25–50 µg/hr) reduces hepatic blood flow and helps stop esophageal variceal bleeding.

SANDOSTATIN, OCTRIDE 50 µg, 100 µg in 1 ml amps.
SANDOSTATIN LAR (microsphere formulation) 20 mg/5 ml inj.

Lanreotide Another long-acting analogue of somatostatin, very similar in actions and specificity to octreotide, which on i.m. injection acts for 10–15 days. It is indicated for pharmacotherapy of acromegaly.

Pegvisomant This polyethylene glycol complexed mutant GH binds to the GH receptor but does not trigger signal transduction: acts as a GH antagonist. It is approved for treatment of acromegaly due to small pituitary adenomas.

PROLACTIN

It is a 199 amino acid, single chain peptide of MW 23000; quite similar chemically to GH. Prolactin was originally described as the hormone which causes secretion of milk from crop glands of pigeon and later found to be of considerable importance in human beings as well.

Physiological function Prolactin is the primary stimulus which in conjunction with estrogens, progesterone and several other hormones, causes growth and development of breast during pregnancy. It promotes proliferation of ductal as well as acinar cells in the breast and induces synthesis of milk proteins and lactose. After parturition, prolactin induces milk secretion, since the inhibitory influence of high estrogen and progesterone levels is withdrawn.

Prolactin suppresses hypothalamo-pituitary-gonadal axis by inhibiting GnRH release. Continuous high level of prolactin during breastfeeding is responsible for lactational amenorrhoea, inhibition of ovulation and infertility for several months postpartum. Prolactin may affect immune response through action on T-lymphocytes.

A specific prolactin receptor is expressed on the surface of target cells, which is structurally and functionally analogous to GH receptor: action is exerted by transmembrane activation of JAK—cytoplasmic tyrosine protein kinases and STAT.

Regulation of secretion Prolactin is under predominant inhibitory control of hypothalamus through PRIH which is dopamine that acts on pituitary lactotrope D2 receptor. Dopaminergic agonists (DA, bromocriptine, cabergoline) decrease plasma prolactin levels, while dopaminergic antagonists (chlorpromazine, haloperidol, metoclopramide) and DA depleter (reserpine) cause hyperprolactinemia.

Prolactin levels in blood are low in childhood, increase in girls at puberty and are higher in adult females than in males. A progressive increase occurs during pregnancy, peaking at term. Subsequently, high prolactin secretion is maintained by suckling: it falls if breast feeding is discontinued.

Physio-pathological involvement Hyperprolactinaemia is responsible for the galactorrhoea–amenorrhoea–infertility syndrome in women. In males it causes loss of libido and depressed

fertility. The most important cause of hyperprolactinaemia is prolactin secreting tumours (micro- or macroprolactinomas). Others are—hypothalamic disorders weakening its inhibitory control over pituitary, antidopaminergic drugs or high TRH levels (due to hypothyroidism) which stimulates prolactin secretion.

Use There are no clinical indications for prolactin.

Prolactin inhibitors

Bromocriptine

This synthetic ergot derivative 2-bromo-α-ergocryptine is a potent dopamine agonist. It has greater action on D2 receptors, while at certain dopamine sites in the brain it acts as a partial agonist or antagonist of D1 receptor. It is also a weak α adrenergic blocker but not an oxytocic. Actions of bromocriptine are:

1. Decreases prolactin release from pituitary and is a strong antigalactopoietic.
2. Increases GH release in normal individuals, but decreases the same from pituitary tumours that cause acromegaly.
3. Has levodopa like actions in CNS—antiparkinsonian and behavioural effects.
4. Produces nausea and vomiting by stimulating dopaminergic receptors in the CTZ.
5. Hypotension—due to central suppression of postural reflexes and weak peripheral a adrenergic blockade.
6. Decreases gastrointestinal motility.

Only 1/3 of an oral dose of bromocriptine is absorbed; bioavailability is further lowered by high first pass metabolism in liver. Metabolites are excreted mainly in bile. Its plasma t½ is 3–6 hours.

PROCTINAL, PARLODEL, SICRIPTIN, 1.25 mg, 2.5 mg tabs.

Uses Bromocriptine is infrequently used now; has been largely superseded by newer D2 agonists. Conditions in which it can be used are:

1. *Hyperprolactinemia* due to microprolactinomas causing galactorrhoea, amenorrhoea and infertility in women; gynaecomastia, impotence and sterility in men but has been replaced by cabergoline.

2. *Acromegaly* Bromocriptine is indicated when acromegaly is due to small pituitary tumours and for inoperable cases; but cabergoline is preferred now.

3. *Parkinsonism* Relatively higher doses are required, which are poorly tolerated. Newer D2 receptor agonists, ropinirole and pramipexole are used now.

4. *Diabetes mellitus (DM)* A new use of bromocriptine based on its dopamine D2 agonistic action in the hypothalamus has been found in type 2 DM, and it has been approved by US-FDA as an adjunctive drug.

Side effects: Side effects are frequent and dose related.

Early: Nausea, vomiting, constipation, nasal blockage. Postural hypotension may be marked at initiation of therapy—syncope may occur if starting dose is high. Hypotension is more likely in patients taking antihypertensives.

Late: Behavioural alterations, mental confusion, hallucinations, psychosis. These side effects are more prominent than with levodopa.
Abnormal movements, livedo reticularis.

Cabergoline

It is a newer D2 agonist; more potent; more selective for pituitary lactotrope D2 receptors, and longer acting (t½ > 60 hours) than bromocriptine. It needs to be given only twice weekly. Incidence of nausea and vomiting is also lower; some patients not tolerating or not responding to bromocriptine have been successfully treated with cabergoline. It is the first choice drug for treatment of hyper-prolactinaemia; serum prolactin levels fall to the normal range in 2–4 weeks, and many women conceive within one year. Cabergoline should be stopped when pregnancy occurs, though no teratogenic effect has been observed. Most micro- and some macroprolactinomas show regression during therapy, and neurological symptoms (visual field defects, etc.) due to pressure on optic chiasma are relieved. Response is generally maintained only till the drug is given, with recurrence on stoppage. Some patients who achieve total regression of prolactinoma and normalization of prolactin levels can stop cabergoline without recurrence.

Cabergoline is also beneficial in acromegaly due to pituitary adenoma, but efficacy is lower. It may be used to supplement surgery/radiation/octreotide.

Dose: Start with 0.25 mg twice weekly; if needed increase after every 4–8 weeks to max. of 1 mg twice weekly.

CABERLIN 0.5 mg tab, CAMFORTE 0.5, 1 mg tabs. COLETTE 0.25, 0.5 mg tabs.

GONADOTROPINS (Gns)

The anterior pituitary secretes two Gns *viz.* FSH and LH. Both are glycoproteins containing 23–28% sugar and consist of two peptide chains. The α-chain (92AA) is common between FSH and LH, but their β-chains are different: FSH (111 AA), LH (121 AA). Paradoxically the MW of FSH (~33KD) is greater than that of LH (~30 KD), because of the sugar moieties.

Physiological functions FSH and LH act in concert to promote gametogenesis and secretion of gonadal hormones.

FSH In the female it induces follicular growth, development of ovum and secretion of estrogens. In the male it supports spermatogenesis and has a trophic influence on seminiferous tubules. Ovarian and testicular atrophy occurs in the absence of FSH.

LH It induces preovulatory swelling of the ripe graafian follicle and triggers ovulation followed by luteinization of the ruptured follicle and sustains the corpus luteum till the next menstrual cycle. It is also probably responsible for atresia of the remaining follicles. Progesterone secretion occurs only under the influence of LH. In the male LH stimulates testosterone secretion by the interstitial cells and is designated interstitial cell stimulating hormone (ICSH).

Distinct LH and FSH receptors are expressed on the target cells. Both are G protein coupled receptors which on activation increase cAMP production. This in turn stimulates gametogenesis and conversion of cholesterol to pregnenolone—the first step in progesterone, testosterone and estrogen synthesis.

Regulation of secretion A single releasing factor (decapeptide designated *GnRH*) is produced by the hypothalamus which stimulates synthesis and release of both FSH and LH from pituitary. It is, therefore, also referred to as *FSH/LH-RH* or simply *LHRH* or *gonadorelin*. It has been difficult to explain how hypothalamus achieves a divergent pattern of FSH and LH secretion in menstruating women through a single releasing hormone. Since GnRH is secreted in pulses and the frequency as well as amplitude of the pulses differs during follicular (high frequency, low amplitude) and luteal (lower frequency, higher amplitude) phases, it is considered that frequency and amplitude of GnRH pulses determines whether FSH or LH or both will be secreted, as well as the amount of each. Further, the feedback regulation of FSH and LH may be different. In general, feedback inhibition of LH is more marked than that of FSH. In addition there are other regulatory substances, e.g. *Inhibin*—a peptide from ovaries and testes, selectively inhibits FSH release, but not LH release. *Dopamine* inhibits only LH release. Testosterone is weaker than estrogens in inhibiting Gn secretion, but has effect on both FSH and LH. GnRH acts on gonadotropes through a G-protein coupled receptor which acts by increasing intracellular Ca^{2+} through PIP_2 hydrolysis.

The Gn secretion increases at puberty and is higher in women than in men. In men, the levels of FSH and LH remain practically constant (LH > FSH) while in menstruating women they fluctuate cyclically. During the follicular phase, moderate levels of FSH and low levels of LH prevail. There is a midcycle surge of both, but more of LH, just before ovulation, followed by progressive fall during the luteal phase. Gn levels are high in menopausal women due to loss of feedback inhibition by sex steroids and inhibin.

Pathological involvement Disturbances of Gn secretion from pituitary may be responsible for delayed puberty or precocious puberty in girls as well as in boys.

Inadequate Gn secretion results in amenorrhoea and sterility in women; oligozoospermia, impotence and infertility in men. Excess production of Gn in adult women causes polycystic ovaries.

Preparations

All earlier gonadotropin preparations were administered by i.m. route. The newer more purified preparations can be given s.c. They are partly metabolized, but mainly excreted unchanged in urine: t½ 2–6 hours.

1. *Menotropins (FSH + LH):* is a preparation obtained from urine of menopausal women:
PREGNORM, PERGONAL, GYNOGEN 75/150; 75 IU FSH + 75 IU LH activity per amp, also 150 IU FSH + 150 IU LH per amp.

2. *Urofollitropin or Menotropin (pure FSH):* METRODIN, FOLGEST, FOLICULIN, PUREGON 75 IU and 150 IU per amp. This preparation has been preferred over the combined FSH + LH preparation for induction of ovulation in women with polycystic ovarian disease. These patients have elevated LH/FSH ratio; use of FSH alone is considered advantageous. This preparation is also claimed to improve chances of obtaining good quality ova for *in vitro* fertilization.

3. *Human chorionic gonadotropin (hCG):* is derived from urine of pregnant women.

CORION, PROFASI, PUBERGEN 1000 IU, 2000 IU, 5000 IU, 10,000 IU, all as dry powder with separate solvent for injection.

The foetal placenta secretes hCG which is absorbed in maternal circulation and maintains corpus luteum of pregnancy. It is a glycoprotein with 33% sugar and 237 amino acids in two chains, MW 38000. It is excreted in urine by the mother from which it is commercially obtained. hCG binds to LH receptor with equal avidity; action of hCG is indistinguishable from that of LH.

Recombinant human FSH (rhFSH or *Follitropin* α and *follitropin* β) and recombinant human LH (rhLH or *Lutropin*) as well as recombinant hCG (rhCG or *Choriogonadotropin* α) have been produced. These are more purified and have vertually replaced the urine derived preparations in the developed countries. They are more expensive. Lutropin (rhLH) has been withdrawn.

Uses

1. *Amenorrhoea and infertility* Exogenous Gns may help when amenorrhoea/infertility is due to deficient production of Gns by pituitary. Gns are generally tried when attempts to induce ovulation with clomiphene have failed or when nonovulation is due to polycystic ovaries. Several protocols for use of Gns have been employed, one of which is to give 1 injection of menotropins (75 IU FSH + 75 IU LH or 75 IU pure FSH)) i.m. daily for 10 days followed the next day by 10,000 IU of hCG. Ovulation occurs within the next 24–48 hours in upto 75% cases and the woman may conceive if inseminated at this time. However, rates of abortion and multiple pregnancy are high, but not of teratogenesis.

To improve the predictability of time of *ovulation* (*controlled ovarian stimulation*), it is the standard practice now to concurrently suppress endogenous FSH/LH secretion either by continuous pretreatment with a superactive GnRH agonist or by a GnRH antagonist.

2. *To aid in vitro fertilization* Menotropins (FSH + LH or pure FSH) is used along the GnRH agonist/antagonist (for suppressing endogenous FSH/LH) to induce simultaneous maturation of several ova and to precisely time ovulation so as to facilitate their harvesting for assisted reproductive techniques.

3. *Male hypogonadotropic hypogonadism* It manifests as delayed puberty or defective spermatogenesis producing oligozoospermia and male sterility. Generally, sexual maturation is induced by androgens and therapy with hCG is started when fertility is desired. Start with hCG i.m. 2–3 times a week (to stimulate testosterone secretion), add FSH 75 IU + LH 75 IU after 3–4 months (to stimulate spermatogenesis) and reduce dose of hCG. Treatment is continued for 6–12 months for optimum results, which nevertheless are not always impressive.

4. *Cryptorchidism* A 2–6 weeks course of hCG was used to treat undescended testes in early childhood. However, this is not practiced now due to poor efficacy, risk of precocious puberty and other concerns. Surgical correction is the preferred modality.

Adverse effects and precautions

Ovarian hyperstimulation syndrome is the most serious complication. Polycystic ovary, pain in lower abdomen and even ovarian bleeding and shock can occur in females during ovulation induction.

Multiple pregnancy is another complication.

Precocious puberty is a risk when given to children.

Allergic reactions have occurred and skin tests are advised. Hormone dependent malignancies (prostate, breast) must be excluded.

Other side effects are edema, headache, mood changes.

GONADOTROPIN RELEASING HORMONE (GnRH) (GONADORELIN)

Synthetic human GnRH (gonadorelin) injected i.v. (100 μg) induces prompt release of LH and FSH followed by elevation of gonadal steroid levels. It has a short plasma t½ (4–8 min) due to rapid enzymatic degradation. It has been used for testing pituitary-gonadal axis in male as well as female hypogonadism.

Only pulsatile exposure to GnRH induces FSH/LH secretion, while sustained exposure desensitizes the pituitary gonadotropes resulting in loss of Gn release. Therapy with GnRH is not useful in the treatment of hypogonadism.

Superactive/long-acting GnRH agonists

Many analogues of GnRH, e.g. Goserelin, Leuprolide, Nafarelin, Triptorelin, have been developed which are 15–150 times more potent than natural GnRH and longer acting (t½ 2–6 hours) because of high affinity for GnRH receptor and resistance to enzymatic hydrolysis. Because physiological release of GnRH is in pulses, whereas these agonists act continuously; they only initially trigger Gn secretion. After 1–2 weeks they cause desensitization and down regulation of GnRH receptors causing inhibition of FSH and LH secretion followed by suppression of gonadal function. Spermatogenesis or ovulation cease and testosterone or estradiol levels fall to castration levels. Recovery occurs within 2 months of stopping treatment.

The superactive GnRH agonists are used as nasal spray or injected s.c/i.m. Long-acting preparations for once a month s.c. injection have been produced (triptorelin, goserelin depot). The resulting reversible pharmacological oophorectomy/orchidectomy is being used in *precocious puberty*, *prostatic carcinoma*, *endometriosis*, *premenopausal breast cancer*, *uterine leiomyoma*, *polycystic ovarian disease* and to *assist induced ovulation*. They also have potential to be used as contraceptive for both males and females.

Menopausal symptoms, *viz.* headache, sweating, hot flashes, mood changes, vaginal dryness amenorrhoea and loss of libido can occur due to suppression of ovarian function. Use of GnRH agonists for more than 6 months carries risk of developing osteoporosis.

Nafarelin This long-acting GnRH agonist is 150 times more potent than native GnRH. It is used as intranasal spray from which bioavailability is only 4–5%.

NASAREL 2 mg/ml soln for nasal spray; 200 µg per actuation.

Down regulation of pituitary GnRH receptors occurs in10 days but peak inhibition of Gn release occurs at one month. It is broken down in the body to shorter peptide segments; plasma t½ is 2–3 hours. Uses are:

Assisted reproduction: Endogenous LH surge needs to be suppressed when controlled ovarian stimulation is attempted by exogenous FSH and LH injection, so that precisely timed mature oocytes can be harvested. This is achieved by 400 µg BD intranasal nafarelin, reduced to 200 µg BD when menstrual bleeding occurs.

Uterine fibroids: Nafarelin 200 µg BD intranasal for 3–6 months can reduce the size of leiomyoma and afford symptomatic relief.

Endometriosis: 200 µg in alternate nostril BD for upto 6 months. It is as effective as danazol, but second course cannot be given due to risk of osteoporosis.

Central precocious puberty: 800 µg BD by nasal spray; breast and genital development is arrested in girls and boys. Treatment is generally carried out till the age of 11 years in girls or 12 years in boys. The effect is reversible; pubertal changes resume when therapy is discontinued.

Adverse effects: Hot flashes, loss of libido, vaginal dryness, osteoporosis, emotional lability.

Goserelin Another long-acting GnRH agonist available as a depot s.c./i.m. injection to be used both for endogenous Gn suppression before ovulation induction, as well as for endometriosis, carcinoma prostate, etc. To achieve pituitary desensitization before ovulation induction with exogenous Gns; 3.6 mg of depot goserelin injection is given once in the anterior abdominal wall 1–3 weeks earlier.

For *endometriosis and carcinoma prostate* 3.6 mg is injected in the same way every 4 weeks or 10.8 mg is injected every 3 months. An androgen antagonist (bicalutamide) is given concurrently for 3–4 weeks when goserelin is used for carcinoma prostate. This is needed to block the effect of androgen secreted under the influence of enhanced Gn production by initial agonistic action of the GnRH agonist on gonadotropes.

ZOLADEX 3.6 mg prefilled syringe, ZOLDEX L-A 10.8 mg vial depot injection.

Triptorelin: This long acting GnRH agonist is formulated as a regular release daily s.c. injection for short term indications, such as female infertility, and as a depot i.m. monthly injection for long-term Gn suppression in the treatment of carcinoma prostate, endometriosis, precocious puberty and uterine leiomyoma. For prostate cancer, it is combined with an androgen antagonist flutamide or bicalutamide to prevent the initial flare up of the tumour that occurs due to increase in Gn secretion for the first 1–2 weeks.

Fibroids, endometriosis, carcinoma prostate: 3.75–7.5 mg i.m. every 4 weeks.

Precocious puberty: 50 µg/kg i.m. of depot inj. every 4 weeks.

Assisted reproduction: 0.1 mg s.c. daily for 10 days from 2nd day of cycle.

DECAPEPTYL DAILY 0.1 mg inj., DECAPEPTYL DEPOT 3.75 mg inj.

Leuprolide This long acting GnRH agonist is injected s.c./i.m. daily or as a depot injection once a month for palliation of carcinoma prostate alongwith an androgen antagonist, as well as for other conditions needing long term Gn suppression. Daily s.c. injections are also used for assisted reproduction.

LUPRIDE 1 mg inj., 3.75 mg depot inj., PROGTASE 1 mg/ml inj.

GnRH antagonists Four analogues of GnRH, *Ganirelix*, *Cetrorelix*, *Degarelix* and *Abarelix* which are more extensively substituted act as GnRH receptor antagonists. They inhibit Gn secretion without causing initial stimulation. *Ganirelix* and *Cetrorelix* are relatively short acting. Administered daily by s.c. injection, they are approved for inhibiting LH surges during controlled ovarian stimulation in women undergoing *in vitro* fertilization. Their advantages over long-acting GnRH agonists include:

- They produce quick Gn suppression by competitive antagonism, and need to be started only from 6th day of attempting ovarian stimulation with Gns.
- They carry a lower risk of ovarian hyperstimulation syndrome.
- They achieve more complete suppression of endogenous Gn secretion.

However, pregnancy rates are similar or may even be lower.

Degarelix and *Abarelix* are long acting GnRH antagonists, approved for androgen withdrawal therapy of advanced carcinoma prostate.

THYROID STIMULATING HORMONE (TSH, THYROTROPIN)

It is a 210 amino acid, two chain glycoprotein (22% sugar), MW 30000.

Physiological function TSH stimulates thyroid to synthesize and secrete thyroxine (T_4) and triiodothyronine (T_3) (*see* Fig. 18.1). Its actions are:

- Induces hyperplasia and hypertrophy of thyroid follicles and increases blood supply to the gland.
- Promotes trapping of iodide into thyroid by increasing Na^+: Iodide symporter (NIS).
- Promotes organification of trapped iodine and its incorporation into T_3 and T_4 by increasing peroxidase activity.
- Enhances endocytotic uptake of thyroid colloid by the follicular cells and proteolysis of thyroglobulin to release more of T_3 and T_4. This action starts within minutes of TSH administration.

The TSH receptor present on thyroid cells is a GPCR which utilizes the adenylyl cyclase-cAMP transducer mechanism (by coupling to Gs protein) to produce its effects. In human thyroid cells high concentration of TSH also induces PIP_2 hydrolysis by the linking of TSH receptor to Gq protein. The resulting increase in cytosolic Ca^{2+} and protein kinaseC activation may also mediate TSH action, particularly generation of H_2O_2 needed for oxidation of iodide and iodination of tyrosil residues.

Regulation of secretion Synthesis and release of TSH by pituitary is controlled by hypothalamus primarily through TRH (*see* Fig. 18.3), while somatostatin inhibits TSH secretion. The TRH receptor on pituitary thyrotrope cells is a GPCR which is linked to Gq protein and activates PLC–IP_3/DAG–cytosolic Ca^{2+} pathway to enhance TSH synthesis and release. The negative feedback for inhibiting TSH secretion is provided by the thyroid hormones which act primarily at the level of the pituitary, but also in the hypothalamus.

Pathological involvement Only few cases of hypo- or hyperthyroidism are due to inappropriate TSH secretion. In majority of cases of myxoedema TSH levels are markedly elevated because of deficient feedback inhibition. Graves' disease is due to an immunoglobulin of the IgG class which attaches to the thyroid cells and stimulates them in the same way as TSH. Consequently, TSH levels are low.

Use Thyrotropin has no therapeutic use. Thyroxine is the drug of choice even when hypothyroidism is due to TSH deficiency. The diagnostic application is to differentiate myxoedema due to pituitary dysfunction from primary thyroid disease.

ADRENOCORTICOTROPIC HORMONE (ACTH, CORTICOTROPIN)

It is a 39 amino acid single chain peptide, MW 4500, derived from a larger peptide *pro-opio melanocortin* (MW 30,000) which also gives rise to endorphins, two lipotropins and two MSHs.

Physiological function ACTH promotes steroidogenesis in adrenal cortex by stimulating cAMP formation in cortical cells (through specific cell surface GPCRs). This inturn rapidly increases the availability of cholesterol for conversion to pregnenolone which is the rate limiting step in the production of gluco, mineralo and weakly androgenic steroids (*see* Fig. 20.1). Induction of steroidogenic enzymes occurs after a delay resulting in 2nd phase ACTH action. The stores of adrenal steroids are very limited and rate of synthesis primarily governs the rate of release. ACTH also exerts trophic influence on adrenal cortex (again through cAMP): high doses cause hypertrophy and hyperplasia. Lack of ACTH results in adrenal atrophy. However, zona glomerulosa is little affected because angiotensin II also exerts trophic influence on this layer and sustains aldosterone secretion.

Regulation of secretion Hypothalamus regulates ACTH release from pituitary through corticotropin-releasing hormone (CRH). The CRH receptor on corticotropes is also a GPCR which increases ACTH synthesis as well as release by raising cytosolic cAMP. Secretion of ACTH has a circadian rhythm. Peak plasma levels occur in the early morning, decrease during day and are lowest at midnight. Corticosteroids exert inhibitory feedback influence on ACTH production by acting directly on the pituitary as well as indirectly through hypothalamus.

A variety of stressful stimuli, e.g. trauma, surgery, severe pain, anxiety, fear, blood loss, exposure to cold, etc. generate neural impulses which converge on median eminence to cause elaboration of CRH. The feedback inhibition appears to be overpowered during stress—rise in ACTH secretion continues despite high plasma level of cortisol induced by it.

Pathological involvement Excess production of ACTH from basophil pituitary tumours is responsible for some cases of Cushing's syndrome. Hypocorticism occurs in pituitary insufficiency due to low ACTH production. Iatrogenic suppression of ACTH secretion and pituitary adrenal axis is the most common form of abnormality encountered currently due to the use of pharmacological doses of glucocorticoids in nonendocrine diseases.

Use ACTH is used rarely for the diagnosis of disorders of pituitary adrenal axis. Direct assay of plasma ACTH level is now preferred.

For therapeutic purposes, ACTH does not offer any advantage over corticosteroids.

Chapter 18 Thyroid Hormones and Thyroid Inhibitors

THYROID HORMONES

The thyroid gland secretes 3 hormones—thyroxine (T_4), triiodothyronine (T_3) and calcitonin. The former two are produced by thyroid follicles, have similar biological activity and the term 'thyroid hormone' is restricted to these only. *Calcitonin* produced by interfollicular 'C' cells is chemically and biologically entirely different. It is considered along with parathormone (*see* Ch. 24) with which it regulates calcium metabolism.

The physiological significance of thyroid gland was recognized only after Graves and Basedow (1835, 1840) associated the clinical features of the 'Graves' disease' with swelling of thyroid gland and Gull (1874) correlated myxoedema with its atrophy. Kendall (1915) obtained crystalline thyroxine and postulated its chemical formula which was confirmed in 1926. Thyroxine was the first hormone to be synthesized in the laboratory. Since T_4 could not account for all the biological activity of thyroid extract, search was made and more potent T_3 was discovered in 1952.

Chemistry and Synthesis

Both T_4 and T_3 are iodine containing derivatives of *thyronine* which is a condensation product of two molecules of the amino acid *tyrosine*. *Thyroxine* is 3, 5, 3′, 5′–tetraiodothyronine while T_3 is 3, 5, 3′ triiodothyronine.

The thyroid hormones are synthesized and stored in the thyroid follicles as part of *thyroglobulin* molecule—which is a glycoprotein synthesized by thyroid cells, MW 660 KDa, contains 10% sugar. The synthesis, storage and release of T_4 and T_3 is summarized in Fig. 18.1 and involves the following processes.

1. *Iodide uptake* The total body content of I_2, obtained from food and water, is 30–50 mg, out of which about 1/5 is present in the thyroid. Concentration of iodide in blood is low (0.2–0.4 µg/dl) but thyroid cells have an active transport process Na^+: *iodide symporter (NIS)* to concentrate this anion; this trapping is stimulated by thyroid stimulating hormone (TSH) to exceed a gradient of more than 100 fold by inducing and activating NIS. The I_2 content of thyroid gland somehow regulates the uptake mechanism: meagre store activating and large store inhibiting it. The iodide concentrating mechanism is not peculiar to thyroid. Skin, salivary glands, gastric mucosa, intestine, mammary glands and placenta also possess it, but uptake in these organs is not stimulated by TSH.

2. *Oxidation and iodination* Iodide trapped by follicular cells is carried across the apical membrane by another transporter termed '*pendrin*' and oxidized by the membrane bound thyroid peroxidase enzyme to iodinium (I^+) ions or hypoiodous acid (HOI) or enzyme-linked hypoiodate (E-OI) with the help of H_2O_2. These forms of iodine combine avidly with tyrosil residues of thyroglobulin, apparently without any enzymatic intervention, to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) while these residues are still attached to the thyroglobulin chains.

3. *Coupling* Pairs of iodinated tyrosil residues couple together (Fig. 18.2) to form T_3 and T_4.

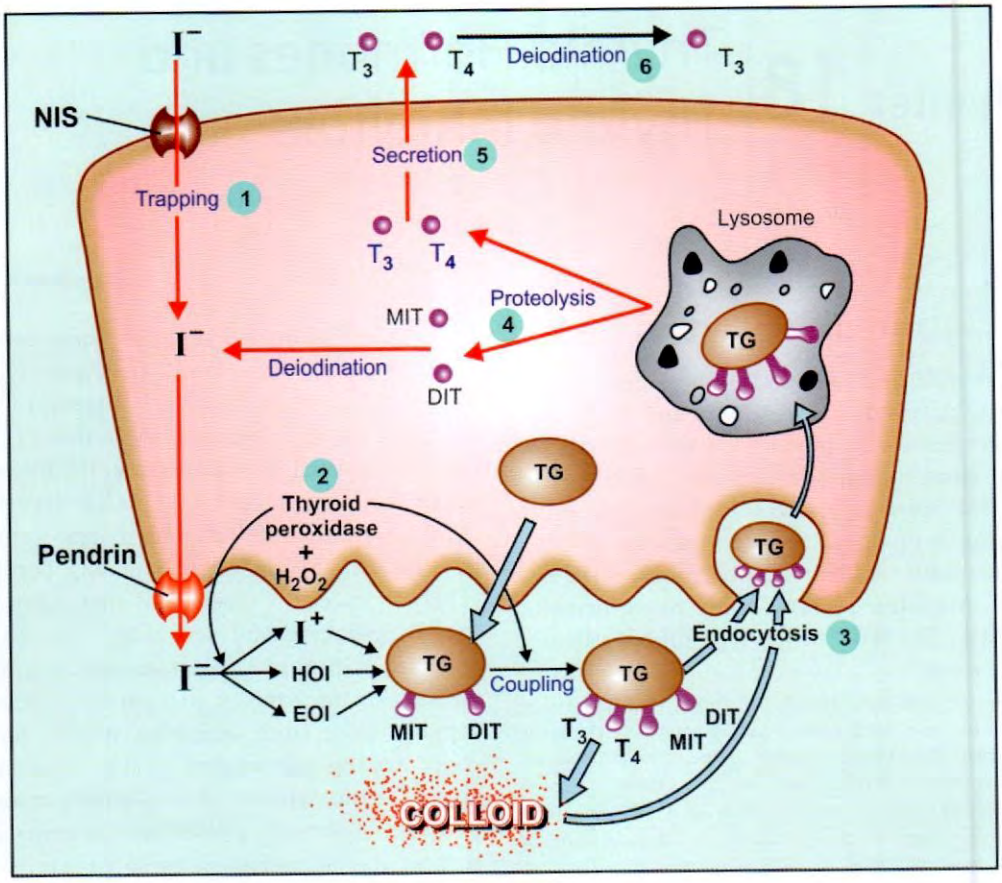


Fig. 18.1: Synthesis, storage and secretion of thyroid hormone
TG—Thyroglobulin; MIT—Monoiodotyrosine; DIT—Diiodotyrosine; T_3—Triiodothyronine; T_4—Thyroxine (Tetraiodothyronine); HOI—Hypoiodous acid; EOI—Enzyme linked hypoiodate; NIS—Na^+-iodide symporter; Thyroid-stimulating hormone (TSH) activates steps 1, 2, 3, 4, and 5; Ionic inhibitors block step 1; Excess iodide interferes with steps 1, 2, 3 and 5 with primary action on step 3 and 5; Propylthiouracil inhibits steps 2 and 6; Carbimazole inhibits step 2 only

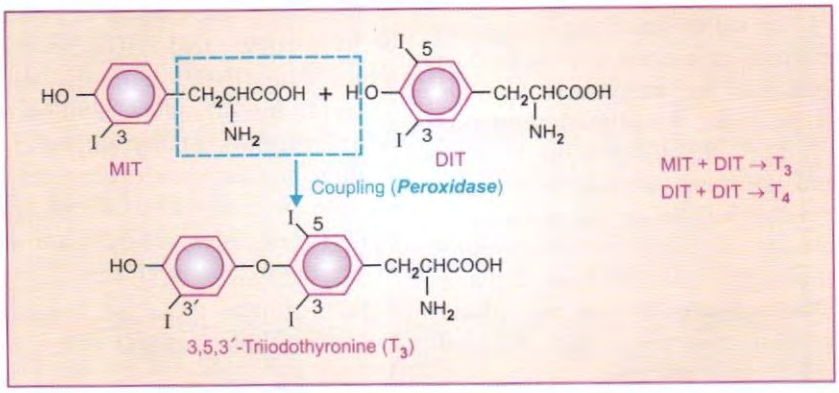


Fig. 18.2: Coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT) to produce triiodothyronine (T_3)

Normally much more T_4 than T_3 is formed, but during I_2 deficiency relatively more MIT is available and a greater proportion of T_3 is formed. The result is—more active hormone is generated with lesser amount of I_2.

Coupling is an oxidative reaction and is catalysed by the same thyroid peroxidase. Thyroglobulin is the most efficient protein, compared to other similar proteins, in supporting coupling by providing favourable spatial configuration to facilitate the reaction. Oxidation of iodide and coupling are both stimulated by TSH.

4. *Storage and release* Thyroglobulin containing iodinated tyrosil and thyronil residues is transported to the interior of the follicles and remains stored as thyroid colloid till it is taken back into the cells by endocytosis and broken down by lysosomal proteases. The T_4 and T_3 so released is secreted into circulation while MIT and DIT residues are deiodinated and the iodide released is reutilized. The uptake of colloid and proteolysis are stimulated by TSH: the quiscent gland has follicles distended with colloid and cells are flat or cubical, while the TSH stimulated gland has columnar cells and colloid virtually disappears.

Normal human thyroid secretes 60–90 µg of T_4 and 10–30 µg of T_3 daily.

5. *Peripheral conversion of T_4 to T_3* Peripheral tissues, especially liver and kidney, convert T_4 to T_3. About 1/3 of T_4 secreted by thyroid undergoes this change and most of the T_3 in plasma is derived from liver. Target tissues take up T_3 from circulation for their metabolic need, except brain and pituitary which take up T_4 and convert it to T_3 within their own cells. Almost equal amounts of 3, 5, 3′ triiodothyronine (normal T_3 : active) and 3, 3′, 5′ triiodothyronine (reverse T_3 or rT_3: inactive) are produced in the periphery. The T_4 to T_3 conversion is carried out by the enzyme *iodothyronine deiodinase* which exists in 3 forms (D1, D2, D3). These forms differ in their organ and cellular localization as well as in the product formed. Whereas type 2 deiodinase (D2) generates T_3 and D3 generates rT_3, the D1 form generates both T_3 and rT_3. The antithyroid drug propylthiouracil (but not carbimazole) inhibits Type1 deiodinase and the antiarrhythmic amiodarone inhibits both D1 and D2 forms. Propranolol (high dose) and glucocorticoids also inhibit peripheral conversion of T_4 to T_3 (except in brain and in pituitary).

Transport, Metabolism and Excretion

Thyroid hormones are avidly bound to plasma proteins—only 0.03–0.08% of T_4 and 0.2–0.5% of T_3 are in the free form. Almost all protein bound iodine (PBI) in plasma is thyroid hormone, of which 90–95% is T_4 and the rest T_3. Binding occurs to 3 plasma proteins in the following decreasing order of affinity for T_4:

(i) Thyroxine binding globulin (TBG)
(ii) Thyroxine binding prealbumin (trans-thyretin)
(iii) Albumin

The normal concentration of PBI is 4–10 µg/dl; only 0.1–0.2 µg/dl of this is T_3, rest is T_4. During pregnancy thyroxine binding globulin is increased—PBI levels are elevated, but there is no effect on thyroid status because the concentration of free hormone remains unaltered.

Only the free hormone is available for action as well as for metabolism and excretion. Metabolic inactivation of T_4 and T_3 occurs by deiodination and glucuronide or sulfate conjugation of the hormones as well as that of their deiodinated products. Liver is the primary site (also salivary glands and kidneys). The conjugates are excreted in bile, of which a significant fraction is deconjugated in intestines and reabsorbed (enterohepatic circulation) to be finally excreted in urine.

Plasma t½ of T_4 is 6–7 days, while that of T_3 is 1–2 days. The half-lives are shortened in hyperthyroidism and prolonged in hypothyroidism due respectively to faster and slower metabolism.

Regulation of Secretion

The secretion of hormones from the thyroid is controlled by anterior pituitary by the elaboration of TSH, while TSH secretion itself is

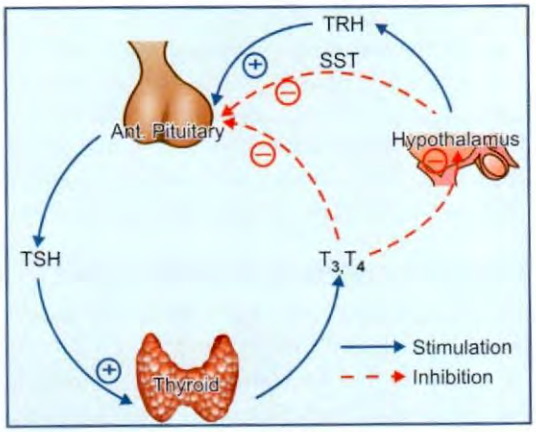


Fig. 18.3: Regulation of thyroid function
TSH—Thyroid stimulating hormone; TRH—Thyrotropin releasing hormone; T_3—Triiodothyronine; T_4—Thyroxine; SST—Somatostatin

regulated by TRH produced in hypothalamus (*see* p. 265). Somatostatin elaborated by hypothalamus inhibits not only GH and prolactin, but also TSH secretion from pituitary. The relation between thyroid, anterior pituitary and hypothalamus is depicted in Fig. 18.3. The negative feedback by the thyroid hormones is exercised directly on the pituitary as well as through hypothalamus. The action of TRH on pituitary and that of TSH on thyroid cells is mediated by enhanced cAMP synthesis. High concentration of TSH also acts *via* IP_3/DAG–increased intracellular Ca^{2+} pathway in the thyroid cells.

The blood iodine level and iodine content of thyroid also regulate thyroid function (*see* p. 277).

Actions

The actions of T_4 and T_3 are qualitatively similar and are nicely depicted in the features of hypo- and hyperthyroidism. They affect the function of practically every body cell.

1. *Growth and development* T_4 and T_3 are essential for normal growth and development. The most remarkable action is metamorphosis of tadpole to frog: the tail is used-up to build lungs, limbs and other organs. The actions cannot be broadly labelled as catabolic or anabolic, and are exerted through a critical control of protein synthesis in the translation of the genetic code. Congenital deficiency of thyroid hormone resulting in cretinism emphasizes its importance. The milestones of development are delayed and practically every organ and tissue of the body suffers. The greatest sufferer, however, is the nervous system. Retardation and nervous deficit is a consequence of paucity of axonal and dendritic ramification, synapse formation and impaired myelination. In adult hypothyroidism also, intelligence is impaired and movements are slow.

2. *Intermediary metabolism* Thyroid hormones have marked effect on lipid, carbohydrate and protein metabolism.

Lipid T_4 and T_3 indirectly enhance lipolysis by potentiating the action of catecholamines and other lipolytic hormones. As a result plasma free fatty acid levels are elevated. Lipogenesis is also stimulated. All phases of cholesterol metabolism are accelerated, but its conversion to bile acids dominates. Thus, hyperthyroidism is characterized by hypocholesterolemia. Plasma LDL levels are reduced.

Carbohydrate Carbohydrate metabolism is also stimulated. Though utilization of sugar by tissues is increased (mainly secondary to increased BMR), glycogenolysis and gluconeogenesis in liver as well as faster absorption of glucose from intestines more than compensate it producing hyperglycaemia and a diabetic-like state with insulin resistance in hyperthyroidism.

Protein Synthesis of certain proteins is increased, but the overall effect of T_3 is catabolic—increased amounts of protein being used as energy source. Prolonged action results in negative nitrogen balance and tissue wasting. Weight loss is a feature of hyperthyroidism. T_3, T_4 inhibit mucoprotein synthesis which so characteristically accumulates in myxoedema.

3. *Calorigenesis* T_3 and T_4 increase BMR by stimulation of cellular metabolism and resetting of the energystat. This is important

for maintaining body temperature. However, metabolic rate in brain, gonads, uterus, spleen and lymph nodes is not significantly affected. The mechanism of calorigenesis was believed to be uncoupling of oxidative phosphorylation: excess energy being released as heat. However, this occurs only at very high doses and is not involved in mediating the physiological actions of T_3, T_4.

4. *CVS* T_3 and T_4 cause a hyperdynamic state of circulation which is partly secondary to increased peripheral demand and partly due to direct cardiac actions. Heart rate, contractility and output are increased resulting in a fast, bounding pulse. T_3 and T_4 stimulate heart by direct action on contractile elements (increasing the myosin fraction having greater Ca^{2+} ATPase activity) as well as by up regulation of β adrenergic receptors. Atrial fibrillation and other irregularities are common in hyperthyroidism. Thyroid hormones can also precipitate CHF and angina. BP, specially systolic, is often raised. Myocardial O_2 consumption can be markedly reduced by induction of hypothyroidism.

5. *Nervous system* T_3, T_4 have profound functional effect on CNS. Mental retardation is the hallmark of cretinism; sluggishness and other behavioral features are seen in myxoedema. Hyperthyroid individuals are anxious, nervous, excitable, exhibit tremors and hyperreflexia.

6. *Skeletal muscle* Muscles are flabby and weak in myxoedema, while thyrotoxicosis produces increased muscle tone, tremor and weakness due to myopathy.

7. *GIT* Propulsive activity of gut is increased by T_3/T_4. Hypothyroid patients are often constipated, while diarrhoea is common in hyperthyroidism.

8. *Kidney* T_3 and T_4 do not cause diuresis in euthyroid individuals, but the rate of urine flow is often increased when myxoedematous patients are treated with it.

9. *Haemopoiesis* Hypothyroid patients suffer from some degree of anaemia which is restored only by T_4 treatment. Thus, T_4 appears to be facilitatory to erythropoiesis.

10. *Reproduction* Thyroid has an indirect effect on reproduction. Fertility is impaired in hypothyroidism and women suffer from oligomenorrhoea. Normal thyroid function is required for maintenance of pregnancy and lactation.

Mechanism of action

Both T_3 and T_4 penetrate cells by active transport and produce majority of their actions by combining with a nuclear thyroid hormone receptor (TR) which belongs to the steroid and retinoid superfamily of intracellular receptors.

Two TR isoform families (TRα and TRβ) have been identified. Both bind T_3 and function in similar manner, but their tissue distribution differs, which may account for quantitative differences in the sensitivity of different tissues to T_3.

In contrast to the steroid receptor, the TR resides in the nucleus even in the unliganded inactive state. It is bound to the *'thyroid hormone response element'* (TRE) in the enhancer region of the target genes along with corepressors (Fig. 18.4). This keeps gene transcription suppressed. When T_3 binds to the ligand-binding domain of TR, it heterodimerizes with retinoid X receptor (RXR) and undergoes a conformation change releasing the corepressor and binding the coactivator. This induces gene transcription followed by production of specific mRNA and a specific pattern of protein synthesis which produces the various metabolic and anatomic effects. The expression of certain genes is repressed by T_3. In their case, the unliganded TR allows gene transcription, while binding of T_3 to TR halts the process.

Many of the effects of T_3 e.g. tachycardia, arrhythmias, raised BP, tremor, hyperglycaemia are mediated, at least partly, by sensitization of adrenergic receptors to catecholamines. Induction of adenylyl cyclase, proliferation of β adrenoceptors and a better coupling between these two has been demonstrated.

Apart from the nuclear T_3 receptor, other sites of thyroid hormone action have been described. It acts on cell membrane to enhance amino acid and glucose entry and on mitochondria to increase oxygen consumption. At these sites T_4 appears to be equipotent to T_3, while at the nuclear receptor T_4 has much lower affinity. Moreover, even on binding to the TR, T_4 does not promote gene transcription.

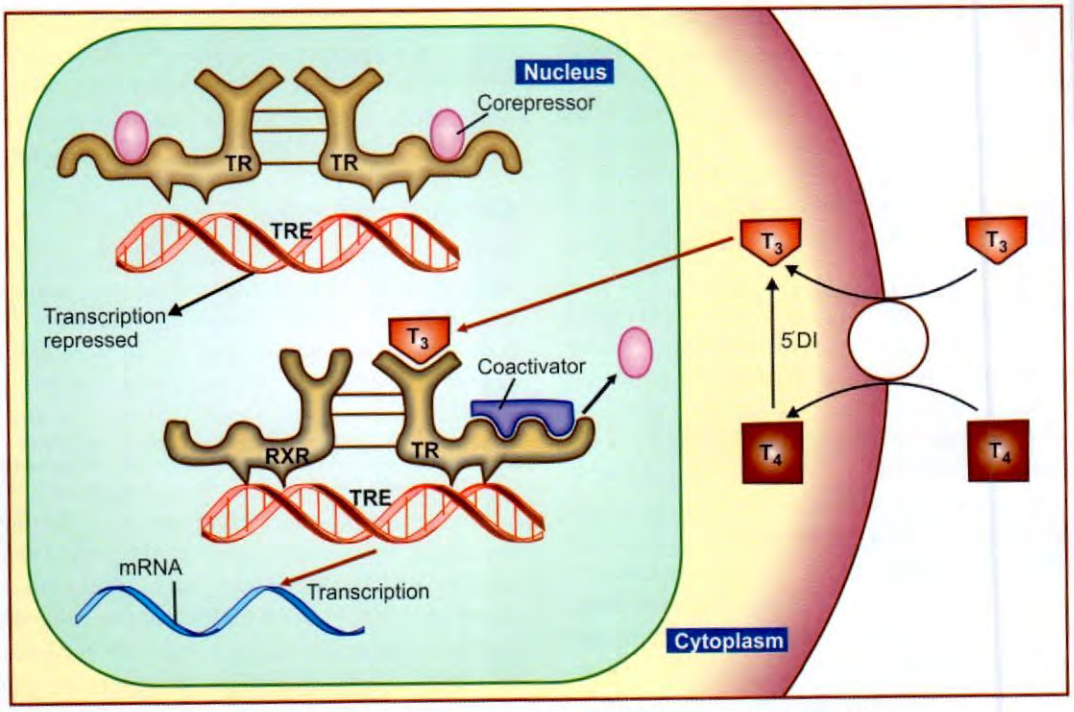


Fig. 18.4: Mechanism of action of thyroid hormone on nuclear thyroid hormone receptor (TR)
T_3—Triiodothyronine; T_4—Thyroxine; TRE—Thyroid hormone response element; RXR—Retinoid X receptor; mRNA—Messenger ribonucleic acid; 5'DI—5'Deiodinase (See text for explanation)

SECTION 5

Relation between T_4 and T_3

- Thyroid secretes more T_4 than T_3, but in iodine deficient state this difference is reduced.
- T_4 is the major circulating hormone because it is 15 times more tightly bound to plasma proteins.
- T_3 is 5 times more potent than T_4 and acts faster. Peak effect of T_3 comes in 1–2 days while that of T_4 takes 6–8 days.
- T_3 is more avidly bound to the nuclear receptor than T_4 and the T_4-receptor complex is unable to activate/derepress gene transcription.
- About 1/3 of T_4 is converted to T_3 in the thyroid cells, liver and kidney by type 1 deiodinase (D1) and released into circulation. In addition, T_3 is generated within the target cells (skeletal muscle, heart, brain, pituitary) by another type (D2) of deiodinase.

Thus, it may be concluded that T_3 is the active hormone, while T_4 is mainly a transport form which functions as a prohormone of T_3. However, it may directly produce some non-genomic actions.

Preparations

l-thyroxine sod. (synthetic levothyroxine sod.): ELTROXIN 25 µg, 50 µg, 100 µg tabs, ROXIN 100 µg tab, THYRONORM 12.5 µg, 25 µg, 50 µg, 62.5 µg, 75 µg, 88 µg, 100 µg, 112 µg, 125 µg, 137 µg, 150 µg tabs, THYROX 25 µg, 50 µg, 75 µg, 100 µg tabs. An injectable preparation for i.v. use is available elsewhere.

Triiodothyronine (Liothyronine) is not freely available in India. It is occasionally used i.v. along with l-thyroxine in myxoedema coma.

Clinically, l-thyroxine is preferred over liothyronine for routine as well as urgent indications, because of more sustained and uniform action as well as lower risk of cardiac arrhythmias.

Pharmacokinetics and interactions

Oral bioavailability of l-thyroxine is ~ 75%, but severe hypothyroidism can reduce oral absorption. It should be administered in empty stomach to avoid interference by food. Sucralfate, iron, calcium and proton pump inhibitors also reduce l-thyroxine absorption. CYP3A4 inducers like rifampin, phenytoin and carbamazepine

accelerate metabolism of T_4; dose of l-thyroxine may need enhancement.

Uses

The most important use of thyroid hormone is for *replacement therapy* in deficiency states. Synthetic l-thyroxine is the preparation of choice:

1. *Cretinism* It is either due to failure of thyroid development or a defect in hormone synthesis (sporadic cretinism) or due to extreme iodine deficiency (endemic cretinism). Cretinism is usually detected during infancy or childhood; but screening of neonates is the best preventive strategy. Treatment with thyroxine (8–12 µg/kg) daily should be started as early as possible, because mental retardation that has already ensued is only partially reversible. Response is dramatic: physical growth and development are restored and further mental retardation is prevented.

2. *Adult hypothyroidism* (Myxoedema) This is one of the commonest endocrine disorders which develops as a consequence of autoimmune thyroiditis or thyroidectomy. It may accompany simple goiter if iodine deficiency is severe. Antibodies against thyroid peroxidase or thyroglobulin are responsible for majority of cases of adult hypothyroidism. Important drugs that can cause hypothyroidism are ^{131}I, iodides, lithium and amiodarone.

Treatment with T_4 is most gratifying. Though in younger patients, full replacement doses may be started from the beginning, in those >50 years it is wise to start with a lower dose (50 µg/day), while in the elderly or in those with heart disease, the initial dose should be 12.5–25 µg/day. Doses may be increased every 2–3 weeks to an optimum of 100–150 µg/day (adjusted by clinical response as well as serum TSH and free T_4 levels). Further dose adjustments are made at 4–6 week intervals needed for reaching steady-state. Individualization of proper dose is critical, aiming at normalization of serum TSH levels. Increase in dose is mostly needed during pregnancy.

Subclinical hypothyroidism characterized by euthyroid status and normal free serum thyroxine (FT_4) level (≥ 9 pmol/L) but raised TSH level (>10 mU/L) should be treated with T_4. For TSH level between 6–10 mU/L, replacement therapy is optional. Replacement is preferable if patient has other cardiovascular risk factors.

3. *Myxoedema coma* It is an emergency; characterized by progressive mental deterioration due to acute hypothyroidism: carries significant mortality. Rapid thyroid replacement is crucial. Though liothyronine (T_3) acts faster, its use is attended by higher risk of cardiac arrhythmias, angina, etc. Drug of choice is l-thyroxine (T_4) 200–500 µg i.v. followed by 100 µg i.v. OD till oral therapy can be instituted. Some authorities recommend adding low dose i.v. T_3 10 µg 8 hourly in younger patients with no arrhythmia or ischaemia. Alternatively oral T_4 500 µg loading dose followed by 100–300 µg daily may be used, but in severe hypothyroidism, oral absorption is delayed and inconsistent.

Other essential measures needed are—warming the patient, i.v. corticosteroids to cover attendant adrenal insufficiency, ventilatory and cardiovascular support, correction of hyponatraemia and hypoglycaemia.

4. *Nontoxic goiter* This is characterized by enlargement of thyroid with euthyroid status. It may be endemic or sporadic. Endemic is due to iodine deficiency which may be accentuated by factors present in water (excess calcium), food or milk (goitrin, thiocyanates). A defect in hormone synthesis may be responsible for sporadic cases. In both types, deficient production of thyroid hormone leads to excess TSH → thyroid enlarges, more efficient trapping of iodide occurs and probably greater proportion of T_3 is synthesized → enough hormone to meet peripheral demands is produced so that the patient is clinically euthyroid. Thus, treatment with T_4 is in fact replacement therapy in this condition as well, despite no overt hypothyroidism. Full maintenance doses must be given. Most cases of recent diffuse enlargement of thyroid regress. Long-standing goiter with degenerative

and fibrotic changes and nodular goiter regress little or not at all. Thyroxine therapy may be withdrawn after a year or so in some cases if adequate iodine intake is ensured. Others need life-long therapy.

Endemic goiter and cretinism due to iodine deficiency in pregnant mother is preventable by ensuring daily ingestion of 150–200 µg of iodine. This is best achieved by iodizing edible salt by adding iodate (preferred over iodide). In India iodization of table salt (100 µg iodine/g salt) is required under the National Programme, but recently mandatory iodization rule has been withdrawn.

5. *Thyroid nodule* Certain benign functioning nodules regress when TSH is suppressed by T_4 therapy. Nonfunctional nodules and those non-responsive to TSH (that are associated with low TSH levels) do not respond and should not be treated with levothyroxine. T_4 therapy should be stopped if the nodule does not decrease in size within 6 months, as well as when it stops regressing after the initial response.

6. *Papillary carcinoma of thyroid* This type of cancer is often responsive to TSH. In nonresectable cases, full doses of T_4 suppress endogenous TSH production and may induce temporary regression.

7. *Empirical uses* T_4 has been sometimes used in the following conditions without any rationale; response is unpredictable.

Refractory anaemias.
Mental depression.
Menstrual disorders, infertility not corrected by usual treatment.
Chronic/non-healing ulcers.
Obstinate constipation.

Thyroxine is not to be used for obesity and as a hypocholesterolemic agent.

THYROID INHIBITORS

These are drugs used to lower the functional capacity of the hyperactive thyroid gland.

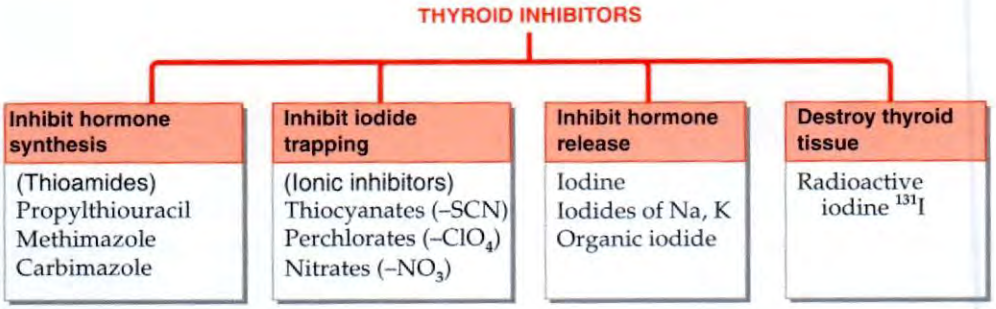
Thyrotoxicosis is due to excessive secretion of thyroid hormones. The two main causes are *Graves' disease* and *toxic nodular goiter*. Graves' disease is an autoimmune disorder due to production of an IgG class of antibody called 'thyroid stimulating immunoglobulin.' It binds to the TSH receptor and causes long lasting stimulation of the thyroid cells. The exophthalmos of Graves' disease appears to be due to stimulation of TSH receptors on the periorbital tissues. Due to feed-back inhibition, TSH levels are low.

Toxic nodular goiter, which produces thyroid hormone independent of TSH, is less common and mostly supervenes on old nontoxic goiters. It is more common in the elderly; ocular changes are generally absent.

The thioamide antithyroid drugs and ionic inhibitors are also called *goitrogens* because, if given in excess, they cause enlargement of thyroid by feedback release of TSH.

In addition, certain drugs used in high doses for prolonged periods cause hypothyroidism/goiter as a side effect:

- Lithium: inhibits thyroid hormone release.
- Amiodarone: inhibits peripheral conversion of T_4 to T_3; also interferes with thyroid hormone action.
- Sulfonamides, paraaminosalicylic acid: inhibit thyroglobulin iodination and coupling reaction.
- Phenobarbitone, phenytoin, carbamazepine, rifampin: induce metabolic degradation of T_4/T_3.



Goitrin—found in plants (cabbage, turnip, mustard, etc.), is the cause of goiter in cattle who feed on these plants. Goitring may contribute to endemic goiter in certain iodine deficient regions.

THIOAMIDES (Antithyroid drugs)

By convention, only the thioamide hormone synthesis inhibitors are called '*antithyroid drugs*', though this term has also been applied to all thyroid inhibitors.

Thiourea derivatives were found to produce goiter and hypothyroidism in rats in the 1940s. Open chain thiourea compounds were found to be toxic. Subsequently, methyl and propyl thiouracil and thioimidazole derivatives methimazole and carbimazole were found to be safe and effective.

Thioamides bind to the thyroid peroxidase and prevent oxidation of iodide and iodotyrosyl residues, thereby;

(i) Inhibit iodination of tyrosine residues in thyroglobulin

(ii) Inhibit coupling of iodotyrosine residues to form T_3 and T_4.

Action (ii) has been observed at lower concentration of antithyroid drugs than action (i). Thyroid colloid is depleted over time and blood levels of T_3/T_4 are progressively lowered.

Thioamides do not interfere with trapping of iodide and do not modify the action of T_3 and T_4 on peripheral tissues or on pituitary. Goiter that occurs with higher doses is not the result of potentiation of TSH action on thyroid, but is due to increased TSH release as a consequence of reduction in feedback inhibition. No goiter occurs if antithyroid drugs are given to hypophysectomised animals or if T_4 is given along with them. Antithyroid drugs do not affect release of T_3 and T_4—their effects are not apparent till thyroid is depleted of its hormone content.

Propylthiouracil also inhibits peripheral conversion of T_4 to T_3 by D1 type of 5-DI, but not by D2 type. This may partly contribute to its antithyroid effects. Methimazole and carbimazole do not have this action (Table 18.1).

Pharmacokinetics The antithyroid drugs are quickly absorbed orally, widely distributed in the body, enter milk and cross placenta; are metabolized in liver and excreted in urine primarily as metabolites. All are concentrated in thyroid; the intrathyroid t½ is longer: effect of a single dose lasts longer than would be expected from the plasma t½. Carbimazole acts largely by getting converted to methimazole in the body and is longer acting than propythiouracil.

Adverse effects Hypothyroidism and goiter can occur due to overtreatment, but this is reversible on stopping the drug. Enlargement of thyroid is an indication of hypothyroidism and is due to excess feedback TSH production. Goiter does not develop with appropriate doses which restore T_4 concentration to normal so that feedback TSH inhibition is maintained.

Important side effects are: g.i. intolerance, skin rashes and joint pain. Liver damage can occur, especially with propylthiouracil.

Loss or graying of hair, loss of taste and fever are infrequent.

Table 18.1: Differences between propylthiouracil and carbimazole

Propylthiouracil	*Carbimazole*
1. Dose to dose less potent	About 5 × more potent
2. Highly plasma protein bound	Less bound
3. Less transferred across placenta and in milk	Larger amounts cross to foetus and in milk
4. Plasma t½ 1–2 hours	6–10 hours
5. Single dose acts for 4–8 hours	12–24 hours
6. No active metabolite	Produces active metabolite—methimazole
7. Multiple (2–3) daily doses needed	Mostly single daily dose
8. Inhibits peripheral conversion of T_4 to T_3	Does not inhibit T_4 to T_3 conversion

A rare but serious adverse effect is agranulocytosis (1 in 500 to 1000 cases); It is mostly reversible. There is partial cross reactivity between propylthiouracil and carbimazole.

Preparations and dose

Propylthiouracil: 50–150 mg TDS followed by 25–50 mg BD–TDS for maintenance. PTU 50 mg tab.
Methimazole: 5–10 mg TDS initially, maintenance dose 5–15 mg daily in 1–2 doses.
Carbimazole: 5–15 mg TDS initially, maintenance dose 2.5–10 mg daily in 1–2 divided doses, NEO MERCAZOLE, THYROZOLE, ANTITHYROX 5, 10, 20 mg tab.

Carbimazole is used in India while methimazole is not marketed. Since popylthiouracil has shorter duration of action and carries risk of severe hepatitis, it should be reserved for use in early pregnancy (due to less placental transfer than carbimazole) and in thyroid storm for its inhibitory action on peripheral conversion of T_4 to more active T_3. It may be tried in patients developing adverse effects with carbimazole.

Use Antithyroid drugs control thyrotoxicosis in both Graves' disease and toxic nodular goiter. Clinical improvement starts after 1–2 weeks or more (depending on hormone content of thyroid gland). Iodide loaded patients (who have received iodide containing contrast media/cough mixtures, amiodarone) are less responsive. Maintenance doses are titrated on the basis of clinical status of the patient. The following strategies are adopted.

(i) *As definitive therapy* (a) Remission may occur in upto half of the patients of Graves' disease after 1–2 years of treatment: the drug can then be withdrawn. If symptoms recur—treatment is reinstituted. This is preferred in young patients with a short history of Graves' disease and a small goiter.

(b) Remissions are rare in toxic nodular goiter; surgery (or ^{131}I) is preferred. However, in frail elderly patients with multinodular goiter who may be less responsive to ^{131}I, permanent maintenance therapy with antithyroid drugs can be employed.

(ii) *Preoperatively* Surgery in thyrotoxic patients is risky. Young patients with florid hyperthyroidism and substantial goiter are rendered euthyroid with carbimazole before performing subtotal thyroidectomy.

(iii) *Along with ^{131}I* Initial control with antithyroid drug—1 to 2 weeks gap—radioiodine dosing—resume antithyroid drug after 5–7 days and gradually withdraw over 3 months as the response to ^{131}I develops. This approach is preferred in older patients and in those with heart disease who are to be treated with ^{131}I, but require prompt control of severe hyperthyroidism. This will also prevent initial disease flare-up following ^{131}I due to release of stored T_4.

Advantages of antithyroid drugs over surgery and ^{131}I are:

(a) No surgical risk, scar or chances of injury to parathyroid glands or recurrent laryngeal nerve.
(b) Hypothyroidism, if induced, is reversible.
(c) Can be used even in children and young adults.

Disadvantages are:

(a) Prolonged (often life-long) treatment is needed because relapse rate is high.
(b) Not practicable in uncooperative/unintelligent patient.
(c) Drug toxicity.

Thyroidectomy and ^{131}I are contraindicated during pregnancy. With antithyroid drugs risk of foetal hypothyroidism and goiter is there. However, low doses of propylthiouracil may be used: its greater protein binding allows less transfer to the foetus. However, methimazole has also now been found safe during pregnancy.

Propylthiouracil is used in thyroid storm as well (*see* p. 279).

IONIC INHIBITORS

Certain monovalent anions inhibit iodide trapping by NIS into the thyroid. Consequently, T_4/T_3 cannot be synthesized. Perchlorate is 10 times more potent than thiocyanate in blocking NIS, while nitrate is very weak.
These ions are toxic and not clinically used.

IODINE AND IODIDES

Though iodine is a constituent of thyroid hormones, it is the fastest acting thyroid inhibitor. In Graves' disease the gland, if enlarged, shrinks,

becomes firm and less vascular. The thyroid status starts returning to normal at a rate commensurate with complete stoppage of hormone release from the gland. The thyroid gland involutes and colloid is restored. The response to iodine and iodides is identical, because elemental iodine is reduced to iodide in the intestines. With daily administration, peak effects are seen in 10–15 days, after which 'thyroid escape' occurs and thyrotoxicosis may return with greater vengeance. Worsening of hyperthyroidism occurs, especially in multinodular goiter.

All facets of thyroid function seem to be affected, but the most important action is inhibition of hormone release—'thyroid constipation'. Endocytosis of colloid and proteolysis of thyroglobulin comes to a halt. The mechanism of action is not clear. Excess iodide inhibits its own transport into thyroid cells by interfering with expression of NIS on the cell membrane. In addition, it attenuates TSH and cAMP induced thyroid stimulation. Excess iodide rapidly and briefly interferes with iodination of tyrosil and thyronil residues of thyroglobulin (probably by altering redox potential of thyroid cells) resulting in reduced T_3/T_4 synthesis (Wolff-Chaikoff effect). However, within a few days, the gland 'escapes' from this effect and hormone synthesis resumes.

Preparations and dose Lugol's solution (5% iodine in 10% Pot. iodide solution): LUGOL'S SOLUTION, COLLOID IODINE 10%: 5–10 drops/day. COLLOSOL 8 mg iodine/5 ml liq.

Iodide (Sod./Pot.) 100–300 mg/day before thyroidectomy, 5–10 mg/day (prophylactic) for endemic goiter.

Uses

1. *Preoperative preparation* for thyroidectomy in Graves' disease: Iodine is generally given for 10 days just preceding surgery. The aim is to make the gland firm, less vascular and easier to operate on. Though iodide itself will lower the thyroid status, it cannot be relied upon to attain euthyroidism which is done by use of carbimazole before starting iodide. Propranolol may be given additionally for rapid control of symptoms.

2. *Thyroid storm* Lugol's iodine (6–10 drops) or iodine containing radiocontrast media (iopanoic acid/ipodate) orally are used to stop any further release of T_3/T_4 from the thyroid and to decrease T_4 to T_3 conversion.

3. *Prophylaxis of endemic goiter* It is generally used as "iodized salt"(*see* p. 274).

4. *Antiseptic* As tincture iodine, povidone iodine, etc. (*see* Ch. 67).

Adverse effects

1. *Acute reaction* It occurs only in rare individuals sensitive to iodine, and can be triggered even by a minute quantity. Manifestations are swelling of lips, eyelids, angioedema of larynx (may be dangerous), fever, joint pain, petechial haemorrhages, thrombocytopenia, lymphadenopathy. Further exposure to iodine should be stopped immediately.

2. *Chronic overdose (iodism)* Inflammation of mucous membranes, salivation, rhinorrhoea, sneezing, lacrimation, swelling of eyelids, burning sensation in mouth, headache, rashes, g.i. symptoms, etc. The symptoms regress on stopping iodide ingestion.

Long-term use of high doses can cause hypothyroidism and goiter.

Iodide may cause flaring of acne in adolescents. Given to pregnant or nursing mothers, it may be responsible for foetal/infantile goiter and hypothyroidism. Thyrotoxicosis may be aggravated in multinodular goiter.

RADIOACTIVE IODINE

The stable isotope of iodine is ^{127}I. Its radioactive isotope of medicinal importance is:

^{131}I: physical half-life 8 days.

The chemical behaviour of ^{131}I is similar to that of the stable isotope.

^{131}I emits γ-rays (higher energy X-rays emitted by atomic nuclei), as well as β particles (electrons). The former are useful in tracer studies, because they traverse the tissues and can be monitored by a counter, while the latter are utilized for their destructive effect on thyroid cells. ^{131}I is concentrated by thyroid and incorporated in the colloid. Thus, it emits radiation from within the

follicles. The β particles penetrate only 0.5–2 mm of tissue. The thyroid follicular cells are affected from within, undergo pyknosis and necrosis followed by fibrosis when a sufficiently large dose has been administered, without damage to neighbouring tissues. With carefully selected doses, it is possible to achieve partial ablation of thyroid.

Radioactive iodine is administered as sodium salt of ^{131}I dissolved in water and taken orally.

Diagnostic 25–100 μ curie is given; counting or scanning is done at intervals. No damage to thyroid cells occurs at this dose.

Therapeutic The most common indication is *hyperthyroidism* due to Graves' disease or toxic nodular goiter. The average therapeutic dose is 3–6 m curie—calculated on the basis of previous tracer studies and thyroid size. Higher doses are generally required for toxic multinodular goiter than for Graves' disease. The clinical response is slow—starts after 2 weeks and gradually increases, reaching peak at 3 months or so. Thyroid status is evaluated after 3 months, and a repeat dose, if needed, is given. About 20–40% patients require one or more repeat doses.

Advantages

1. Treatment with ^{131}I is simple, conveniently given on outpatient basis and inexpensive.
2. No surgical risk, scar or injury to parathyroid glands/recurrent laryngeal nerves.
3. Once hyperthyroidism is controlled, cure is permanent.

Disadvantages

1. Hypothyroidism: About 5–10% patients of Graves' disease treated with ^{131}I become hypothyroid every year (upto 50% or more patients may ultimately require supplemental thyroxine treatment). This probably reflects the natural history of Graves' disease, because only few patients of toxic nodular goiter treated with ^{131}I develop hypothyroidism. Moreover, eventual hypothyroidism is a complication of subtotal thyroidectomy/prolonged carbimazole therapy as well.
2. Long latent period of response.
3. Contraindicated during pregnancy—foetal thyroid will also be destroyed resulting in cretinism, other abnormalities if given during first trimester.
4. Not suitable for young patients: they are more likely to develop hypothyroidism later and would then require life-long T_4 treatment.

^{131}I is the treatment of choice after 25 years of age and if CHF, angina or any other contraindication to surgery is present.

Metastatic carcinoma of thyroid (especially papillary or those cases of follicular carcinoma which concentrate iodine), ^{131}I may be used as palliative therapy after thyroidectomy. Much higher doses are required and prior stimulation with TSH is recommended.

β ADRENERGIC BLOCKERS

Propranolol (and other nonselective β blockers) have emerged as an important form of therapy to rapidly alleviate manifestations of thyrotoxicosis that are due to sympathetic overactivity, *viz.* palpitation, tremor, nervousness, severe myopathy, sweating. They have little effect on thyroid function and the hypermetabolic state. They are used in hyperthyroidism in the following situations.

(a) While awaiting response to carbimazole or ^{131}I.

(b) Along with iodide for preoperative preparation before subtotal thyroidectomy.

(c) *Thyroid storm (thyrotoxic crisis):* This is an emergency due to decompensated hyperthyroidism. Vigorous treatment with the following is indicated:

Nonselective β blockers (e.g. propranolol) are the most valuable measure. They afford dramatic symptomatic relief. In addition, higher doses reduce peripheral conversion of T_4 to T_3. Propranolol 1–2 mg slow i.v. may be followed by 40–80 mg oral every

6 hours. It may be withdrawn gradually when T_4 levels normalise.

- Propylthiouracil 200–300 mg oral 6 hourly: reduces hormone synthesis as well as peripheral T_4 to T_3 conversion.
- Iopanoic acid (0.5–1 g OD oral one hour after propylthiouracil) or ipodate are iodine containing radiocontrast media. They are potent inhibitors of thyroid hormone release from thyroid, as well as of peripheral T_4 to T_3 conversion.
- Corticosteroids (hydrocortisone 100 mg i.v. 8 hourly followed by oral prednisolone): help to tide over crisis, cover any adrenal insufficiency and reduce conversion of T_4 to T_3 in periphery.
- Diltiazem 60–120 mg BD oral may be added if tachycardia is not controlled by propranolol alone, or when it is contraindicated.
- Rehydration, anxiolytics, external cooling and appropriate antibiotics are the other measures.

PROBLEM DIRECTED STUDY

18.1 A 20-year girl was diagnosed as a case of recent onset Graves' disease with mild diffuse pulsatile thyroid enlargement. She was treated with tab. Carbimazole 5 mg 2 tab 3 times a day. Her symptoms started subsiding after 2 weeks and were fully controlled after 3 months. The thyroid swelling also subsided and she was maintained on a dose of carbimazole 5 mg twice daily. After one year she noticed that the neck swelling was reappearing and her body weight increased by 2 kg in the last one month, but without recurrence of her earlier symptoms. She rather felt dull, sleepy and depressed. The serum TSH was 12 μU/ml and free thyroxine (FT_4) was 9 pmol/L.

(a) Why was the initial response to carbimazole delayed? Could any additional medicine be given to her initially to afford more rapid symptomatic relief?

(b) What was the cause of reappearance of the neck swelling and her condition after 1 year? What measures need to be taken at this stage?

(see Appendix-1 for solution)

Chapter 19 Insulin, Oral Antidiabetic Drugs and Glucagon

Diabetes mellitus (DM) It is a metabolic disorder characterized by hyperglycaemia, (fasting plasma glucose ≥ 126 mg/dL and/or ≥ 200 mg/dL 2 hours after 75 g oral glucose), glycosuria, hyperlipidaemia, negative nitrogen balance and sometimes ketonaemia. A widespread pathological change is thickening of capillary basement membrane, increase in vessel wall matrix and cellular proliferation resulting in vascular complications like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy and peripheral vascular insufficiency.

Enhanced nonenzymatic glycosylation of tissue proteins due to persistent exposure to high glucose concentrations and the accumulation of larger quantities of sorbitol (a reduced product of glucose) in tissues are believed to be causative in the pathological changes of diabetes. The concentration of glycosylated haemoglobin (HbA_{1c}) is taken as an index of protein glycosylation: it reflects the state of glycaemia over the preceding 2–3 months.

Two major types of diabetes mellitus are:

Type I Insulin-dependent diabetes mellitus (IDDM)/juvenile onset diabetes mellitus:

There is β cell destruction in pancreatic islets; majority of cases are autoimmune (type 1A) antibodies that destroy β cells are detectable in blood, but some are idiopathic (type 1B)—no β cell antibody is found. In all type 1 cases circulating insulin levels are low or very low, and patients are more prone to ketosis. This type is less common and has a low degree of genetic predisposition.

Type II Noninsulin-dependent diabetes mellitus (NIDDM)/maturity onset diabetes mellitus:

There is no loss or only moderate reduction in β cell mass; insulin in circulation is low,

Approaches to drug therapy in type 2 DM	
Improve insulin availability	*Overcome insulin resistance*
Exogenous insulin	Biguanides (Metformin)
Sulfonylureas	Thiazolidinediones (Pioglitazone)
Meglitinide/phenylalanine analogues	α glucosidase inhibitors
Dipeptidyl peptidase-4 inhibitors (DPP-4Is)	
GLP-1 receptor agonists	
Major limitations (except for DPP-4Is and GLP1 agonists)	*Major limitations*
Multiple daily injections (Insulins)	Inability to achieve normoglycaemia by themselves in many patients, especially moderate-to-severe cases
Hypoglycaemic episodes	
Weight gain	
Concern about premature atherosclerosis due to hyperinsulinaemia	

normal or even high, no anti-β-cell antibody is demonstrable; has a high degree of genetic predisposition; generally has a late onset (past middle age). Over 90% cases of diabetes are type 2 DM. Causes may be:

- Abnormality in gluco-receptor of β cells so that they respond at higher glucose concentration or relative β cell deficiency. In either way, insulin secretion is impaired; may progress to β cell failure.
- Reduced sensitivity (relative resistance); of peripheral tissues to insulin: reduction in number of insulin receptors, i.e. 'down regulation' of insulin receptors. Many hypertensives are hyperinsulinaemic, but normoglycaemic; and have associated dyslipidaemia, hyperuricaemia, abdominal obesity (metabolic syndrome). Thus, there is relative insulin resistance, particularly at the level of liver, muscle and fat. Hyperinsulinaemia *per se* has been implicated in causing angiopathy.
- Excess of hyperglycaemic hormones (glucagon, etc.)/obesity: cause relative insulin deficiency—the β cells lag behind.

In most cases, both relative insulin resistance and β cell insufficiency are produced by a combination of genetic and environmental factors.

Other rare forms of DM are those due to specific genetic defects (type-3) like 'maturity onset diabetes of young' (MODY), other endocrine disorders, pancreatectomy and 'gestational diabetes mellitus' (GDM, type-4).

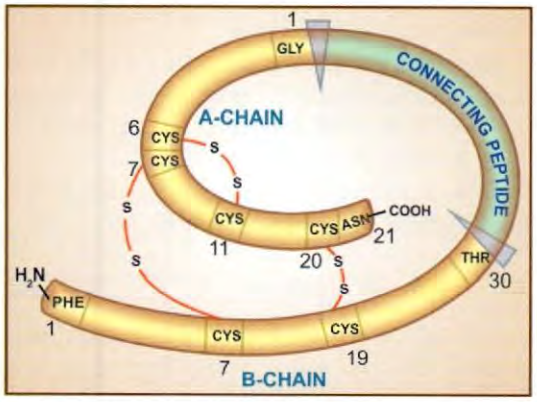


Fig. 19.1: Human proinsulin; simplified structure depicting the main features. The connecting peptide, having 35 amino acids, is split off leaving insulin molecule with two chains joined by two disulfide bridges

INSULIN

Insulin was discovered in 1921 by Banting and Best who demonstrated the hypoglycaemic action of an extract of pancreas prepared after degeneration of the exocrine part due to ligation of pancreatic duct. It was first obtained in pure crystalline form in 1926 and the chemical structure was fully worked out in 1956 by Sanger.

Insulin is a two chain polypeptide having 51 amino acids and MW about 6000. The A-chain has 21 while B-chain has 30 amino acids. There are minor differences between human, pork and beef insulins:

Species	*A-chain*		*B-chain*
	8th AA	*10th AA*	*30th AA*
Human	THR	ILEU	THR
Pork	THR	ILEU	ALA
Beef	ALA	VAL	ALA

Thus, pork insulin is more homologous to human insulin than is beef insulin. The A and B chains are held together by two disulfide bonds.

Insulin is synthesized in the β cells of pancreatic islets as a single chain peptide *Preproinsulin* (110 AA) from which 24 AAs are first removed to produce *Proinsulin* (Fig. 19.1). The connecting or 'C' peptide (35 AA) is split off by proteolysis in Golgi apparatus; both insulin and C peptide are stored in granules within the cell. The C peptide is secreted in the blood along with insulin.

Assay Insulin was bioassayed either by measuring blood sugar depression in rabbits or by its potency to induce hypoglycaemic convulsions in mice. With the availability of pure preparations, insulin is now assayed chemically and the quantity expressed by weight (1 mg of International standard of insulin = 28 Units). Plasma insulin can be measured by radioimmunoassay or enzyme immunoassay.

Regulation of insulin secretion

Under basal condition ~1U insulin is secreted per hour by human pancreas. Much larger quantity is secreted after every meal. Secretion of insulin from β cells is regulated by chemical, hormonal and neural mechanisms.

Chemical The β cells have a glucose sensing mechanism dependent on entry of glucose into

the β cells (through the aegis of a glucose transporter GLUT1) and its phosphorylation by *glucokinase*. Glucose entry and metabolism leads to activation of the glucosensor and production of ATP which inhibits the ATP-sensitive K^+ channel (K^+_{ATP}) resulting in partial depolarization of the β cells (*see* Fig. 19.6). This increases intracellular Ca^{2+} availability (due to increased influx, decreased efflux and release from intracellular stores) → exocytotic release of insulin storing granules. Other nutrients that can evoke insulin release are—amino acids, fatty acids and ketone bodies, but glucose is the principal regulator and it stimulates the synthesis of insulin as well. Glucose induces a brief pulse of insulin output within 2 min (*first phase*) followed by a delayed but more sustained *second phase* of insulin release.

Glucose and other nutrients are 2–4 times more effective in invoking insulin release when given orally than i.v. They generate chemical signals *'incretins'* from the gut which act on β cells in the pancreas to cause anticipatory release of insulin. The incretins involved are glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), vasoactive intestinal peptide (VIP), pancreozymin-cholecystokinin, etc.; but various incretins may mediate signal from different nutrients. Glucagon and some of these peptides enhance insulin release by increasing cAMP formation in the β cells.

Hormonal A number of hormones, e.g. growth hormone, corticosteroids, thyroxine modify insulin release in response to glucose. More important are the intra-islet paracrine interactions between the hormones produced by different types of islet cells. The β cells constitute the core of the islets and are the most abundant cell type. The α cells, comprising 25% of the islet cell mass, surround the core and secrete glucagon. The δ cells (5–10%) elaborating somatostatin are interspersed between the α cells. There are some PP (pancreatic polypeptide containing) cells as well.

- Somatostatin inhibits release of both insulin and glucagon.

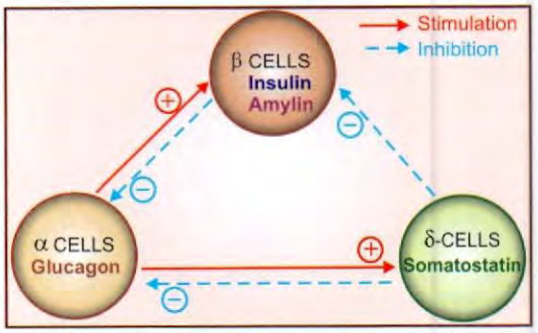


Fig. 19.2: Paracrine modulation of hormone secretion within the pancreatic islets of Langerhans

- Glucagon evokes release of insulin as well as somatostatin.
- Insulin inhibits glucagon secretion. Amylin, another β cell polypeptide released with insulin, inhibits glucagon secretion through a central site of action in the brain.

The three hormones released from closely situated cells influence each other's secretion and appear to provide fine tuning of their output in response to metabolic needs (Fig. 19.2).

Neural The islets are richly supplied by sympathetic and vagal nerves.

- Adrenergic α_2 receptor activation decreases insulin release (predominant) by inhibiting β cell adenylyl cyclase.
- Adrenergic β_2 stimulation increases insulin release (less prominent) by stimulating β cell adenylyl cyclase.
- Cholinergic—muscarinic activation by ACh or vagal stimulation causes insulin secretion through IP_3/DAG-increased intracellular Ca^{2+} in the β cells.

However, neural influences have only modulatory effect on insulin secretion.

ACTIONS OF INSULIN

The overall effects of insulin are to dispose meal derived glucose, amino acids, fatty acids and favour storage of fuel. It is a major anabolic hormone: promotes synthesis of gylcogen, lipids and protein. The actions of insulin and the results of its deficiency can be summarized as:

1. *Insulin facilitates glucose transport across cell membrane:* skeletal muscle and fat are highly sensitive. The availability of glucose intracellularly is the limiting factor for its utilization. However, glucose entry in liver, brain, RBC, WBC and renal medullary cells is largely independent of insulin. Ketoacidosis interferes with glucose utilization by brain and contributes to diabetic coma. Muscular activity induces glucose entry in muscle cells without the need for insulin. As such, exercise has insulin sparing effect.

The intracellular pool of vesicles containing glucose transporter glycoproteins GLUT4 (insulin activated) and GLUT1 is in dynamic equilibrium with the GLUT vesicles inserted into the membrane. This equilibrium is regulated by insulin to favour translocation to the membrane. Moreover, on a long-term basis, synthesis of GLUT4 is upregulated by insulin.

2. The first step in intracellular utilization of glucose is its phosphorylation to form glucose-6-phosphate. This is enhanced by insulin through *increased production of glucokinase*. Insulin facilitates glycogen synthesis from glucose in liver, muscle and fat by stimulating the enzyme glycogen synthase. It also inhibits glycogen degrading enzyme phosphorylase → decreased glycogenolysis in liver.

3. *Insulin inhibits gluconeogenesis* (from protein, FFA and glycerol) in liver by gene mediated decreased synthesis of phosphoenol pyruvate carboxykinase. In insulin deficiency, proteins and amino acids are funneled from peripheral tissues to liver where these substances are converted to carbohydrate and urea. Thus, in diabetes there is underutilization and over production of glucose leading to hyperglycaemia and glycosuria.

4. *Insulin inhibits lipolysis* in adipose tissue and favours triglyceride synthesis. In diabetes increased amount of fat is broken down due to unchecked action of lipolytic hormones (glucagon, Adr, thyroxine, etc.) → increased FFA and glycerol in blood → taken up by liver to produce acetyl-CoA. Normally acetyl-CoA is resynthesized to fatty acids and triglycerides, but this process is reduced in diabetics and acetyl CoA is diverted to produce ketone bodies (acetone, acetoacetate, β-hydroxy-butyrate). The ketone bodies are released in blood and partly used up by muscle and heart as energy source, but when their capacity is exceeded, ketonaemia and ketonuria result.

5. Insulin enhances transcription of vascular endothelial lipoprotein lipase, thereby accelerating clearance of VLDL and chylomicrons.

6. Insulin facilitates AA entry into muscles and most other cells. Their synthesis into proteins is enhanced, and protein breakdown is inhibited. Insulin deficiency leads to protein breakdown → AAs are released in blood → taken up by liver and converted to pyruvate, glucose and urea. The excess urea produced is excreted in urine resulting in negative nitrogen balance. Thus, catabolism takes the upper hand over anabolism in the diabetic state.

Most of the above metabolic actions of insulin are exerted within seconds or minutes and are

Actions of insulin producing hypoglycaemia

Liver	*Muscle*	*Adipose tissue*
▲ Increases glucose uptake and glycogen synthesis	▲ Increases glucose uptake and utilization	▲ Increases glucose uptake and storage as fat and glycogen
▲ Inhibits glycogenolysis and glucose output ▲ Inhibits gluconeogenesis from protein, pyruvate, FFA and glycerol	▲ Inhibits proteolysis and release of amino acids, pyruvate, lactate into blood which form the substrate for gluconeogenesis in liver	▲ Inhibits lipolysis and release of FFA + glycerol which form substrate for gluconeogenesis in liver

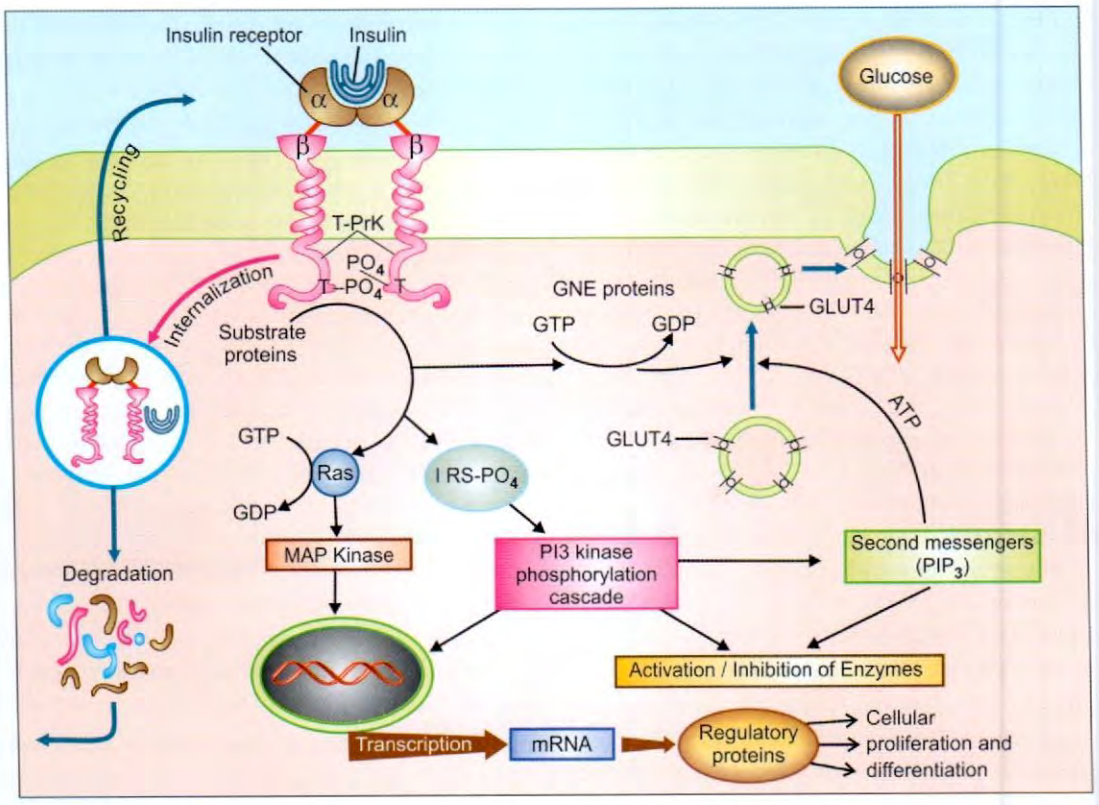


Fig. 19.3: A model of insulin receptor and mediation of its metabolic and cellular actions
T—Tyrosine residue; GLUT4—Insulin dependent glucose transporter; IRS—Insulin receptor substrate proteins; PIP_3—Phosphatidyl inositol trisphosphate; PI_3 kinase—Phosphatidylinositol-3 kinase; GNE proteins—Guanine nucleotide exchange proteins; MAP kinase—Mitogen-activated protein kinase; T-PrK—Tyrosine protein kinase; Ras—Regulator of cell division and differentiation (protooncogene product).

called the *rapid actions*. Others involving DNA mediated synthesis of glucose transporter and some enzymes of amino acid metabolism have a latency of few hours—the *intermediate* actions. In addition insulin exerts major *long-term* effects on multiplication and differentiation of many types of cells.

Mechanism of action Insulin acts on specific receptors located on the cell membrane of practically every cell, but their density depends on the cell type: liver and fat cells are very rich. The insulin receptor is a receptor tyrosine kinase (RTK) which is a heterotetrameric glycoprotein consisting of 2 extracellular α and 2 transmembrane β subunits linked together by disulfide bonds. It is oriented across the cell membrane as a heterodimer (Fig. 19.3). The α subunits carry insulin binding sites, while the β subunits have tyrosine protein kinase activity.

Binding of insulin to α subunits induces aggregation and internalization of the receptor along with the bound insulin molecules. This activates tyrosine kinase activity of the β subunits → pairs of β subunits phosphorylate tyrosine residues on each other → expose the catalytic site to phosphorylate tyrosine residues of Insulin Receptor Substrate proteins (IRS1, IRS2, etc) and other caveolar/noncaveolar proteins. In turn, a cascade of phosphorylation and dephosphorylation reactions involving phosphatidyl inositol 3 kinase (PI3 kinase) and other kinases is set into motion which amplifies the signal and results in stimulation or inhibition of enzymes involved in the rapid metabolic actions of insulin.

Second messengers like phosphatidyl inositol trisphosphate (PIP_3) which are generated through activation of a specific PI3-kinase also mediate the action of insulin on metabolic enzymes.

Insulin stimulates glucose transport across cell membrane by ATP dependent translocation of glucose transporter

GLUT4 to the plasma membrane. The second messenger PIP_3 and certain tyrosine phosphorylated guanine nucleotide exchange proteins play crucial roles in the insulin sensitive translocation of GLUT4 from cytosol to the plasma membrane, especially in skeletal muscle and adipose tissue. Over a period of time insulin also promotes expression of the genes directing synthesis of GLUT4. Genes for a large number of enzymes and carriers are regulated by insulin through Ras/Raf and MAP-Kinase as well as through the phosphorylation cascade. Long-term effects of insulin are exerted by generation of transcription factors promoting proliferation and differentiation of specific cells.

The internalized receptor-insulin complex is either degraded intracellularly or returned back to the surface from where the insulin is released extracellularly. The relative preponderance of these two processes differs among different tissues: maximum degradation occurs in liver, least in vascular endothelium.

Fate of insulin Insulin is distributed only extracellularly. It is a peptide, and gets degraded in the g.i.t. if given orally. Injected insulin or that released from pancreas is metabolized primarily in liver and to a smaller extent in kidney and muscles. Nearly half of the insulin entering portal vein from pancreas is inactivated in the first passage through liver. Thus, normally liver is exposed to a much higher concentration (4–8 fold) of insulin than are other tissues. As noted above, degradation of insulin after receptor mediated internalization occurs to variable extents in most target cells. During biotransformation the disulfide bonds are reduced—A and B chains are separated. These are further broken down to the constituent amino acids. The plasma t½ of insulin is 5–9 min.

Preparations of insulin

The older commercial insulin preparations were produced from beef and pork pancreas. They contained ~1% (10,000 ppm) of other proteins (proinsulin, other polypeptides, pancreatic proteins, insulin derivatives, etc.) which were potentially antigenic. Such insulins are no longer produced and have been totally replaced by highly purified pork/beef insulins, recombinant human insulins and insulin analogues.

Highly purified insulin preparations

In the 1970s improved purification techniques like gel filtration and ion-exchange chromatography were applied to produce 'single peak' and 'monocomponent (MC)' insulins which contain <10 ppm proinsulin. The MC insulins are more stable and cause less insulin resistance or injection site lipodystrophy. The immunogenicity of pork MC insulin is similar to that of recombinant human insulin.

Table 19.1: Types of insulin preparations and insulin analogues

Type	*Appearance*	*Onset (hr)*	*Peak (hr)*	*Duration (hr)*	*Can be mixed with*
Rapid acting					
Insulin lispro	Clear	0.2–0.3	1–1.5	3–5	Regular, NPH
Insulin aspart	Clear	0.2–0.3	1–1.5	3–5	Regular, NPH
Insulin glulisine	Clear	0.2–0.4	1–2	3–5	Regular, NPH
Short acting					
Regular (soluble) insulin	Clear	0.5–1	2–3	6–8	All preparations (except insulin glargine/ detemir)
Intermediate acting					
Insulin zinc suspension or Lente*	Cloudy	1–2	8–10	12–20	Regular
Neutral protamine hagedorn (NPH) or isophane insulin	Cloudy	1–2	8–10	12–20	Regular
Long acting					
Insulin glargine	Clear	2–4	—	24	None
Insulin detemir	Clear	1–4	—	20–24	None

* Lente insulin is a 7:3 mixture of ultralente (crystalline) and semilente (amorphous) insulin zinc suspension. Ultralente (long-acting) and semilente (short-acting) are not separately marketed. The older protamine zinc insulin is also not marketed.

Types of insulin preparations

Regular (soluble) insulin It is a buffered neutral pH solution of unmodified insulin stabilized by a small amount of zinc. At the concentration of the injectable solution, the insulin molecules self aggregate to form hexamers around the zinc ions. After s.c. injection, insulin monomers are released gradually by dilution, so that absorption occurs slowly. Peak action is produced only after 2–3 hours and action continues upto 6–8 hours. The absorption pattern is also affected by dose; higher doses act longer. When injected s.c. just before a meal, this pattern often creates a mismatch between the need and the availability of insulin to result in early postprandial hyperglycaemia and late postprandial hypoglycaemia. Regular insulin is optimally injected 1 hour before a meal. Regular insulin injected s.c. is also not suitable for providing a low constant basal level of action in the interdigestive period. However, the slow onset of action is not applicable to i.v. injection, because the insulin hexamer dissociates rapidly to produce prompt action. Regular insulin is the only insulin used for i.v. injection.

To overcome the above problems, some long-acting 'modified' or 'retard' preparations of insulin were soon developed. Recently, both rapidly acting as well as peakless and long-acting insulin analogues have become available.

For obtaining retard preparations, insulin is rendered insoluble either by complexing it with protamine (a small molecular basic protein) or by precipitating it with excess zinc and increasing the particle size.

Lente insulin (Insulin-zinc suspension): Two types of insulin-zinc suspensions have been produced. The one with large particles is crystalline and practically insoluble in water (ultralente). It is long-acting. The other has smaller particles and is amorphous (semilente), is short-acting. Their 7:3 ratio mixture is called 'Lente insulin' and is intermediate-acting.

Isophane (Neutral Protamine Hagedorn or NPH) insulin: Protamine is added in a quantity just sufficient to complex all insulin molecules; neither insulin nor protamine is present in free form and pH is neutral. On s.c. injection, the complex dissociates slowly to yield an intermediate duration of action. However, the time course of absorption and intensity of action of NPH insulin is relatively inconsistent. It is mostly combined with regular insulin (70:30 or 50:50) and injected s.c. twice daily before breakfast and before dinner (split-mixed regimen).

1. Highly purified (monocomponent) pork regular insulin: ACTRAPID MC, RAPIDICA 40 U/ml inj.
2. Highly purified (MC) pork lente insulin: LENTARD, MONOTARD MC, LENTINSULIN-HPI, ZINULIN 40 U/ml
3. Highly purified (MC) pork isophane (NPH) insulin: INSULATARD 40 U/ml inj.
4. Mixture of highly purified pork regular insulin (30%) and isophane insulin (70%): RAPIMIX, MIXTARD 40 U/ml inj.

Human insulins In the 1980s, the human insulins (having the same amino acid sequence as human insulin) were produced by recombinant DNA technology in *Escherichia coli*—'proinsulin recombinant bacterial' (prb) and in yeast—'precursor yeast recombinant' (pyr), or by 'enzymatic modification of porcine insulin' (emp).

1. HUMAN ACTRAPID: Human *regular* insulin; 40 U/ml, 100 U/ml, ACTRAPID HM PENFIL 100 U/ml pen inj., WOSULIN-R 40 U/ml inj vial and 100 U/ml pen injector cartridge.
2. HUMAN MONOTRAD, HUMINSULIN-L: Human *lente* insulin; 40 U/ml, 100 U/ml.
3. HUMAN INSULATARD, HUMINSULIN-N: Human *isophane* insulin 40 U/ml. WOSULIN-N 40 U/ml inj. vial and 100 U/ml pen injector cartridge.
4. HUMAN ACTRAPHANE, HUMINSULIN 30/70, HUMAN MIXTARD: Human *soluble* insulin (30%) and *isophane* insulin (70%), 40 U/ml. and 100 U/ml vials. WOSULIN 30/70: 40 U/ml vial and 100 U/ml cartridge.
5. ACTRAPHANE HM PENFIL: Human *soluble* insulin 30% + isophane insulin 70% 100 U/ml pen injector.
6. INSUMAN 50/50: Human *soluble* insulin 50% + *isophane* insulin 50% 40 U/ml inj; HUMINSULIN 50:50, HUMAN MIXTARD 50; WOSULIN 50/50 40 U/ml vial, 100 U/ml cartridge.

In the USA pork and beef insulins are no longer manufactured, but they are still available in U.K., India and some European countries. In Britain now > 90% diabetics who use insulin

are taking human insulins or insulin analogues. In India also human insulins and analogues are commonly used, except for considerations of cost. Human insulin is more water soluble as well as hydrophobic than porcine or bovine insulin. It has a slightly more rapid s.c. absorption, earlier and more defined peak concentration and slightly shorter duration of action. Human insulin is also modified similarly to produce isophane (NPH) and lente preparations. Lente human insulin is no longer prepared in the USA.

The allegation that human insulin produces more *hypoglycaemic unawareness* has not been substantiated. However, after prolonged treatment, irrespective of the type of insulin used, many diabetics develop relative hypoglycaemic unawareness/change in hypoglycaemic symptoms, because of autonomic neuropathy, changes in perception/attitude and other factors.

Clinical superiority of human insulin over pork MC insulin has not been demonstrated. Though new patients may be started on human insulins, the only indication for transfer from purified pork to human insulin is allergy to pork insulin. It is unwise to transfer stabilized patients from one to another species insulin without good reason.

Insulin analogues

Using recombinant DNA technology, analogues of insulin have been produced which have modified pharmacokinetics on s.c. injection, but similar pharmacodynamic effects and immunogenicity. Greater stability and consistency of the preparations are the other advantages.

Insulin lispro: Produced by reversing proline and lysine at the carboxy terminus B 28 and B 29 positions, it forms very weak hexamers that dissociate rapidly after s.c. injection resulting in a quick and more defined peak as well as shorter duration of action. Individual variability in absorption is minimized. Unlike regular insulin, it is best injected s.c. 0–20 min before a meal. A better control of meal-time glycaemia and a lower incidence of late post-prandial hypoglycaemia have been obtained. Using a regimen of 2–3 daily meal-time insulin lispro injections, a slightly greater reduction in HbA_{1c} compared to regular insulin has been reported. Fewer hypoglycaemic episodes occurred.

HUMALOG 100 U/ml, 3 ml cartridge, 10 ml vial.

Insulin aspart: The proline at B 28 of human insulin is replaced by aspartic acid. This change reduces the tendency for self-aggregation, and a time-action profile similar to insulin lispro is obtained. It more closely mimics the physiological insulin release pattern after a meal, with the same advantages as above.

NOVOLOG, NOVORAPID 100 U/ml inj.

Biphasic insulin aspart: The 70:30 mixture of isophane complex of insulin aspart with uncomplexed insulin aspart has the advantage of rapid and predictable onset along with intermediate duration of action. It is called 'biphasic insulin aspart', and can be injected twice daily just before each major meal.

NOVOMIX 30 FLEXPEN 100 U/mL in 3 mL inj., also as PENFIL injection.

Insulin glulisine: Another rapidly acting insulin analogue with lysine replacing asparagine at B 23 and glutamic acid replacing lysine at B 29. Properties and advantages are similar to insulin lispro. It has been particularly used for continuous subcutaneous insulin infusion (CSII) by a pump.

Insulin glargine: This long-acting biosynthetic insulin has 2 additional arginine residues at the carboxy terminus of B chain and glycine replaces asparagine at A 21. This analogue remains soluble at pH4 of the formulation, but precipitates at neutral pH encountered on s.c. injection. A depot is created from which monomeric insulin dissociates slowly to enter the circulation. Onset of action is delayed, but relatively low blood levels of insulin are maintained for upto 24 hours. A smooth 'peakless' effect is obtained. Thus, it is suitable for once daily injection to provide background insulin action. Fasting and interdigestive blood glucose levels are effectively lowered irrespective of time of the day when injected or the site of s.c. injection. It is mostly injected at bed time. Lower incidence of night-time hypoglycaemic episodes compared to isophane insulin has been reported. However, it does not control meal-time glycaemia, for which a rapid acting insulin or an oral hypoglycaemic is used concurrently. Because of acidic pH, it cannot be mixed with any other insulin preparation; must be injected separately.

LANTUS OPTISET 100 U/ml in 5 ml vial and 3 ml prefilled pen injector.

Insulin detemir Myristoyl (a fatty acid) radical is attached to the amino group of lysine at B29 of insulin chain. As a result, it binds to albumin after s.c. injection from which the free form becomes available slowly. A pattern of insulin action almost similar to that of insulin glargine is obtained, but twice daily dosing may be needed. LEVEMIR FLEXPEN 100 U/mL in 3 mL prefilled pen injector.

Insulin degludec It is a new ultra long-acting insulin analogue with a flat plasma glucose lowering effect lasting for ~ 40 hours, suitable for meeting *basal insulin requirement* in type 1 and type 2 diabetic patients. After single daily injection the day-to-day variability in response and risk of nocturnal hypoglycaemia are less than with insulin glargine. An alternate day regimen has also been tried, but may not be satisfactory. It has also been coformulated with rapid-acting insulin aspart.

REACTIONS TO INSULIN

1. Hypoglycaemia This is the most frequent and potentially the most serious reaction. Hypoglycaemic episodes are more common in patients of 'labile' diabetes in whom insulin requirement fluctuates unpredictably. Hypoglycaemia can occur in any diabetic following inadvertent injection of large dose, by missing a meal after injection or by performing vigorous exercise. The symptoms can be divided into those due to counter-regulatory sympathetic stimulation, *viz.* sweating, anxiety, palpitation, tremor; and those due to deprivation of the brain of its essential nutrient glucose (neuroglucopenic symptoms)—dizziness, headache, behavioural changes, visual disturbances, hunger, fatigue, weakness, muscular incoordination and sometimes fall in BP. Generally, the reflex sympathetic symptoms occur, before the neuroglucopenic, but the warning symptoms of hypoglycaemia differ from patient to patient and also depend on the rate of fall in blood glucose level. Diabetic neuropathy can abolish the autonomic symptoms. *Hypoglycaemic unawareness* (loss of warning symptoms) tends to develop in patients who experience frequent episodes of hypoglycaemia.

Finally, when blood glucose falls further (to < 40 mg/dl) mental confusion, abnormal behaviour, seizures and coma occur. Irreversible neurological deficits are the sequelae of prolonged hypoglycaemia.

Treatment Glucose (or glucose yielding carbohydrate, e.g. sugar) 15–20 g orally reverses the symptoms rapidly in most cases. If no improvement occurs, the same amount may be repeated after 15–20 min. In severe cases 30–50 ml of 50% glucose may be injected i.v. over 10 min. Glucagon 0.5–1 mg i.v. or Adr 0.2 mg s.c. (less desirable) may be given as an expedient measure in patients who are not able to take sugar orally and injectable glucose is not available.

2. Local reactions Swelling, erythema and stinging sometimes occur at the injected site, especially in the beginning. *Lipodystrophy* of the subcutaneous fat around the injection site occurred occasionally with the older pork/beef insulin preparations. This is rare with the newer preparations.

3. Allergy This is due to contaminating proteins, and is very rare with human/highly purified insulins.

Urticaria, angioedema and anaphylaxis are the manifestations.

4. Edema Some patients develop short-lived dependent edema (due to Na^+ retention) when insulin therapy is started.

Drug interactions

1. β adrenergic blockers prolong hypoglycaemia by inhibiting compensatory mechanisms operating through β_2 receptors (β_1 selective blockers are less liable). Warning signs of hypoglycaemia like palpitation, tremor and anxiety are masked.

2. Thiazides, furosemide, corticosteroids, oral contraceptives, salbutamol, nifedipine tend to raise blood sugar and reduce effectiveness of insulin.

3. Acute ingestion of alcohol can precipitate hypoglycaemia by depleting hepatic glycogen.

4. Lithium, high dose aspirin and theophylline may also accentuate hypoglycaemia by enhancing insulin secretion, as well as peripheral glucose utilization.

USES OF INSULIN

Diabetes mellitus The purpose of therapy in diabetes mellitus is to restore metabolism to normal, avoid symptoms due to hyperglycaemia and glucosuria, prevent short-term complications (infection, ketoacidosis, etc.) and long-term sequelae (cardiovascular, retinal, neurological, renal, etc.).

The generally accepted criteria for adequate glycaemia control in an adult diabetic treated with insulin or oral antidiabetics are:

- Fasting (morning) blood glucose levels 90–130 mg/dl
- Blood glucose levels ≤150 mg/dl 2 hours after meals
- HbA_{1C} levels < 7%.

Insulin is effective in all forms of diabetes mellitus and is a must for type 1 cases, as well as for post pancreatectomy diabetes and gestational diabetes. Many type 2 cases can be controlled by lifestyle measures like diet, reduction in body weight and appropriate exercise supplemented, if required, by oral antidiabetics. Insulin is needed by such patients when:

- Not controlled by diet and exercise or when these are not practicable.
- Primary or secondary failure of oral antidiabetics or when these drugs are not tolerated.
- Under weight patients.
- Temporarily to tide over infections, trauma, surgery, pregnancy. In the perioperative period and during labour, monitored i.v. insulin infusion is preferable.
- Any complication of diabetes, e.g. ketoacidosis, nonketotic hyperosmolar coma, gangrene of extremities.

When instituted, insulin therapy has to be tailored according to the requirement and convenience of each patient. A tentative regimen is instituted and the insulin requirement is assessed by testing blood glucose levels (portable glucometers are available). Most type 1 patients require 0.4–0.8 U/kg/day. In type 2 patients, insulin dose varies (0.2–1.6 U/kg/day) with the severity of diabetes and body weight: obese patients require higher per kg doses due to relative insulin resistance.

Any satisfactory insulin regimen should provide basal control by inhibiting hepatic glucose output, lipolysis and protein breakdown, as well as supply extra amount to meet postprandial needs for disposal of absorbed glucose and amino acids. A single daily injection of any long-acting or intermediate-acting or short-acting insulin or a mixture of these cannot fulfil both these requirements. Either multiple (2–4) injections daily of long and short acting insulins or a single injection daily of long-acting insulin supplemented by oral hypoglycaemics for meal time glycaemia is used.

Split-mixed regimen: A frequently selected regimen utilizes mixture of regular with lente or isophane insulin. The total daily dose of a 30:70 or 50:50 mixture of regular and NPH insulin is usually split into two and injected s.c. before breakfast and before dinner. Several variables, *viz.* site and depth of s.c. injection, posture, regional muscular activity, injected volume and type of insulin alter the rate of absorption of s.c. injected insulin, so that variability in time-course of insulin action within the same patient is large. The advantage is that only two daily injections are required, but the post-lunch glycaemia may not be adequately covered (*see* Fig. 19.4 A), and late postprandial hypoglycaemia may occur.

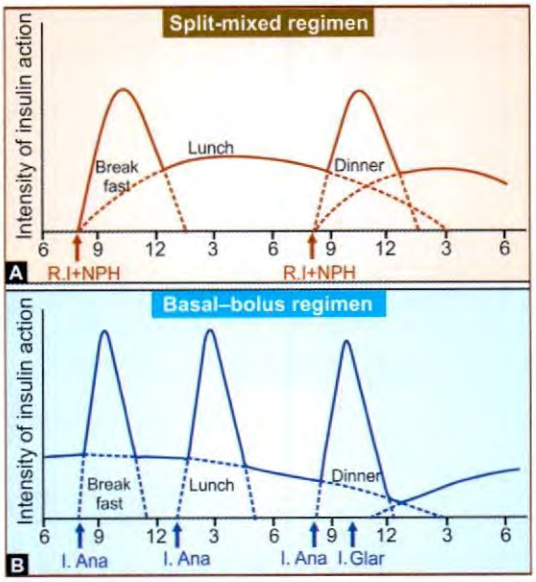


Fig. 19.4: Diagrammatic depiction of pattern of insulin action obtained with two commonly employed insulin regimens
Arrow indicates subcutaneous insulin injection.
I. Ana—Insulin analogue (rapid acting); I. Glar—Insulin glargine; R.I—Regular insulin; NPH—Neutral protamine Hagedorn (isophane) insulin

Basal-bolus regimen: This is a more intensive regimen that is now advised. It needs 3–4 daily injections (*see* Fig. 19.4B). A long-acting insulin (glargine) is injected once daily either before breakfast or before bed-time for basal coverage along with 2–3 meal-time injections of a rapid acting preparation (insulin lispro or aspart). The dose of basal insulin is usually kept constant for a patient, while that of meal time rapid acting insulin is varied according to carbohydrate content of food consumed. Such intensive regimens more completely meet the objective of achieving round-the-clock euglycaemia, but are more demanding and expensive.

The large multicentric Diabetes Control and Complications Trial (DCCT) among type 1 patients has established that intensive insulin therapy markedly reduces the occurrence of primary diabetic retinopathy, neuropathy, nephropathy and slows progression of these complications in those who already have them, in comparison to conventional regimens which attain only intermittent euglycaemia. Thus, the risk of microvascular disease appears to be related to the glycaemia control. The 'UK Prospective Diabetes Study' (UK PDS, 1998) has extended these observations to type 2 DM patients as well. Since the basis of pathological changes in both type 1 and type 2 DM is accumulation of glycosylated proteins and sorbitol in tissues as a result of exposure to high glucose concentrations, tight glycaemia control can delay end-organ damage in all diabetic subjects.

However, regimens attempting near normoglycaemia are associated with higher incidence of severe hypoglycaemic episodes. Moreover, injected insulin fails to reproduce the normal pattern of enhanced insulin secretion in response to each meal, and liver is exposed to the same concentration of insulin as other tissues, while normally it receives much higher concentration through portal circulation. As such, the overall desirability and practicability of intensive insulin therapy has to be determined in individual patients. Intensive insulin therapy is best avoided in young children (risk of hypoglycaemic brain damage) and in the elderly (more prone to hypoglycaemia and its serious consequences).

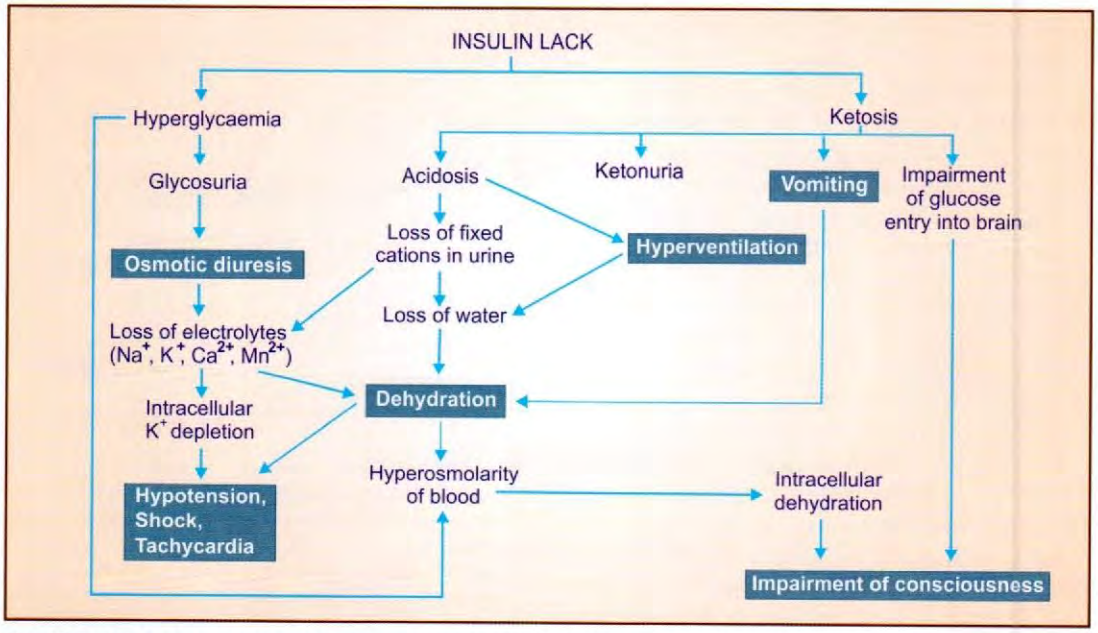


Fig. 19.5: Schematic depiction of the development of diabetic ketoacidosis due to insulin lack. Symptoms produced are shown within boxes

Diabetic ketoacidosis (Diabetic coma) Ketoacidosis of different grades generally occurs in insulin dependent diabetics, and is due to inadequate/no insulin replacement. It is infrequent in type 2 DM. The most common precipitating cause is infection; others are trauma, stroke, pancreatitis, stressful conditions and inadequate doses of insulin.

The development of cardinal features of diabetic ketoacidosis is outlined in Fig. 19.5. Patients may present with varying severity. Typically they are dehydrated, hyperventilating and have impaired consciousness. The principles of treatment remain the same, irrespective of severity, only the vigour with which therapy is instituted is varied. Close monitoring of vital signs, plasma glucose, blood pH, electrolytes, plasma acetone, etc. is needed.

1. *Insulin* Regular insulin is used to rapidly correct the metabolic abnormalities. A bolus dose of 0.1–0.2 U/kg i.v. is followed by 0.1 U/kg/hr infusion; the rate is doubled if no significant fall in blood glucose occurs in 2 hr. Fall in blood glucose level by 10% per hour can be considered adequate response.

Usually, within 4–6 hours blood glucose reaches 300 mg/dl. Then the rate of infusion is reduced to 2–3 U/hr. This is maintained till the patient becomes fully conscious and routine therapy with s.c. insulin is instituted.

2. *Intravenous fluids* Correction of dehydration is vital. Normal saline is infused i.v., initially at the rate of 1 L/hr, reducing progressively to 0.5 L/4 hours depending on the volume status. Once BP and heart rate have stabilized and adequate renal perfusion is assured change over to ½N saline. After the blood sugar has reached 300 mg/dl, 5% glucose in ½N saline is the most appropriate fluid because blood glucose falls before ketones are fully cleared from the circulation. Also glucose is needed to restore the depleted hepatic glycogen.

3. *KCl* Though upto 300 mEq of K^+ may be lost in urine during ketoacidosis, serum K^+ is usually normal due to exchange with intracellular stores. When insulin therapy is instituted ketosis subsides and K^+ is driven back intracellularly—dangerous hypokalemia can occur. After 2–3 hours it is appropriate to add 10–20 mEq/hr KCl to the i.v. fluid.

4. *Sodium bicarbonate* It is not routinely needed. Acidosis subsides as ketosis is controlled. However, if arterial blood pH is < 7.0, acidosis is not corrected spontaneously or hyperventilation is exhausting, 50 mEq of sod. bicarbonate is added to the i.v. fluid. Bicarbonate infusion is discontinued when the blood pH rises above 7.1.

5. *Phosphate* When serum PO_4 is in the low-normal range, 3–4 m mol/hr of pot. phosphate infusion is advocated. Faster phosphate infusion can precipitate tetany, and its routine use is not required.

6. *Antibiotics* and other supportive measures as well as treatment of precipitating cause must be instituted simultaneously.

Hyperosmolar (nonketotic hyperglycaemic) coma This is characterized by high blood glucose (>600 mg/dl) and serum osmolality (>320 mOsm/L) along with deteriorating mental status. It generally occurs in elderly type 2 patients. The cause is obscure, but appears to be precipitated by the same factors as ketoacidosis, especially those resulting in dehydration. Uncontrolled glycosuria of DM produces diuresis resulting in dehydration and haemoconcentration over several days. Urine output is finally reduced and glucose accumulates in blood rapidly raising blood osmolality leading to coma. Death can occur if not vigorously treated.

The general principles of treatment are the same as for ketoacidotic coma, except that faster fluid replacement is to be instituted, insulin requirement is lower, less potassium replacement is generally needed and alkali is usually not required. These patients are prone to thrombosis (due to hyperviscosity and sluggish circulation), prophylactic heparin therapy is recommended.

Despite intensive therapy, mortality in hyperosmolar coma remains high. Treatment of precipitating factor and associated illness is vital.

Insulin resistance

Insulin resistance refers to suboptimal response of body tissues, especially liver, skeletal muscle and fat to physiological amounts of insulin. As already stated, relative insulin resistance is integral to type 2 DM. Advanced age, obesity and sedentary life-style promote insulin resistance. Women with polycystic ovarian disease (PCOD) often exhibit insulin resistance.

Insulin sensitivity has been found to decline with age. Obesity is the most important factor causing insulin resistance. Glucose entry into muscle and liver in response to insulin is deficient in individuals with large stores of body fat. Bigger adipocytes have fewer insulin receptors. However, in most type 2 diabetics the transducer mechanism linking insulin receptor to the response appears to be faulty, rather than the receptor itself. Exercise increases insulin sensitivity and lack of it contributes to insulin resistance.

Pregnancy and oral contraceptives often induce relatively low grade and reversible insulin resistance. Other rare causes are—acromegaly, Cushing's syndrome, pheochromocytoma, lipoatrophic diabetes mellitus and production of insulin neutralizing antibody. Hypertension accompanied with relative insulin resistance is a part of metabolic syndrome.

Acute insulin resistance This form of insulin resistance develops rapidly and is usually a short term problem. Causes are—

(a) Infection, trauma, surgery, emotional stress induce release of corticosteroids and other hyperglycaemic hormones which oppose insulin action.

(b) Ketoacidosis—ketone bodies and FFA inhibit glucose uptake by brain and muscle. In addition insulin binding may increase resulting in insulin resistance.

Treatment of acute insulin resistance is to overcome the precipitating cause and to give high doses of regular insulin. The insulin requirement comes back to normal once the condition has been controlled.

Newer insulin delivery devices A number of innovations have been made to improve ease and accuracy of insulin administration as well as to achieve tight glycaemia control. These are:

1. *Insulin syringes* Prefilled disposable syringes contain specific types or mixtures of regular and modified insulins. These are in common use now, and avoid the need for carrying insulin vials and syringes.

2. *Pen devices* Fountain pen like; they use insulin cartridges for s.c. injection through a needle. Preset amounts (in 2 U increments) are propelled by pushing a plunger. They are convenient in carrying and injecting.

3. *Inhaled insulin* The early inhaled insulin formulations were found to be unsatisfactory for clinical use due to risk of pulmonary complications.

A new dry powder formulation (AFREZZA) of recombinant human insulin called '*Technosphere insulin*' (TI) has been found satisfactory for use in both type 1 and 2 diabetics. Administered by a breath-powered inhaler, it is absorbed from the alveoli and acts rapidly within 10–15 min. The action is terminated by 3 hours. Thus, it is suitable for use just before a meal to control prandial glycaemia. Combined with basal insulin injection (insulin glargine, etc.), it has been found equi-effective in lowering blood glucose and HbA_{1c} levels as prandial insulin aspart injected s.c. (along with basal insulin). Weight gain and risk of hypoglycaemic episodes is claimed to be lower compared to rapid acting s.c. insulin. Cough is the most common adverse effect reported by >25% patients. It is not to be used in smokers and COPD patients.

Another newer inhaled insulin (EXUBERA) has been discontinued by its menufacturer.

4. *Insulin pumps* Portable infusion devices connected to a subcutaneously placed cannula—provide 'continuous subcutaneous insulin infusion' (CSII). Only regular insulin or a fast acting insulin analogue is used. The pump can be programmed to deliver insulin at a low basal rate (approx. 1 U/hr) and premeal boluses (4–15 times the basal rate) to control post-prandial glycaemia. Though, theoretically more appealing, no definite advantage of CSII over multidose s.c. injection has been demonstrated. Moreover, cost, strict adherence to diet, exercise, care of the device and cannula, risk of pump failure, infusion site infection, are too demanding on the patient. The CSII may be appropriate for selected type 2 DM cases only.

5. *Implantable pumps* These consist of an electromechanical mechanism which regulates insulin delivery from a percutaneously refillable reservoir. Mechanical pumps, propellant driven and osmotic pumps have been utilized.

Glucagon-like peptide-1 (GLP-1) receptor agonists

GLP-1 is an important incretin released from the gut in response to ingested glucose. It

induces insulin release from pancreatic β cells, inhibits glucagon release from α cells, slows gastric emptying and suppresses appetite by activating specific GLP-1 receptors, which are cell surface GPCRs (*see* Fig. 19.6) expressed on β and α cells, central and peripheral neurones, gastrointestinal mucosa, etc. Characteristically, GLP-1 induces insulin release only at high glucose concentration. The incretin system appears to promote β cell health as well by decreasing islet cells apoptosis. Failure of incretins has been implicated in the pathogenesis of β cell dysfunction of type 2 DM, particularly for progression of the disease. GLP-1 based therapy appears to be the most effective measure to preserve β cell function in type 2 DM.

GLP-1 itself is not suitable for clinical use because of rapid degradation by the enzyme *dipeptidyl peptidase-4 (DPP-4)* which is expressed on the luminal membrane of capillary endothelial cells, kidney, liver, gut mucosa and immune cells. Another incretin *glucose-dependent insulinotropic peptide* (GIP) also induces insulin release, but in human-beings GLP-1 is the more important incretin and GIP has poor action in type 2 diabetics. The GIP receptor is distinct from GLP-1 receptor, but mediates mostly similar responses. Some metabolically stable analogues of GLP-1 have been produced for clinical use in type-2 DM.

Exenatide It is a synthetic DPP-4 resistant analogue which activates GLP-1 receptors (Fig. 19.6) and produces the same responses. Being a peptide, it is inactive orally. After s.c. injection its plasma t½ is ~ 3 hours and duration of action 6–10 hours. Injected s.c. before breakfast and dinner, it is used as add-on drug to metformin/SU or a combination of these or pioglitazone in poorly controlled type 2 diabetics. Benefits noted are lowering of postprandial as well as fasting blood glucose, HbA_{1C}, and body weight. The most important side effect is nausea and vomiting occurring in ~ 50% recipients, but tolerance develops later. Many patients develop antibodies to exenatide, but its response is attenuated only in a few. Acute pancreatitis is a risk.

Dose: Initially 5 μg s.c. before breakfast and dinner; increase to 10 μg BD if needed.

EXAPRIDE 250 μg/vial inj.

Liraglutide This recently developed longer-acting GLP-1 agonist is closely related to the native peptide but its tight binding to plasma proteins extends t½ to > 12 hours and duration of action to > 24 hours. Injected s.c. once daily, alone or added to oral metformin ± SU or pioglitazone, it has achieved improved glycaemic control in type 2 diabetics. Nausea and diarrhoea are the frequent side effects, but decrease in incidence over time. Use of liraglutide is attended by weight loss and it is approved for use in obesity.

Hypoglycaemia is rare with exenatide/liraglutide monotherapy, but can occur when combined with SUs/metformin. Acute pancreatitis is reported in few patients taking GLP-1 agonists.

Albiglutide and *dulaglutide* are very long acting GLP-1 receptor agonists which need to be injected once weekly.

Amylin analogue

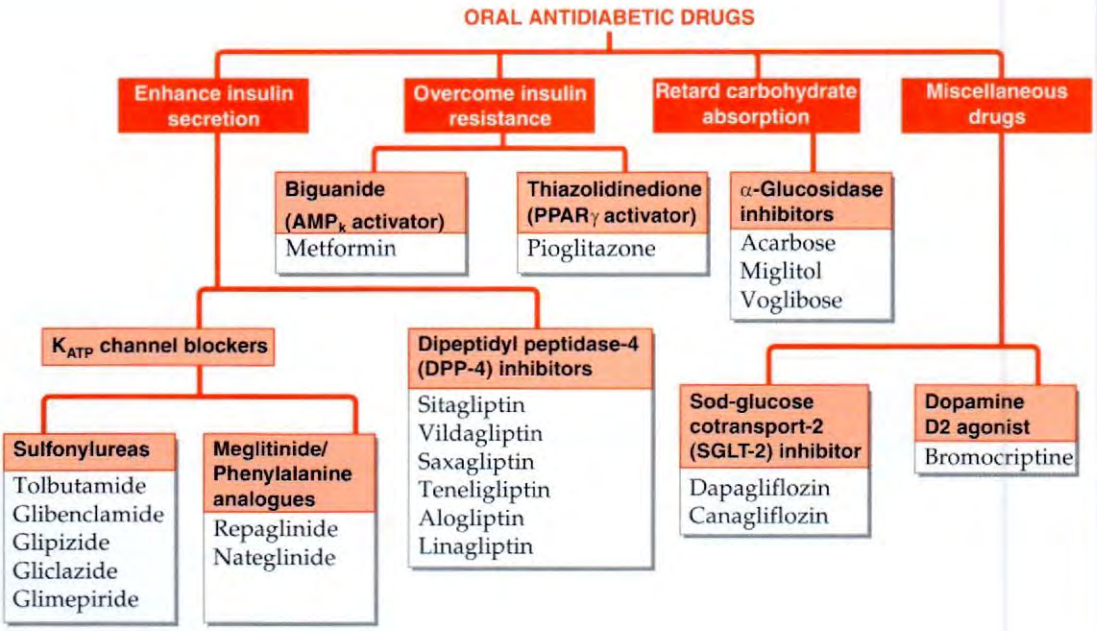
Amylin, also called 'islet amyloid polypeptide' (IAP), is produced by pancreatic β cells and is stored in the same granules as insulin. As such, it is secreted along with insulin, acts in the brain to reduce glucagon secretion from α cells, delay gastric emptying, retard glucose absorption and promote satiety.

Pramlintide It is a synthetic amylin analogue which on s.c. injection before meal attenuates postprandial glycaemia and exerts a centrally mediated anorectic action. The duration of action is 2–3 hours. It is used to supplement meal time insulin injection when insulin alone fails to control post prandial glycaemic peak, in both type 1 and type 2 diabetics. Hypoglycaemia is the most important adverse effect. Loss of appetite, nausea and vomiting are the other side effects. Reduction in body weight is an additional benefit.

ORAL ANTIDIABETIC DRUGS

These drugs lower blood glucose levels in diabetics and are effective orally. The chief drawback of insulin is—it must be given by injection. Orally active drugs have always been saught.

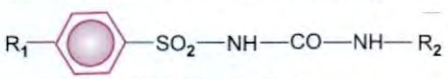
The early sulfonamides tested in 1940s produced hypoglycaemia as side effect. Taking this lead, the first clinically acceptable sulfonylurea *tolbutamide* was introduced in 1957. Others followed soon after. In the 1970s many so called 'second generation' sulfonylureas were developed which are >100 times more potent than tolbutamide. Clinically useful biguanide *phenformin* was produced parallel to sulfonylureas in 1957. Newer approaches have constantly been explored and have successively yielded *thiazolidinediones*, *meglitinide analogues*, *α-glucosidase inhibitors*, *dipeptidyl peptidase-4 (DPP-4) inhibitors* and *sod-glucose cotransport* (SGLT-2) *inhibitors*, etc.



SECTION 5

Sulfonylureas (K_{ATP} Channel blockers)

The generic formula of sulfonylureas (SUs) is—



SULFONYLUREA

All SUs have similar pharmacological profile, their sole significant action being lowering of blood glucose level in normal subjects and in type 2 diabetics, but not in type 1 diabetics. Being more potent and clinically superior, only the second generation SUs are employed now. All first generation compounds have been discontinued except tolbutamide which is infrequently used.

Mechanism of action Sulfonylureas bind to a specific 'sulfonylurea receptor' (SUR1) located on the pancreatic β cell membrane and provoke a brisk release of insulin, the mechanism of which is detailed in Fig. 19.6. The rate of insulin secretion at any glucose concentration is increased, i.e. insulin release is provoked even at low-glucose concentration risking production of severe and unpredictable hypoglycaemia. In type 2 DM the kinetics of insulin release in response to glucose or meals is delayed and subdued. The SUs primarily augment the 2nd phase insulin secretion with little effect on the 1st phase. That they do not cause hypoglycaemia in pancreatectomised animals and in type 1 diabetics (presence of at least 30% functional β cells is essential for their action), confirms their indirect action through pancreas.

A minor action reducing glucagon secretion, probably by increasing insulin and somatostatin release has been demonstrated. Hepatic degradation of insulin is also slowed.

Extrapancreatic action After few months of administration, the insulinaemic action of SUs declines, probably due to down regulation of sulfonylurea receptors (SUR1) on β cells, but improvement in glucose tolerance is maintained. In this phase, they sensitize the target tissues (especially liver) to the action of insulin. It is hypothesized that long-term improvement in carbohydrate tolerance leads to overall lowering of circulating insulin concentration which reverses the down regulation of insulin receptors. An apparent increase in their number

Table 19.2: Important features of oral antidiabetics

Drug	Preparations	Plasma t½ (hr)	Duration of action (hr)	Clearance route*	Daily dose	No. of doses per day	Remarks
SULFONYLUREAS							
1. Tolbutamide	RASTINON, 0.5 g tab.	6	6–8	L	0.5–3 g	2–3	Weaker, shorter acting, flexible dosage, safer in elderly and in those prone to hypoglycaemia.
2. Glibenclamide (Glyburide)	DAONIL, EUGLUCON, BETANASE 2.5, 5 mg tab.	2–4	24	L	2.5–15 mg	1–2	Potent but slow acting, higher incidence of hypoglycaemia, single daily dose despite short t½ due to active metabolite and sequestration in β cells.
3. Glipizide	GLYNASE, GLIDE, MINIDIAB 5 mg tab	3–5	12	L	5–20 mg	1–2	Fast and shorter acting, higher daily dose to be devided, hypoglycaemia and weight gain less likely, preferable in elderly.
4. Gliclazide	DIAMICRON 80 mg tab. DIAZIDE 20, 80 mg tab GLIZID 30, 40, 80 mg tab	8–20	12–24	L	40–240 mg	1–2	Has antiplatelet action, generates only inactive metabolite, daily dose > 80 mg to be divided.
5. Glimepiride	AMARYL, GLYPRIDE GLIMER 1, 2 mg tab	5–7	24	L	1–6 mg	1–2	Long acting, only inactive metabolite. Stronger extra-pancreatic action.
MEGLITINIDE / PHENYLALANINE ANALOGUES							
1. Repaglinide	EUREPA, RAPLIN, NOVONORM, REGAN 0.5, 1, 2 mg tab	≤ 1	3–5	L	1–8 mg	3–4	Given ½ hr before each meal for limiting post-prandial hyperglycaemia.
2. Nateglinide	GLINATE, NATELIDE 60,120 mg tab	1.5	2–3	L	180–480 mg	3–4	Stimulates 1st phase insulin secretion, less likely to cause delayed hypoglycaemia.
DPP-4 INHIBITORS							
1. Sitagliptin	JANUVIA 50, 100 mg tab.	~12	24	K	100 mg	1	Non-covalent binding to DPP-4; excreted unchanged in urine. Low risk of hypoglycaemia. Body weight neutral.
2. Vildagliptin	GALVUS, JALRA, ZOMELIS 50 mg cap	2–4	12–24	L,K	50–100 mg	1–2	Covalent binding to DPP-4; Metabolized in liver. Hepatotoxicity reported.
BIGUANIDE							
1. Metformin	GLYCIPHAGE, GLYCOMET 0.5, 0.85 g tab, 0.5 g and 1.0 g SR tabs	1.5–3	6–8	K	0.5–2.5 g	1–2	No hypoglycaemia. Not metabolized. Lactic acidosis rare and only in kidney disease.
THIAZOLIDINEDIONE							
1. Pioglitazone	PIONORM, PIOREST, PIOZONE 15, 30 mg tab	3–5	24	L	15–45 mg	1	May improve lipid profile. Reverses insulin resistance. No hypoglycaemia, C/I in liver and heart disease.

* L—Metabolized in liver; K—Excreted unchanged by kidney

occurs, and/or a post receptor action improves translation of receptor activation.

Pharmacokinetics All SUs are well absorbed orally, and are 90% or more bound to plasma proteins: have low volumes of distribution (0.2–0.4 L/kg). They are primarily metabolized—may produce active metabolite. The metabolites (active/inactive) are excreted in urine. As such, they should be used cautiously in patients with liver or kidney dysfunction.

The distinctive features of different SUs are given in Table 19.2.

Interactions

Drugs that enhance SU action (may precipitate hypoglycaemia) are—

(a) *Displace from protein binding:* Phenylbuta-zone, sulfinpyrazone, salicylates, sulfonamides.

(b) *Inhibit metabolism/excretion:* Cimetidine ketoconazole, sulfonamides, warfarin, chloramphenicol, acute alcohol intake (also synergises by causing hypoglycaemia).

(c) *Synergise with or prolong pharmacodynamic action:* Salicylates, propranolol (cardioselective β_1 blockers are less liable), sympatholytic antihypertensives, lithium, theophylline, alcohol (by inhibiting gluconeogenesis).

Drugs that decrease SU action (vitiate diabetes control) are—

(a) *Induce metabolism:* Phenobarbitone, phenytoin, rifampicin, chronic alcoholism.

(b) *Opposite action/suppress insulin release:* Corticosteroids, thiazides, furosemide, oral contraceptives.

Adverse effects Incidence of adverse effects is quite low (3–7%).

1. *Hypoglycaemia* It is the commonest problem, may occasionally be severe and rarely fatal. It is more common in elderly, liver and kidney disease patients and when potentiating drugs are added. Tolbutamide carries lowest risk due to its low potency and short duration of action.

Treatment of hypoglycaemic episode is to give glucose, may be for a few days because hypoglycaemia may recur.

2. *Nonspecific side effects* Majority of diabetics started on SUs tend to gain 1–3 kg weight. This may be a consequence of insulinaemic action of SUs. Nausea, vomiting, flatulence, diarrhoea or constipation, headache and paresthesias are generally mild and infrequent.

3. *Hypersensitivity* Rashes, photosensitivity, purpura, transient leukopenia, rarely agranulocytosis.

Flushing and a disulfiram-like reaction after alcohol is reported to occur in some individuals taking SUs.

Tolbutamide reduces iodide uptake by thyroid but hypothyroidism does not occur.

Safety of SUs during pregnancy is not established. Change over to insulin is advised. Sulfonylureas are secreted in milk; they should not be given to nursing mothers.

Meglitinide/D-phenylalanine analogues (K_{ATP} Channel blockers)

These are K_{ATP} channel blockers with a quick and short lasting insulinemic action.

Repaglinide This meglitinide analogue oral hypoglycaemic is designed to normalise meal-time glucose excursions. Though not a sulfonylurea, it acts in an analogous manner by binding to SUR → closure of ATP sensitive K^+ channels → depolarisation → insulin release (*see* Fig. 19.6).

Repaglinide is quickly absorbed and rapidly metabolized. It induces fast onset short-lasting insulin release. Because of this characteristic its pattern of use is different from that of SUs. It is administered before each major meal to control postprandial hyperglycaemia; the dose should be omitted if a meal is missed. Because of short lasting action it may have a lower risk of serious hypoglycaemia. Side effects are mild headache, dyspepsia, arthralgia and weight gain.

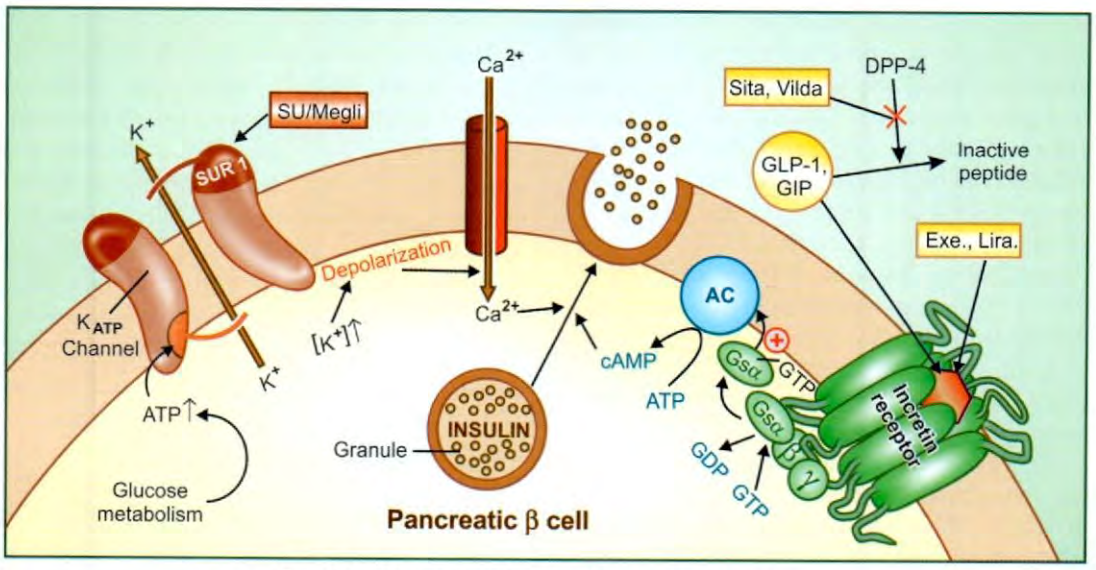


Fig. 19.6: Mechanism of action of insulin secretagogues

The sulfonylureas (SU) and meglitinide analogues (Megli) act on the sulfonylurea receptor (SUR1) which constitutes a subunit of the inwardly rectifying ATP-sensitive K^+ channel (K_{ATP}) in the membrane of pancreatic β cells. The outward flow of K^+ ions is thereby restricted, intracellular K^+ concentration rises and the membrane is partially depolarized augmenting Ca^{2+} channel opening as well as release of Ca^{2+} from intracellular stores. The Ca^{2+} ions promote fusion of insulin containing intracellular granules with the plasma membrane and exocytotic release of insulin.

Incretins such as glucagon-like peptide 1 (GLP1) and glucose-dependent insulinotropic polypeptide (GIP) act upon their own G-protein coupled receptors on the β cell membrane to activate adenylyl cyclase and generate cAMP, which also promotes exocytosis of insulin. Exenatide (Exe) and liraglutide (Lira) are GLP1 receptor agonists—produce the same response as GLP1. The incretins GLP1 and GIP are rapidly inactivated by the capillary endothelial enzyme dipeptidyl peptidase-4 (DPP-4). Their action is enhanced by DPP-4 inhibitors sitagliptin (sita) and vildagliptin (vilda). The DPP-4 inhibitors thus markedly accentuate the insulin response to ingested glucose/meal and attenuate post-prandial glycaemia.

Repaglinide is indicated only in selected type 2 diabetics who suffer pronounced postprandial hyperglycaemia, or to supplement metformin/long-acting insulin. It should be avoided in liver disease.

Nateglinide It is a D-phenylalanine derivative which principally stimulates the 1st phase insulin secretion by closing β cell K_{ATP} channels resulting in faster onset and shorter lasting hypoglycaemia than repaglinide. Ingested 10 min before meal, it limits postprandial hyperglycaemia in type 2 diabetics without producing late phase hypoglycaemia. There is little effect on fasting blood glucose level. Episodes of hypoglycaemia are less frequent than with SUs. Side effects are dizziness, nausea, flu-like symptoms and joint pain. It is used in type 2 DM along with other antidiabetics, to control postprandial rise in blood glucose.

Dipeptidyl peptidase-4 (DPP-4) inhibitors

Realizing the key role of the enzyme DPP-4 in rapid degradation of endogenous GLP-1, orally active inhibitors of this enzyme have been developed as indirectly acting insulin secretagogues. In the past few years, DPP-4 inhibitors have emerged as important adjunctive drugs in type 2 DM, but their blood sugar lowering efficacy is moderate compared to that of SUs.

Sitagliptin This is the first DPP-4 inhibitor introduced in 2006. It is a competitive and selective DPP-4 inhibitor which potentiates the action of GLP-1 (Fig. 19.6) and GIP, boosts postprandial insulin release, decreases glucagon

secretion and lowers meal-time as well as fasting blood glucose in type 2 diabetics. No effect on gastric emptying and appetite have been noted. It carries low risk of hypoglycaemia unless combined with SUs or insulin, because GLP-1 evokes little insulin release at normal plasma glucose levels. The HbA_{1c} lowering achieved by sitagliptin is almost equivalent to that with metformin. Further lowering of HbA_{1c} by 0.5–1.2% occurs when it is added to pioglitazone/SUs/insulin with or without metformin. However, sitagliptin monotherapy is recommended only when metformin cannot be used. Most professional guidelines recommend DPP-4 inhibitors primarily as adjuvant drugs in type 2 diabetics not well controlled by metformin/SUs/pioglitazone or insulin. Though clinical efficacy of all DPP-4 inhibitors is comparable, one metaanalysis has found sitagliptin to cause greater reduction of fasting blood glucose than vildagliptin.

Sitagliptin is well absorbed orally, is little metabolized and is largely excreted unchanged in urine with a t½ averaging 12 hours. Dose reduction is needed in renal impairment, but not in liver disease. Sitagliptin is well tolerated, though nausea may occur, it is not prominent as in the case of GLP-1 agonists. It also does not cause weight loss and is body weight neutral. Side effects are nausea, loose stools, headache, rashes, allergic reactions including some serious ones like, angioedema, exfoliative dermatitis and edema. Nasopharyngitis and cough occurs in some patients. Other DPP-4 inhibitors also produce this side effect, which has been ascribed to prevention of substance P degradation. Pancreatitis is reported.

Vildagliptin This DPP-4 inhibitor binds to the enzyme covalently. The complex dissociates very slowly resulting in persistent DPP-4 inhibition even after the free drug has been cleared from circulation. This explains the longer duration of action (12–24 hours) despite short plasma t½ (2–4 hours). The major route of elimination is by hepatic metabolism; only 20–25% is excreted unchanged in urine. Dose reduction is needed in moderately severe liver and kidney disease. No significant drug interactions have been reported. Vildagliptin is less selective than sitagliptin for DPP-4; causes some inhibition of DPP-8, DPP-9 as well, but the clinical significance of this feature is not known. The tolerability of vildagliptin is similar to that of sitagliptin, but hepatotoxicity has been reported. Vildagliptin may require twice daily dosing; though single daily dose suffices in most cases when combined with another hypoglycaemic.

Saxagliptin Like vildagliptin, saxagliptin binds covalently with DPP-4 and acts for 24 hours despite a plasma t½ of 2–4 hours. Added to metformin/SU ± pioglitazone it causes HbA_{1c} reduction similar to that caused by sitagliptin or vildagliptin. It is metabolized by CYP3A4 and generates an active metabolite that has a t½ of 3–7 hours. Drug interactions with CYP3A4 inhibitors are possible.

Dose: 5 mg OD; reduce by half in moderately severe renal failure, but not in liver disease.

ONGLYZA 2.5, 5 mg tabs

Teneligliptin It is a new DPP-4 inhibitor developed in Japan which exerts long-lasting (>24 hours) DPP-4 inhibition and antiglycaemic effect. Following a single morning dose, postprandial hyperglycaemia is suppressed at all 3 meals of the day. Therapeutic efficacy both as monotherapy as well as in combination with metformin ± SUs or a thiazolidinedione is comparable to other gliptins. Metabolites of teneligliptin are excreted by both liver and kidney; no dose reduction is needed in patients with renal impairment. Though no cardiovascular adverse effects have been noted, caution is to be exercised in patients prone to QT prolongation.

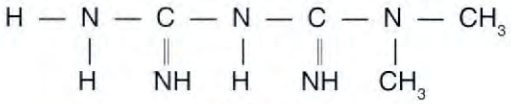
Dose: 20 mg/before breakfast daily, increase to 40 mg/day if needed.

TENGLYN, TENEFIT-20, TENLIMAX 20 mg tab.

Alogliptin and *Linagliptin* are the other DPP-4 inhibitors.

Biguanide (AMPK activator)

Two biguanide antidiabetics, *phenformin* and *metformin* were introduced in the 1950s. Because of higher risk of lactic acidosis, phenformin has been banned in India since 2003.



METFORMIN

Metformin It differs markedly from SUs: causes little or no hypoglycaemia in nondiabetic subjects, and even in diabetics, hypoglycaemia is rare. Thus, it is 'euglycaemic', rather than hypoglycaemic'. It does not stimulate pancreatic β cells. Metformin is reported to improve lipid profile as well in type 2 diabetics.

Mechanism of action Biguanides do not cause insulin release, but presence of insulin is essential for their action. Metformin is not effective in pancreatectomized animals and in type 1 diabetics. Though the details are not clear, recent studies have recognized activation of AMP-dependent protein kinase (AMPK) to play a crucial role in mediating the actions of metformin, the key features of which are:

1. Suppresses hepatic gluconeogenesis and glucose output from liver. This is the major action responsible for lowering of blood glucose in diabetics.
2. Enhances insulin-mediated glucose uptake and disposal in skeletal muscle and fat. Insulin resistance exhibited by type-2 diabetics is thus overcome. This translates into—
   - glycogen storage in skeletal muscle
   - reduced lipogenesis in adipose tissue and enhanced fatty acid oxidation.
3. Interferes with mitochondrial respiratory chain and promotes peripheral glucose utilization through anaerobic glycolysis.

AMPK activation by metformin appears to be an indirect consequence of interference with cellular respiration and lowering of intracellular ATP and other energy sources.

Metformin also retards intestinal absorption of glucose, other hexoses, amino acids and Vit B_{12}.

Pharmacokinetics Metformin is well absorbed orally, not metabolized, but excreted unchanged by kidney (Table 19.2). Clearance of metformin approximates g.f.r. It accumulates in renal failure and increases the risk of lactic acidosis.

Adverse effects Side effects with metformin are frequent, but generally not serious. Abdominal pain, anorexia, bloating, nausea, metallic taste, mild diarrhoea and tiredness are the usual complaints, which tend to subside with time. Metformin does not cause hypoglycaemia except in overdose.

Lactic acidosis Small increase in blood lactate occurs with metformin, but lactic acidosis is rare (<1 per 10,000 patient years) because it is poorly concentrated in hepatic cells. Alcohol ingestion can precipitate lactic acidosis.

Vit B_{12} deficiency due to interference with its absorption can occur with high dose of metformin.

In addition to general restrictions for use of oral hypoglycaemics (*see* below), metformin is contraindicated in renal insufficiency, because risk of lactic acidosis increases. It should also not be given in hypotensive states, heart failure, severe respiratory/hepatic disease, as well as in alcoholics.

Drugs like cimetidine, furosemide may compete with metformin excretion and enhance its toxicity.

Uses Metformin is now established as a first choice drug for all type 2 DM patients, except when not tolerated or contraindicated.

Advantages of metformin are:

- antihyperglycaemic, but not hypoglycaemic
- weight loss promoting
- has potential to prevent macrovascular as well as microvascular complications of diabetes
- no acceleration of β cell exhaustion/ failure in type 2 DM.
- antihyperglycaemic efficacy (HbA_{1c} reduction by 0.8–1.2%) equivalent to other oral drugs.
- can be combined with any other oral or injectable antidiabetic.
- can prevent new onset type 2 DM in obese, middle aged subjects with impaired glucose tolerance (but not in nonobese older subjects) as shown by the Diabetes Prevention Programme.

The limiting feature is g.i. intolerance, especially at higher doses, but lack of serious toxicity is well established by decades of use.

Infertility: Metformin has been found to improve ovulation and fertility in some infertile women with polycystic ovary. This benefit is observed irrespective of the glycaemic status of the woman; may be due to mitigation of insulin resistance and lowering of circulating insulin levels.

Thiazolidinedione (PPARγ agonist)

Pioglitazone Only one thiazolidinedione *Pioglitazone* is currently available in India. *Rosiglitazone,* the other member, is banned in India since 2010 and has been withdrawn in Europe due to unacceptable increase in risk of myocardial infarction, CHF, stroke and death. However, a large recent trial failed to confirm such risk, and restrictions on the use of rosiglitazone have been lifted in the USA.

Because of some reports linking pioglitazone with carcinoma of urinary bladder, it was banned in India in June 2013. However, within 2 months the ban was lifted with a warning label 'not to use it as a first line drug'.

This class of oral antidiabetic drugs are selective agonists for the nuclear *peroxisome proliferator-activated receptor* γ (PPARγ) which is expressed mainly in fat cells, but also in muscle and some other cells. Pioglitazone enhances the transcription of several insulin responsive genes and tends to reverse insulin resistance by enhancing GLUT4 expression and translocation. Entry of glucose into muscle and fat is improved; the primary action is to enhance peripheral insulin sensitivity. Hepatic gluconeogenesis is also suppressed. Activation of genes regulating fatty acid metabolism and lipogenesis in adipose tissue contributes to the insulin sensitizing action. Lipolysis and plasma fatty acid levels are reduced. Adipocyte turnover and differentiation is accelerated by glitazones. Thus, fatty tissue is a major site of their action. The magnitude of blood glucose reduction is somewhat less than SUs and metformin. Improved glycaemic control results in lowering of circulating HbA_{1C} and insulin levels in type 2 DM patients.

Pioglitazone, in addition, lowers serum triglyceride level and raises HDL level without much change in LDL level, probably because it acts on PPARα as well to induce expression of reverse cholesterol transporter and some apoproteins.

Pioglitazone is well tolerated; adverse effects are plasma volume expansion, edema, weight gain, headache, myalgia and mild anaemia. Monotherapy with glitazones is not associated with hypoglycaemic episodes. Few cases of hepatic dysfunction have been reported; CHF may be precipitated or worsened. Monitoring of liver function is advised. Pioglitazone is contraindicated in liver disease and in CHF. Glitazones increase the risk of fractures, especially in elderly women.

Pioglitazone is metabolized by both CYP2C8 and CYP3A4. Ketoconazole inhibits and rifampin induces its metabolism. Failure of oral contraception may occur during pioglitazone therapy.

Pioglitazone is indicated in type 2 DM, but not in type 1 DM. It reduces blood glucose and HbA_{1c} (by 0.5–1.2%) without increasing circulating insulin. About 25% patients may not respond (nonresponders), probably due to low baseline insulin levels. It should be stopped if HbA_{1c} reduction is < 0.5% at 6 months. Pioglitazone is primarily used to supplement SUs/metformin and in case of insulin resistance. However, it is not likely to be effective when β cell failure has set in, which may be responsible for loss of efficacy of combination of SUs + metformin. It may also be used as monotherapy (along with diet and exercise) in mild cases.

Several reports describe greater fluid retention, weight gain and precipitation of CHF after combined use of glitazones with insulin. Experts advise avoiding such combination. Pioglitazone should not be used during pregnancy. The Diabetes Prevention Programme (2005) has shown that glitazones have the potential to delay progression of prediabetics to overt type 2 DM. Pioglitazone may help to conserve β cell function in diabetics.

α Glucosidase inhibitors

Acarbose It is a complex oligosaccharide which reversibly inhibits α-glucosidases, the final enzymes for the digestion of carbohydrates

in the brush border of small intestine mucosa. It slows down and decreases digestion and absorption of polysaccharides (starch, etc.) and sucrose. In addition, GLP-1 release is promoted which may contribute to the effect. Postprandial glycaemia is reduced without significant increase in insulin levels. Regular use lowers HbA_{1c} modestly (by 0.4–0.8%), but change in body weight and lipid levels is minimal. The stop-NIDDM trial (2002) has shown that long-term acarbose treatment in prediabetics reduces occurrence of type 2 DM as well as hypertension and cardiac disease. In diabetics, it reduces cardiovascular events.

Acarbose is a mild antihyperglycaemic and not a hypoglycaemic; may be used as an adjuvant to diet (with or without metformin/SU) in obese diabetics. Acarbose 50–100 mg TDS is taken at the beginning of each major meal. Only a small fraction of the dose is absorbed. Flatulence, abdominal discomfort and loose stool are produced in about 50% patients due to fermentation of unabsorbed carbohydrates. Patient acceptability of α-glucosidase inhibitors is poor due to uncomfortable g.i. symptoms. Hepatic transaminases may rise, but liver damage is rare.

GLUCOBAY 50, 100 mg tabs, ASUCROSE, GLUCAR 50 mg tabs.

Miglitol It has a smaller molecule than acarbose, and it is a stronger inhibitor of sucrase. Potency for other α-glucosidases is equivalent to acarbose. Absorption of miglitol is substantial, but variable. The absorbed drug is excreted by the kidney. No systemic toxicity is known.

Dose: 25–100 mg TDS at beginning of each meal.

MIGTOR, DIAMIG, ELITOX 25, 50 mg tabs.

Voglibose Has properties, use and side effects similar to that of acarbose.

Dose: 200–300 µg TDS just before meals.

VOGLITOR, VOLIX, VOLIBO 0.2, 0.3 mg tabs.

Dopamine D2 agonist

Bromocriptine Recently (2009) a quick release oral formulation of bromocriptine has been approved by US-FDA for adjunctive treatment of type 2 DM. Taken early in the morning it is thought to act on the hypothalamic dopaminergic control of the circadian rhythm of hormone (GH, prolactin, ACTH, etc.) release and reset it to reduce insulin resistance. Bromocriptine can be taken alone to supplement diet+exercise or added to metformin or SU or both. Started at 0.8 mg OD and increased upto 4.8 mg OD (as needed) it has been shown to marginally improve glycaemic control and lower HbA_{1c} by upto 0.5%.

Sodium-glucose co-transport-2 (SGLT-2) inhibitor

Practically all the glucose filtered at the glomerulus is reabsorbed in the proximal tubules. The major transporter which accomplishes this is *SGLT-2*, whose inhibition induces glucosuria and lowers blood glucose in type 2 DM, as well as causes weight loss.

Dapagliflozin, Canagliflozin These SGLT-2 inhibitors are approved for use in type 2 DM patients. After once daily dosing, they produce round-the-clock glucosuria and lower blood glucose levels. Used alone or in combination with other antidiabetic drugs, they reduce HbA_{1C} levels by 0.5–1.0%, but do not cause hypoglycaemia. The concerns which appear inbuilt due to their mechanism of action are—glycosuria which can predispose to urinary and genital infections, electrolyte imbalance, ketoacidosis and increased urinary frequency. They are contraindicated in patients with renal insufficiency. Other long term safety concerns have also been raised.

Bile acid sequestrant

Colesevelam It is a bile acid binding resin which lowers cholesterol as well as glucose levels in blood. It is approved as add-on drug in type 2 DM patients who are not properly controlled by other antidiabetic drugs. The mechanism of action is not clear, but may involve reduction in farnesoid X receptor (FXR) activation. The HbA_{1C} lowering efficacy of colesevelam is modest, and g.i. upset is frequent.

Status of oral antidiabetics in diabetes mellitus

After 8 years of prospective study involving large number of patients, the University Group Diabetes Programme (UGDP) of USA (1970) presented findings that cardiovascular mortality was higher in patients treated with biguanides and SUs than in those treated with diet and exercise alone or with insulin. A decline in the use of oral hypoglycaemics followed. Subsequent studies both refuted and supported these conclusions.

The controversy was settled by the UK PDS trial which found that both SUs and metformin did not increase cardiovascular mortality

over > 10 years observation period. Related to degree of glycaemia control, both insulin and SUs reduced microvascular complications (retinopathy, neuropathy, nephropathy) in type 2 DM, but did not have significant effect on macrovascular complications (coronary artery disease, stroke, etc). Metformin, however, could reduce both microvascular as well as macrovascular complications. It decreased risk of death and other diabetes related endpoints in overweight patients. This may be related to the fact that both SUs and exogenous insulin improve glycaemic control by increasing insulin supply rather than by overcoming insulin resistance, while metformin can decrease insulin resistance which is a pathogenic factor in type 2 DM. All oral hypoglycaemics do however control symptoms that are due to hyperglycaemia and glycosuria, and are much more convenient to use than insulin.

Oral antidiabetics are indicated only in type 2 diabetes, in addition to diet and exercise. They are most effective in patients with—

1. Age above 40 years at onset of disease.
2. Obesity at the time of presentation.
3. Duration of disease < 5 years when starting treatment.
4. Fasting blood sugar < 200 mg/dl.
5. Insulin requirement < 40 U/day.
6. No ketoacidosis or a history of it, or any other complication.

The Diabetes Prevention Programme (2002) has established that in middle aged, obese prediabetics metformin prevented progression to type 2 DM, but not in older nonobese prediabetics. Glitazones also appear to have prophylactic potential. Long-term acarbose therapy as well can delay type 2 DM.

Oral antidiabetics should be used to supplement dietary management and not to replace it. In view of the prophylactic and outcome benefits, current recommendation is to institute metformin therapy right at the diagnosis of type 2 DM, along with dietary and other lifestyle measures, without waiting to see if the latter alone are sufficient. Metformin may delay progression of diabetic severity by favourably affecting β cell health and retarding β cell failure. It is especially valuable for obese patients, because it may also aid weight reduction. Further, it has the potential to reduce the risk of myocardial infarction and stroke. Thus, unless contraindicated or not tolerated, metformin is prescribed to all type 2 diabetics, despite its inferior patient acceptability due to g.i. side effects.

Many type 2 DM patients do not attain the target level of glycaemia control and HbA_{1c} reduction (to < 7%) with metformin alone, and a second drug is needed. SUs are the most commonly selected 2nd drug. They have good patient acceptability, convenient dosing and high efficacy, but can cause weight gain and hypoglycaemia. There is some evidence that SUs given over long-term (2–10 years) expedite β cell apoptosis and failure. Receptor desensitization may also be a cause, and SUs tend to lose efficacy in few years (5–10% per year failure rate). There is no difference in the clinical efficacy of various 2nd generation SUs. However, this does not indicate that choice among them is irrelevant. Differences among them are mainly in dose, onset and duration of action which govern flexibility of regimens. Some specific features of various SUs are given in Table 19.2. If a particular SU proves inadequate in a given patient, another one may still work.

Patients with near normal fasting blood glucose but prominent post-prandial hyperglycaemia, or those experiencing late postmeal hypoglycaemia may do better with premeal repaglinide or nateglinide.

Pioglitazone is usually the 3rd choice drug; may be added to metformin or a combination of metformin + SU. It is particularly useful for patients with prominent insulin resistance. Though it tends to preserve β cell function and does not cause hypoglycaemia, it is rarely selected for monotherapy. Its major limitations are—tendency to fluid retention, weight gain, increased risk of heart failure and fractures, and need to monitor liver function. Moreover, it is ineffective in a significant number of patients.

Acarbose-like drugs are mild antihyperglycaemics, mostly used as supplementary drugs to a hypoglycaemic regimen. They are disliked by many patients because of bloating, indigestion and other abdominal symptoms.

The newer oral antidiabetics that have gained popularity now are the DPP-4 inhibitors. Their favourable features are:

- Insulin release is glucose dependent (occurs only at high glucose concentrations) therefore not likely to induce hypoglycaemia.
- Suppress glucagon release, thus lowering fasting blood glucose level as well.
- Improve β cell health and retard progression of β cell failure.
- Body weight neutral.
- Can be used in patients with renal impairment.
- Mostly single daily dose, well tolerated with few side effects, no drug interactions, except with saxagliptin.

However, the DPP-4 inhibitors cause moderate HbA_{1C} lowering compared to SUs and some serious reactions like angioedema, Stevens-Johnson syndrome, anaphylaxis have been reported. Moreover, they are relatively new drugs and have not withstood the test of time yet. Their impact on cardiovascular mortality and other outcomes is yet to be established. As such, most professional guidelines place them as second line/add on antidiabetic drugs. They are especially valuable for patients having body weight problem and those experiencing frequent episodes of hypoglycaemia.

The SGLT-2 inhibitors (e.g. dapagliflozin) are the newest class of oral drugs that may be considered for addition to a combination oral antidiabetic regime when the latter fails to achieve the target HbA_{1C} level. They predispose to urinary tract infections, genital fungal infections, hypovolaemia and have other limitations

Upto 50% patients of type 2 DM initially treated with oral antidiabetics ultimately need insulin. Moreover, when a diabetic on oral antidiabetics presents with infection, severe trauma or stress, pregnancy, ketoacidosis or any other complication, or has to be operated upon—switchover to insulin (*see* Flow chart in Fig. 19.7). Metformin alone or in combination with SUs or DPP-4 inhibitors is usually continued with insulin, particularly when a single daily injection of long-acting (e.g. glargine) insulin is used to provide basal control. The oral drug given before meals serves to check postprandial glycaemia, while metformin mainly reduces hepatic glucose output.

The GLP-1 agonists (exenatide/liraglutide injected s.c.) are an alternative to insulin in obese type 2 diabetics in whom weight gain is to be avoided. They help weight reduction and are unlikely to induce hypoglycaemia. Frequent nausea and risk of pancreatitis are their drawbacks.

Epalrestat Sorbitol is a minor metabolite of glucose generated by the enzyme *aldose reductase*. In diabetics, excess sorbitol is produced and gets deposited in nerves and other tissues. This is involved in the pathogenesis of diabetic neuropathy and other complications. *Epalrestat* is an aldose reductase inhibitor developed in Japan which has been found to delay sorbitol accumulation in sciatic nerve/other tissues of diabetics imparting potential to delay progression of diabetic neuropathy. In trials it has caused modest improvement in nerve conduction, neuropathic pain and other symptoms. However, magnitude of benefit and safety are yet to be defined. Nausea, vomiting and elevation of liver enzymes are the adverse effects.

Dose: 50 mg TDS before meals; ALRISTA 50 mg tab.

GLUCAGON

A hyperglycaemic principle was demonstrated to be present in the pancreatic islets just two years after the discovery of insulin in 1921. It was named 'glucagon'. Glucagon is a single chain polypeptide containing 29 amino acids, MW 3500. It is secreted by the α cells of the islets of Langerhans and commercially produced now by recombinant DNA technology.

Regulation of Secretion Like insulin, glucagon is also derived by cleavage of a larger peptide prohormone. Its secretion is regulated by glucose levels, other nutrients, paracrine hormones and nervous system. Glucose has opposite effects on insulin and glucagon release, i.e. high glucose level inhibits glucagon secretion. The incretin GLP-1, FFA and ketone bodies also inhibit glucagon release. Amino acids, however, induce both insulin and glucagon secretion. Insulin, amylin and somatostatin, elaborated by the neighbouring β and δ cells, inhibit glucagon secretion. Sympathetic stimulation consistently and parasympathetic stimulation under certain conditions evokes glucagon release.

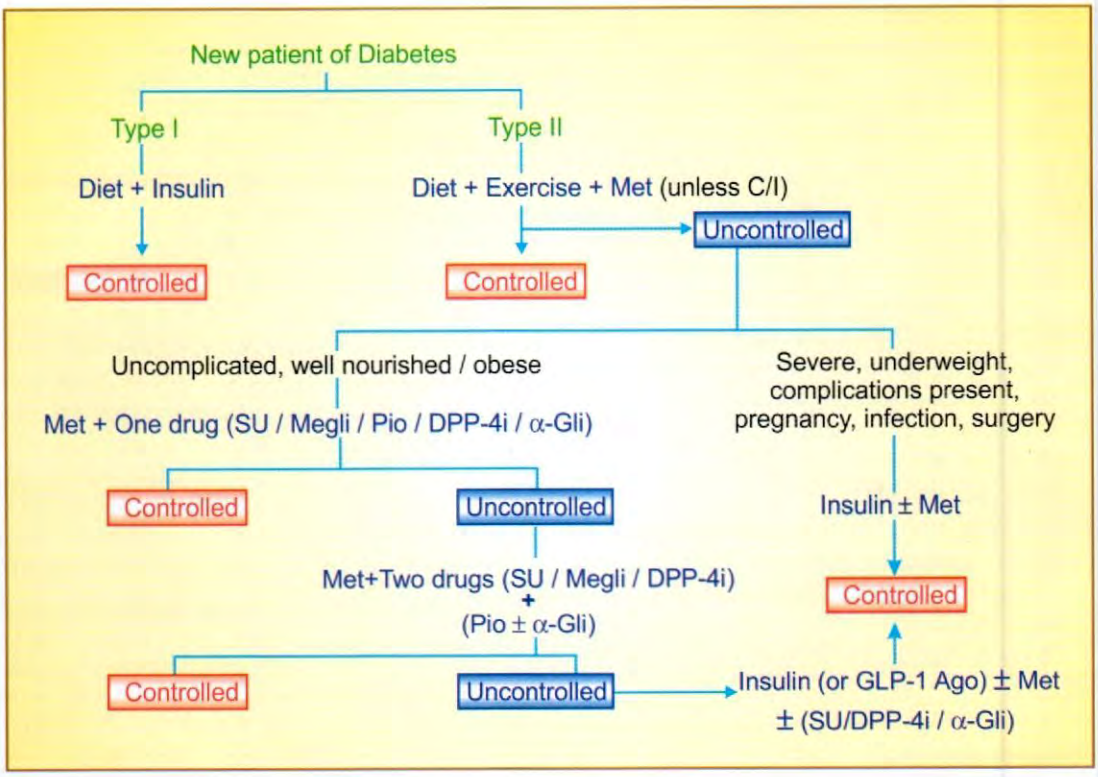


Fig. 19.7: Simplified flow chart of management approaches in diabetes mellitus
Met—Metformin; SU—Sulfonylurea; Megli—Meglitinide/d-phenylalanine analogue; DPP-4i—Dipeptidyl peptidase-4 inhibitor; α Gli—α Glucosidase inhibitor; Pio—Pioglitazone; GLP-1 Ago—GLP-1 receptor agonist.
Note: A meglitinide drug is indicated only in patients with predominant postprandial hyperglycaemia.
An α glucosidase inhibitor can be additional add on drug.

Actions Glucagon is hyperglycaemic; most of its actions are opposite to that of insulin. Glucagon causes hyperglycaemia primarily by enhancing glycogenolysis and gluconeogenesis in liver. Suppression of glucose utilization in muscle and fat contributes modestly. Glucagon is considered to be the hormone of fuel mobilization. Its secretion is increased during fasting, and is largely responsible for the high fasting blood glucose levels in type 2 diabetics. It plays an essential role in the development of diabetic ketoacidosis. Increased secretion of glucagon has been shown to attend all forms of severe tissue injury.

Glucagon increases the force and rate of cardiac contraction and this is not antagonized by β blockers. It has a relaxant action on the gut and inhibits gastric acid production.

Mechanism of action Glucagon, through its own receptor and coupling Gs protein activates adenylyl cyclase and increases cAMP in liver, fat cells, heart and other tissues; most of its actions are mediated through this cyclic nucleotide.

Glucagon is inactive orally; that released from pancreas is broken down in liver, kidney, plasma and other tissues. Its plasma t½ is 3–6 min.

Uses

1. *Hypoglycaemia* Use of glucagon to counteract insulin/oral hypoglycaemic drug induced hypoglycaemia is only an expedient measure for the emergency, and must be followed by oral glucose/sugar given repeatedly till the blood glucose level stabilizes. It may not work if hepatic glycogen is already depleted.
Dose: 0.5–1.0 mg i.v. or i.m.
GLUCAGON 1 mg inj.
2. *Cardiogenic shock* Glucagon may be used to stimulate the heart in β adrenergic blocker treated patients. However, action is not very marked.

Other hyperglycaemics

Diazoxide Chemically related to thiazides, it inhibits insulin release from β cells and causes hyperglycaemia lasting 4–8 hours. Its action on ATP sensitive K^+ channels of β cells is opposite to that of SUs. Other actions which may contribute to hyperglycaemia are decreased peripheral utilization of glucose and release of catecholamines. It has been used to prevent hypoglycaemia in insulinomas. Other actions are vasodilatation, fall in BP and antidiuresis.

Somatostatin It causes hyperglycaemia primarily by inhibiting insulin release.

Streptozocin It is obtained from *Streptomyces achromogenes*. Causes selective damage to insulin secreting β cells. It has been used to produce experimental diabetes in animals and to treat insulin secreting tumours of pancreas.

☞ PROBLEM DIRECTED STUDY

19.1 During routine medical checkup a 50-year male office executive with sedentary lifestyle was diagnosed to have developed type 2 diabetes mellitus. His fasting and post-meal blood glucose was 130 mg/dl and 190 mg/dl respectively, HbA_{1C} was 7.8%, BP was 130/82 mm Hg and body mass index was 27 kg/m^2. He was asymptomatic and investigations revealed no end organ damage. He was advised suitable diet, exercise and other lifestyle modifications.

(a) Should he be prescribed an antidiabetic medication as well? If so, which drug/combination of drugs should be selected, and why?

(see Appendix-1 for solution)

Chapter 20 Corticosteroids

The adrenal cortex secretes steroidal hormones which have glucocorticoid, mineralocorticoid and weakly androgenic activities. Conventionally, the term 'corticosteroid' or 'corticoid' includes natural gluco- and mineralo-corticoids and their synthetic analogues.

By the middle of 19th century it was demonstrated that adrenal glands were essential for life. Later it was appreciated that the cortex was more important than the medulla. A number of steroidal active principles were isolated and their chemical structures were elucidated by Kendall and his coworkers in the 1930s. However, the gate to their great therapeutic potential was opened by Hench (1949) who obtained striking relief in rheumatoid arthritis by using cortisone. The Nobel Prize was awarded the very next year to Kendall, Reichstein and Hench.

BIOSYNTHESIS

The corticoids (both gluco and mineralo) are 21 carbon compounds having a cyclopentano-perhydro-phenanthrene (steroid) nucleus. They are synthesized in the adrenal cortical cells from cholesterol. A simplified version of the biosynthetic pathways is presented in Fig. 20.1. Adrenal steroidogenesis takes place under the influence of ACTH which makes more cholesterol available for conversion to pregnenolone and induces steroidogenic enzymes. Since adrenal cortical cells store only minute quantities of the hormones, rate of release is governed by the rate of biosynthesis. The circulating corticosteroids

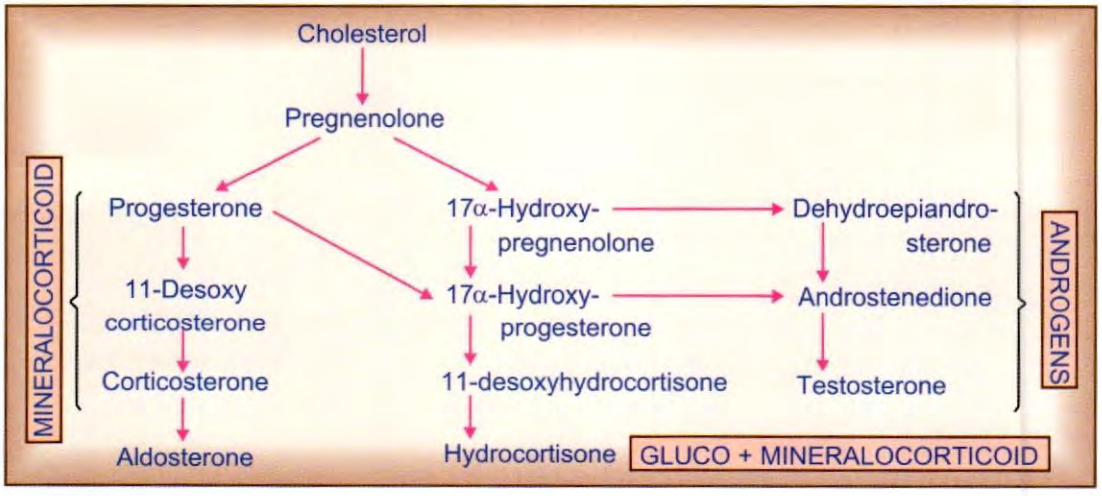


Fig. 20.1: Simplified depiction of the pathways of adrenal steroid hormone biosynthesis

inhibit ACTH release from pituitary as well as CRH production from hypothalamus (*see* Ch. 17) and thus provide negative feed back regulation of the hypothalamo-pituitary-adrenal (HPA) axis.

The normal rate of secretion of the two principal corticoids in man is—

Hydrocortisone — 10–20 mg daily (nearly half of this in the few morning hours).

Aldosterone — 0.125 mg daily.

ACTIONS

The corticoids have widespread actions. They maintain fluid-electrolyte, cardiovascular and energy substrate homeostasis as well as functional status of skeletal muscles and nervous system. They prepare the body to withstand effects of all kinds of noxious stimuli and stress. The involvement of hypothalamo-pituitary-adrenal axis in stress response is depicted in Fig. 20.2.

Corticoids have some *direct* and some *permissive* actions. By permissive action is meant that while they do not themselves produce an effect, their presence facilitates other hormones to exert that action, e.g. they do not have any effect on BP but the pressor action of Adr is markedly blunted in their absence. Actions of corticoids are divided into:

Glucocorticoid Effects on carbohydrate, protein and fat metabolism, and other actions that are inseparably linked to these.

Mineralocorticoid Effects on Na^+, K^+ and fluid balance.

Marked dissociation between these two types of actions is seen among natural as well as synthetic corticoids. Accordingly, compounds are labelled as 'glucocorticoid' or 'mineralocorticoid'.

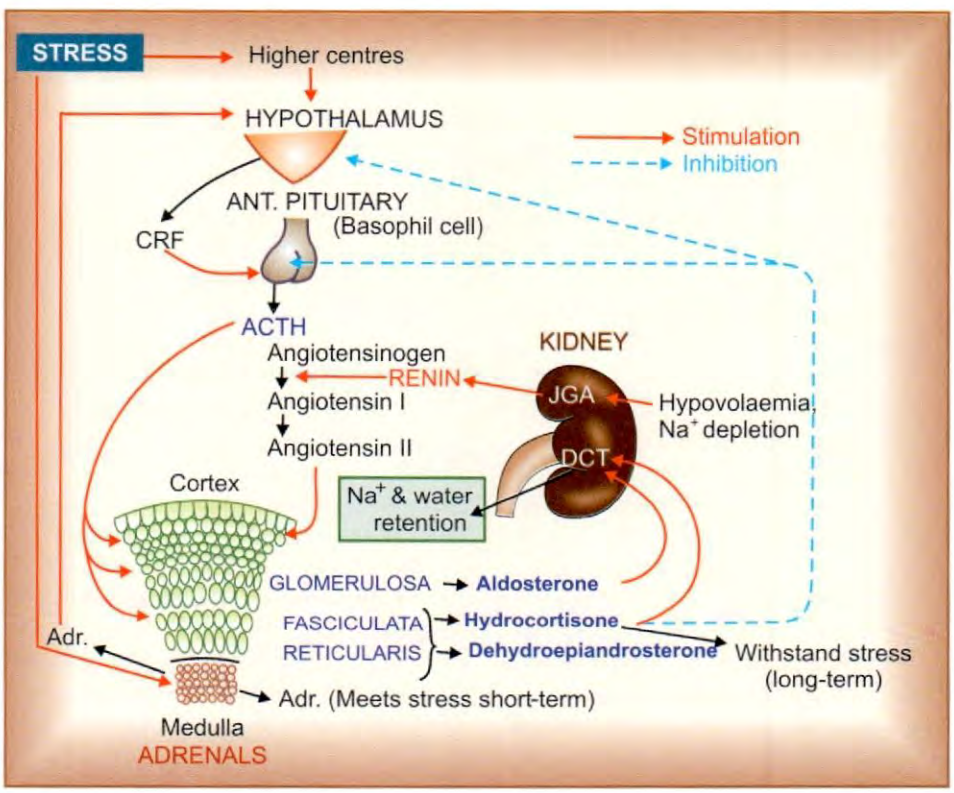


Fig. 20.2: Hypothalamo-pituitary-adrenal (HPA) axis; regulation of corticosteroid production and response to stress which overrides the negative feedback regulation of ACTH release

Mineralocorticoid actions

The principal mineralocorticoid (aldosterone) action is enhancement of Na^+ reabsorption from the distal convoluted tubule in kidney. There is an associated increase in K^+ and H^+ excretion. Its deficiency results in decreased maximal tubular reabsorptive capacity for Na^+; kidney is not able to retain Na^+ even in the Na^+ deficient state so that Na^+ is progressively lost. Kidneys absorb water without the attendant Na^+ (to maintain e.c.f. volume, which nevertheless decreases) leading to dilutional hyponatraemia → excess water enters cells causing cellular hydration, decreased blood volume and raised haematocrit. Hyperkalaemia and acidosis accompany. These distortions of fluid and electrolyte balance progress and contribute to the circulatory collapse. As such, these actions make adrenal cortex essential for survival.

Similar action on cation transport is exerted in other tissues as well. The action of aldosterone is exerted by gene mediated increased transcription of m-RNA in renal tubular cells which directs synthesis of proteins (aldosterone-induced proteins—AIP). The Na^+K^+ ATPase of tubular basolateral membrane responsible for generating gradients for movement of cations in these cells is the major AIP (*see* Fig. 42.3). Synthesis of β subunit of amiloride sensitive Na^+ channel is also induced. Because of the time taken to induce protein synthesis, aldosterone action has a latency of 1–2 hours. In addition, aldosterone rapidly induces phosphorylation and activation of amiloride sensitive Na^+ channel.

The main adverse effect of excessive mineralocorticoid action is fluid retention and hypertension. The natural and some of the synthetic glucocorticoids have significant mineralocorticoid activity responsible for side effects like edema, progressive rise in BP, hypokalemia and alkalosis. The diuretic induced hypokalemia is aggravated by mineralocorticoid excess.

In addition to the actions on Na^+ and K^+ balance, aldosterone has been shown to promote CHF associated myocardial fibrosis and progression of the disease (*see* Ch. 38).

Glucocorticoid actions

1. *Carbohydrate and protein metabolism*
Glucocorticoids promote glycogen deposition in liver (they are assayed on the basis of this action) by inducing hepatic glycogen synthase and promoting gluconeogenesis. They inhibit glucose utilization by peripheral tissues. This along with increased glucose release from liver results in hyperglycaemia, resistance to insulin and a diabetes-like state. They also cause protein breakdown and amino acid mobilization from peripheral tissues. This is responsible for side effects like muscle wasting, lympholysis, loss of osteoid from bone and thinning of skin. The amino acids so mobilized funnel into liver and are used up in gluconeogenesis, excess urea is produced resulting in negative nitrogen balance. Glucocorticoids are thus catabolic. Their function appears to be aimed at maintaining blood glucose levels during starvation—so that brain continues to get its nutrient. When food is withheld from an adrenalectomized animal—liver glycogen is rapidly depleted and hypoglycaemia occurs. Glucocorticoids increase uric acid excretion.

2. *Fat metabolism* The action of glucocorticoids on fat metabolism is primarily permissive in nature. They promote lipolysis due to glucagon, growth hormone, Adr and thyroxine. cAMP induced breakdown of triglycerides is enhanced. Fat depots in different areas of the body respond differently—redistribution of body fat occurs. Subcutaneous tissue over extremities loses fat which is deposited over face, neck and shoulder producing 'moon face', 'fish mouth' and 'buffalo hump'. Explanation offered is—because peripheral adipocytes are less sensitive to insulin and more sensitive to corticosteroid-facilitated lipolytic action of GH and Adr, break down of fat predominates, whereas truncal adipocytes respond mainly to raised insulin levels caused by glucocorticoid induced hyperglycaemia.

Difference in the sensitivity of adipocytes at different locations to glucocorticoids is believed to arise from different levels of expression of the isoenzyme 11β-hydroxysteroid dehydrogenase type 1 (11β HSD1) which generates active hydrocortisone from inactive cortisone in the target tissues. Greater expression of 11βHSD1 in peripheral adipocytes

than in truncal adipocytes would direct glucocorticoid-facilitated lipolysis to the subcutaneous fat in the limbs.

$$\text{Cortisone} \underset{11\beta\text{HSD2}}{\overset{11\beta\text{HSD1}}{\rightleftharpoons}} \text{Hydrocortisone}$$

On the other hand, high expression of the type 2 isoenzyme (11βHSD2) in the kidney tubule (also colon and salivary gland) which express mineralocorticoid receptor (MR) is believed to account for only weak mineralocorticoid activity of hydrocortisone whose inherent potency on MR is similar to that of aldosterone. As shown above, 11βHSD2 catalyses the reverse reaction inactivating hydrocortisone.

3. *Calcium metabolism* Glucocorticoids inhibit intestinal absorption and enhance renal excretion of Ca^{2+}. Loss of osteoid (decreased formation and increased resorption) indirectly results in loss of Ca^{2+} from bone, producing negative calcium balance. Spongy bones (vertebrae, ribs, pelvis, etc.) are more sensitive.

4. *Water excretion* The effect on water excretion is independent of action on Na^+ transport; hydrocortisone and other glucocorticoids, but not aldosterone, maintain normal g.f.r. In adrenal insufficiency, the capacity to excrete a water load is markedly reduced—such patients are prone to water intoxication from i.v. infusions.

Glucocorticoids also enhance secretory activity of renal tubules.

5. *CVS* Glucocorticoids restrict capillary permeability, maintain tone of arterioles and myocardial contractility. Applied topically, they cause cutaneous vasoconstriction. They play a permissive role for the pressor action of Adr and angiotensin, as well as a permissive role in the development of hypertension. Corticosteroids should be used cautiously in hypertensives.

Adrenal insufficiency is attended by low cardiac output, arteriolar dilatation, poor vasoconstrictor response to Adr (repeated doses of Adr cause destructive changes in blood vessels) and increased permeability of capillaries. These changes along with hypovolemia (due to lack of mineralocorticoid) are responsible for cardiovascular collapse.

6. *Skeletal muscles* Optimum level of corticosteroids is needed for normal muscular activity. Weakness occurs in both hypo- and hypercorticism, but the basis are different.

Hypocorticism: diminished work capacity and weakness are primarily due to hypodynamic circulation.

Hypercorticism: excess mineralocorticoid action produces hypokalaemia → weakness;
Excess glucocorticoid action causes muscle wasting and myopathy → weakness.

7. *CNS* Mild euphoria is quite common with pharmacological (supraphysiological) doses of glucocorticoids. This is a direct effect on brain, independent of relief of disease symptoms, and sometimes progresses to cause increased motor activity, insomnia, hypomania or depression. On the other hand, patients of Addison's disease suffer from apathy, depression and occasionally psychosis.

Glucocorticoids also maintain the level of sensory perception and normal level of excitability of neurones. High doses lower seizure threshold. Use of corticosteroids in epileptics requires caution. This action is independent of electrolyte changes in the brain and is not shared by aldosterone.

8. *Stomach* Secretion of gastric acid and pepsin is increased—may aggravate peptic ulcer.

9. *Foetal lungs* Glucocorticoids promote structural and functional maturation of foetal lungs near term. They stimulate production of pulmonary surfactants which are essential for inflation of foetal lungs at birth and air breathing.

10. *Lymphoid tissue and blood cells* Glucocorticoids enhance the rate of destruction of lymphoid cells (T cells are more sensitive than B cells); but in man the effect on normal lymphoid tissue is modest. However, a marked lytic response is shown by malignant lymphatic cells. This is the basis of their use in lymphomas.

Glucocorticoids increase the number of RBCs, platelets and neutrophils in circulation. They decrease lymphocytes, eosinophils and basophils. This is not due to destruction of the concerned cells, but due to their sequestration in tissues. Blood counts come back to normal after 24 hours.

11. *Inflammatory responses* Irrespective of the type of injury or insult, the attending inflammatory response is suppressed by glucocorticoids. This is the basis of most of their clinical uses. The action is nonspecific and covers all components and stages of inflammation. This includes attenuation of—increased capillary permeability, local exudation, cellular infiltration, phagocytic activity and late responses like capillary proliferation, collagen deposition, fibroblastic activity and ultimately scar formation. This action is direct and can be restricted to a site by local administration. The cardinal signs of inflammation—redness, heat, swelling and pain are suppressed.

Glucocorticoids interfere at several steps in the inflammatory response (*see* cellular mechanism below), but the most important overall mechanism appears to be limitation of recruitment of inflammatory cells at the local site and production of proinflammatory mediators like PGs, LTs, PAF through indirect inhibition of phospholipase A_2.

Corticoids are only palliative; do not remove the cause of inflammation; the underlying disease continues to progress while manifestations are dampened. They favour spread of infections because capacity of defensive cells to kill microorganisms is impaired. They also interfere with healing and scar formation: peptic ulcer may perforate asymptomatically. Indiscriminate use of corticoids is hazardous.

12. *Immunological and allergic responses* Glucocorticoids impair immunological competence. They suppress all types of hypersensitization and allergic phenomena. At high concentrations and *in vitro* they have been shown to interfere with practically every step of the immunological response, but at therapeutic

Gene mediated cellular actions of glucocorticoids

Mechanism	*Action*
• Translocation of glucose transporters from plasma membrane to deeper sites.	• ↓ glucose uptake and utilization in peripheral tissues.
• Induction of hepatic gluconeogenetic enzymes.	• ↑ production of glucose from amino acids.
• Induction of hepatic glycogen synthase.	• Deposition of glycogen in hepatocytes.
• Site specific changes in sensitivity of adipocytes to GH, Adr, insulin.	• Altered distribution of body fat.
• ↑ expression of vascular adrenergic and AT_1 receptor.	• Enhanced reactivity to vasopressor substances.
• ↓ expression of POMC gene in pituitary corticotropes	• ↓ production of ACTH.
Antiinflammatory and Immunosuppressant actions	
• Induction of annexins in macrophages, endothelium and fibroblasts.	• Annexins inhibit phospholipase A_2 → decreased production of PGs, LTs & PAF.
• Negative regulation of COX-2	• ↓ inducible PG production.
• Negative regulation of genes for cytokines in macrophages, endothelial cells and lymphocytes.	• ↓ production of IL-1, IL-2, IL-3, IL-6, TNFα, GM-CSF, γ interferon → fibroblast proliferation and T-lymphocyte function are suppressed, chemotaxis interfered.
• ↓ production of acute phase reactants from macrophages and endothelial cells	• Complement function is interfered.
• ↓ production of ELAM-1 and ICAM-1 in endothelial cells.	• Adhesion and localization of leukocytes is interfered.
• ↓ expression of transcription factors AP-1, NF-κB	• ↓ histone acetylation • ↓ MAP kinase
• ↓ production of collagenase and stromolysin	• Prevention of tissue destruction

POMC—Proopiomelanocortin; IL—Interleukin; TNFα—Tumour necrosis factor α; GM-CSF—Granulocyte macrophage colony stimulating factor; ELAM-1—Endothelial leukocyte adhesion molecule-1; ICAM-1—Intracellular adhesion molecule-1; AP-1–Activator protein-1; NF-κB–Nuclear factor κB; MAP kinase–Mitogen activated protein kinase.

doses *in vivo* there is no impairment of antibody production or complement function. The clinical effect appears to be due to suppression of recruitment of leukocytes at the site of contact with antigen and of inflammatory response to the immunological injury.

Glucocorticoids cause greater suppression of CMI in which T cells are primarily involved, e.g. delayed hypersensitivity and graft rejection. Suppression of CMI is the basis of their use in autoimmune diseases and organ transplantation (*see* Ch. 65). Factors involved may be inhibition of IL-1 release from macrophages; inhibition of IL-2 formation and action → T cell proliferation is not stimulated; suppression of natural killer cells, etc.

The broad action seems to be interruption of communication between cells involved in the immune process by interfering with production of lymphokines and/or their action.

Mechanism of action at cellular level

Corticosteroids penetrate cells and bind to a high affinity cytoplasmic receptor protein, due to which a structural change occurs in the steroid receptor complex that allows its migration into the nucleus and binding to glucocorticoid response elements (GRE) on the chromatin promoting transcription of specific m-RNA → regulation of protein synthesis (*see* Fig. 4.10). This process takes at least 30–60 min : effects of corticosteroid are not immediate, and once the appropriate proteins are synthesized—effects persist much longer than the steroid itself. In many tissues, the overall effect is catabolic, i.e. inhibition of protein synthesis. This may be a consequence of steroid directed synthesis of an inhibitory protein.

The glucocorticoid receptor (GR) is very widely distributed (in practically all cells). It has been cloned and its structure determined. It is made up of ~ 800 amino acids.

Several *coactivators* and *corepressors* modulate the interaction of liganded GR with the GREs, altering the intensity of response.

Because the GR largely maintains uniformity throughout the body, tissue specificity is not exhibited by different glucocorticoids, and all members produce the same constellation of effects.

The functional scheme of GR is presented in Fig. 4.10. Direct evidence of gene expression mediated action has been obtained for actions listed in the box (*see* p. 310).

Some actions of corticoids are exerted more rapidly (like inhibition of ACTH release from pituitary). These may be mediated by a cell membrane receptor or a different mechanism not involving protein synthesis.

PHARMACOKINETICS

All natural and synthetic corticoids, except DOCA are absorbed and are effective by the oral route. Absorption into systemic circulation occurs from topical sites of application as well, but the extent varies depending on the compound, site and area of application, and use of occlusive dressing. Water soluble esters, e.g. hydrocortisone hemisuccinate, dexamethasone sod. phosphate can be given i.v. or i.m., act rapidly and achieve high concentrations in tissue fluids. Insoluble esters, e.g. hydrocortisone acetate, triamcinolone acetonide cannot be injected i.v., but are slowly absorbed from i.m. site and produce more prolonged effects.

Hydrocortisone undergoes high first pass metabolism, has low oral: parenteral activity ratio. Oral bioavailability of synthetic corticoids is high.

Hydrocortisone is 90% bound to plasma protein, mostly to a specific cortisol-binding globulin (CBG or transcortin) as well as to albumin. Transcortin concentration is increased during pregnancy and by oral contraceptives—corticoid levels in blood are increased but hypercorticism does not occur, because free cortisol levels are normal.

The corticosteroids are metabolized primarily by hepatic microsomal enzymes. Pathways are—

- Reduction of 4, 5 double bond and hydroxylation of 3-keto group.
- Reduction of 20-keto to 20-hydroxy form.
- Oxidative cleavage of 20C side chain (only in case of compounds having a 17-hydroxyl group) to yield 17-ketosteroids.

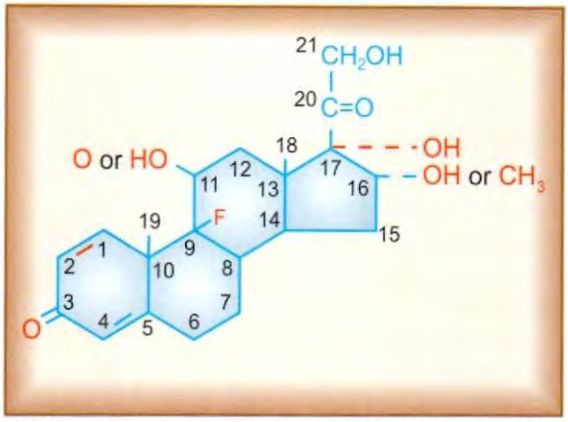


Fig. 20.3: Chemical structure of corticosteroids. The structure in blue is desoxycorticosterone. Important substitutions which yield other useful compounds are shown in red

+ OH at 11	— Corticosterone
+ OH at 11 + OH at 17	— Hydrocortisone
(if O at 11) + OH at 17	— Cortisone
+ OH at 11 + OH at 17 + Δ 1, 2	— Prednisolone
+ OH at 11 + OH at 17 + Δ 1, 2 + F at 9 + OH at 16	— Triamcinolone
+ OH at 11 + OH at 17 + Δ 1, 2 + F at 9 + CH_3 α at 16	— Dexamethasone
+ OH at 11 + OH at 17 + Δ 1, 2 + F at 9 + CH_3 β at 16	— Betamethasone
Hydrocortisone + F at 9	— Fludrocortisone
Corticosterone + CHO at 18	— Aldosterone

SECTION 5

These metabolites are further conjugated with glucuronic acid or sulfate and are excreted in urine.

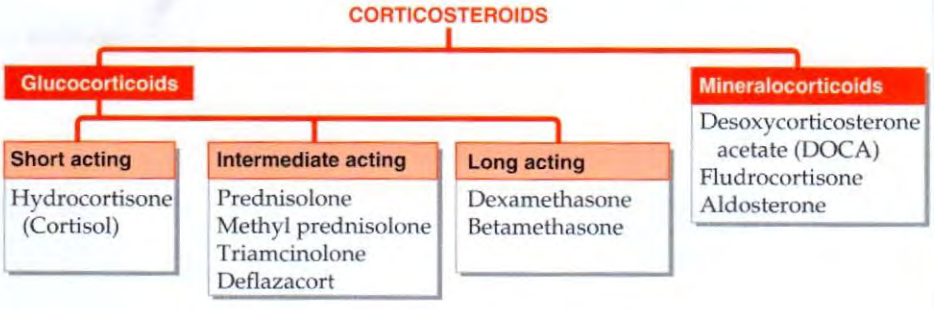
The plasma t½ of hydrocortisone is 1.5 hours. However, the biological t½ is longer because of action through intracellular receptors and regulation of protein synthesis—effects that persist long after the steroid is removed from plasma.

The synthetic derivatives are more resistant to metabolism and are longer acting.

Phenobarbitone and phenytoin induce metabolism of hydrocortisone, prednisolone and dexamethasone, etc. to decrease their therapeutic effect.

CHEMISTRY AND RELATIVE ACTIVITY OF CORTICOIDS

Fig. 20.3 depicts the chemical structure of desoxycorticosterone in blue line. It is a selective mineralocorticoid. Chemical modifications that result in clinically useful compounds are also indicated. Fluorination at position 9 or 6 has resulted in highly potent compounds. Synthetic steroids have largely replaced the natural compounds in therapeutic use, because they are potent, longer acting, more selective for either glucocorticoid or mineralocorticoid action and have high oral activity.



DISTINCTIVE FEATURES

The relative potency and activity of different natural and synthetic corticosteroids employed systemically is compared in Table 20.1.

1. Hydrocortisone (cortisol) It acts rapidly but has short duration of action. In addition to primary glucocorticoid, it has significant mineralocorticoid activity as well. Used for:
Replacement therapy—20 mg morning + 10 mg afternoon orally.
Shock, status asthmaticus, acute adrenal insufficiency—100 mg i.v. bolus + 100 mg 8 hourly i.v. infusion.
Topically (*see* Ch. 66) and as suspension for enema in ulcerative colitis (*see* Ch. 49).

LYCORTIN-S 100 mg/3 ml, 200 mg/5 ml inj; EFCORLIN SOLUBLE 100 mg/2 ml inj. (as hemisuccinate for i.v. inj.) WYCORT, EFCORLIN, HYDROCORTISONE ACETATE 25 mg/ml inj (as acetate for i.m./intraarticular inj.). PRIMACORT 100, 200, 400 mg/vial inj.

2. Prednisolone It is 4 times more potent than hydrocortisone, also more selective glucocorticoid, but fluid retention does occur with high doses. It has intermediate duration of action: causes less pituitary-adrenal suppression when a single morning dose or alternate day treatment is given. Used for allergic, inflammatory, autoimmune diseases and in malignancies: 5–60 mg/day oral, 10–40 mg i.m., intraarticular; also topically.

DELTACORTRIL, HOSTACORTIN-H, 5, 10 mg tab, 20 mg/ml (as acetate) for i.m., intraarticular inj., WYSOLONE, NUCORT, 5, 10, 20, 30, 40 mg tabs, OMNACORTIL 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg tab, 5 mg/ml oral susp, 5 mg/ml oral drops.

3. Methylprednisolone Slightly more potent and more selective than prednisolone: 4–32 mg/day oral. Methylprednisolone acetate has been used as a retention enema in ulcerative colitis.

Pulse therapy with high dose methylprednisolone (1 g infused i.v. every 6–8 weeks) has been tried in nonresponsive active rheumatoid arthritis, renal transplant, pemphigus, etc. with good results and minimal suppression of pituitary-adrenal axis.

SOLU-MEDROL Methylprednisolone (as sod. succinate) 4 mg tab; 40 mg, 125 mg, 0.5 g (8 ml) and 1.0 g (16 ml) inj, for i.m. or slow i.v. inj, DEESOLONE 4, 16 mg tabs, 0.5 g and 1.0 g. inj.

DEPOT MEDROL Methylprednisolone acetate 40 mg/ml and 80 mg/ml susp. for i.m. or intraarticular injection.

The initial effect of methylprednisolone pulse therapy (MPPT) is probably due to its antiinflammatory action, while long term benefit may be due to temporary switching off of the immunodamaging processes as a consequence of lymphopenia and decreased Ig synthesis.

4. Triamcinolone Slightly more potent than prednisolone but highly selective glucocorticoid:

Table 20.1: Relative activity of systemic corticosteroids

		Compound	Relative activity		Equiv. dose (antiinflammatory)
			Gluco	Mineralo	
Glucocorticoids	Short acting (Biological t½ < 12 hr)	1. Hydrocortisone (cortisol)	1	1	20 mg
	Intermediate acting (Biological t½ 12–36 hr)	2. Prednisolone	4	0.8	5 mg
		3. Methylprednisolone	5	0.5	4 mg
		4. Triamcinolone	5	0	4 mg
		5. Deflazacort	3–4	0	6 mg
	Long acting (Biological t½ > 36 hr)	6. Dexamethasone	25	0	0.75 mg
		7. Betamethasone	25	0	0.75 mg
Mineralocorticoids					*Equiv. salt retaining dose*
		8. Desoxycorticosterone acetate (DOCA)	0	100	2.5 mg (sublingual)
		9. Fludrocortisone	10	150	0.2 mg
		10. Aldosterone	0.3	3000	not used clinically

4–32 mg/day oral, 5–40 mg i.m., intraarticular injection. Also used topically.
KENACORT, TRICORT 1, 4, 8 mg tab., 10 mg/ml, 40 mg/ml (as acetonide) for i.m., intraarticular inj., LEDERCORT 4 mg tab.

5. Dexamethasone Very potent and highly selective glucocorticoid. It is also long-acting, causes marked pituitary-adrenal suppression, but fluid retention and hypertension are not a problem.

It is used for inflammatory and allergic conditions 0.5–5 mg/day oral. For shock, cerebral edema, etc. 4–20 mg/day i.v. infusion or i.m. injection is preferred. It can also be used topically.
DECADRON, DEXONA 0.5 mg tab, 4 mg/ml (as sod. phosphate) for i.v., i.m. inj., 0.5 mg/ml oral drops; WYMESONE, DECDAN 0.5 mg tab, 4 mg/ml inj.

6. Betamethasone Similar to dexamethasone, 0.5–5 mg/ day oral, 4–20 mg i.m., i.v. injection or infusion, also topical.
BETNESOL, BETACORTRIL, CELESTONE 0.5 mg, 1 mg tab, 4 mg/ml (as sod. phosphate) for i.v., i.m. inj., 0.5 mg/ml oral drops. BETNELAN 0.5 mg, 1 mg tabs.

Dexamethasone or betamethasone are preferred in cerebral edema and other states in which fluid retention must be avoided.

7. Deflazacort The glucocorticoid potency of this newer steroid is somewhat less than of prednisolone, but it lacks mineralocorticoid activity. It is claimed to produce fewer adverse effects, but that may be due to its lower potency. In some trials it caused lesser growth retardation in children; has been particularly recommended for pediatric patients. It is used mainly for inflammatory and immunological disorders.
Dose: 60–120 mg/day initially, 6–18 mg/day for maintenance; children 0.25–1.5 mg/kg daily or on alternate days.
DEFGLU 6, 30 mg tabs, DEFLAR, DEFZA, DFZ 1, 6, 30 mg tabs, DEFCORT 1 mg, 6 mg, 12 mg, 18 mg, 24 mg, 30 mg tabs, 6 mg/5 ml syr.

8. Desoxycorticosterone acetate (DOCA) It has only mineralocorticoid activity. Used occasionally for replacement therapy in Addison's disease: 2–5 mg sublingual, 10–20 mg i.m. once or twice weekly.

9. Fludrocortisone A potent mineralocorticoid having some glucocorticoid activity as well, orally active, used for:
Replacement therapy in Addison's disease 50–200 µg daily.
Congenital adrenal hyperplasia in patients with salt wasting 50–200 µg/day.
Idiopathic postural hypotension 100–200 µg/day.
FLORICORT 100 µg tab.

10. Aldosterone It is the most potent mineralocorticoid. Not used clinically because of low oral bioavailability and difficulties in regulating doses.

In addition a number of *topically* active glucocorticoids have been developed.

Beclomethasone dipropionate budesonide, fluticasone, etc. are used by inhalation in asthma, as spray in nasal allergy, as well as for skin and mucous membrane lesions (*see* Ch. 16).

Fluocinolone acetonide, fluocortolone, clobetasol propionate and esters of betamethasone, dexamethasone, triamcinolone are described in Ch. 66.

USES

A. Replacement therapy

1. *Acute adrenal insufficiency* It is an emergency. Hydrocortisone (100 mg) or dexamethasone (8–16 mg) are given i.v., first as a bolus injection and then as infusion, along with isotonic saline in glucose solution. The amount of fluid infused i.v. is guided by monitoring central venous pressure, because these patients have reduced capacity to excrete water load. Short-term i.v. infusion of a vasopressor (dopamine) may be needed. The cause of adrenal insufficiency should be treated.

2. *Chronic adrenal insufficiency (Addison's disease)* Hydrocortisone given orally is the most commonly used drug along with adequate salt and water allowance. Some patients who continue to excrete excess Na^+ need additional mineralocorticoid: fludrocortisone is added.

3. *Congenital adrenal hyperplasia (Adrenogenital syndrome)* It is a familial disorder due to genetic deficiency of steroidogenic enzymes, mostly 21-hydroxylase. As a result the synthesis of hydrocortisone and aldosterone suffers. There is compensatory increase in ACTH secretion causing adrenocortical hypertrophy. Enzyme deficiency being only partial in most cases, normal amounts of gluco- and mineralocorticoids are produced along with excessive amounts of weak androgens which produce virilization and/or precocious sexual development. If the deficiency is severe, salt wasting also occurs.

Treatment is to give hydrocortisone 0.6 mg/kg daily in divided doses round the clock to maintain feed back suppression of pituitary. If salt wasting persists—fludrocortisone 50–200 µg/day may be added.

B. Pharmacotherapy (for nonendocrine diseases)

Systemic as well as topical corticosteroids have one of the widest spectrum of medicinal uses for their antiinflammatory and immunosuppressive properties. Corticosteroids are powerful drugs. They have the potential to cause dramatic improvement in many severe diseases as well as produce equally dramatic adverse effects if not properly used. The use of corticosteroids in nonendocrine diseases is empirical and palliative, but may be life saving. The following *general principles* must be observed.

- A single dose (even excessive) is not harmful: can be used to tide over mortal crisis, even when benefit is not certain.
- Short courses (even high dose) are not likely to be harmful in the absence of contraindications; starting doses can be high in severe illness.
- Long-term use is potentially hazardous: keep the duration of treatment and dose to minimum, which is found by trial and error; even partial relief may have to be tolerated.
- Initial dose depends on severity of the disease; start with a high dose in severe illness—reduce gradually after symptoms subside, while in mild cases start with the lowest dose and titrate upwards to find the correct dose. The dose should be reassessed from time-to-time.
- No abrupt withdrawal after a corticoid has been given for > 2 to 3 weeks: may precipitate adrenal insufficiency.
- Infection, severe trauma, surgery or any stress during corticoid therapy—increase the dose.
- Use local therapy (cutaneous, inhaled, intranasal, etc.) wherever possible.

1. *Arthritides*

(i) *Rheumatoid arthritis*: Corticosteroids are indicated only in severe cases as adjuvants to NSAIDs when distress and disability persists despite other measures, or to suppress exacerbations, or when there are systemic manifestations (*see* Ch. 15).

(ii) *Osteoarthritis*: It is treated with analgesics and NSAIDs; systemic use of corticoids is rare. Intraarticular injection of a steroid may be given to control an acute exacerbation. Injections may be repeated 2–3 times a year, but have the potential to cause joint destruction.

(iii) *Rheumatic fever:* Corticoids are used only in severe cases with carditis and CHF with the aim of rapid suppression of symptoms, because they act faster than aspirin, or in patients not responding to aspirin. Aspirin is given in addition and is continued after corticoids have been withdrawn.

(iv) *Gout:* Corticoids (short course) should only be used in *acute gouty arthritis* when NSAIDs have failed to afford relief and colchicine is not tolerated. Intraarticular injection of a soluble glucocorticoid is preferable to systemic therapy but is reserved for selected cases (*see* p. 232).

Though they are uricosuric—use in chronic gout is not recommended.

2. *Collagen diseases*

Most cases of systemic lupus erythematosus, polyarteritis nodosa, dermatomyositis, nephrotic syndrome, glomerulonephritis and related diseases need corticosteroid therapy. They may be life saving in these diseases. Therapy is generally started with high doses which are tapered to maintenance dose when remission occurs. Later other immunosuppressants may be added or substituted.

3. *Severe allergic reactions*

Corticoids may be used for short periods in anaphylaxis, angioneurotic edema, urticaria and serum sickness. However, even i.v. injection of a glucocorticoid takes 1–2 hours to act and is not a substitute for Adr (which acts immediately) in anaphylactic shock and angioedema of larynx. Topical use is made in allergic conjunctivitis and rhinitis.

4. *Autoimmune diseases*

Autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, active chronic hepatitis respond to

corticoids. Prednisolone 1–2 mg/kg/day is given till remission, followed by gradual withdrawal or low-dose maintenance depending on the response. Remission may also be induced in severe cases of myasthenia gravis, in which their use is adjunctive to neostigmine. Patients requiring long term maintenance therapy are better shifted to other immunosuppressants.

5. *Bronchial asthma* Early institution of inhaled glucocorticoid therapy is now recommended in most cases needing inhaled β_2 agonists almost daily (*see* Ch. 16). Systemic corticosteroids are used only for:

- Status asthmaticus: give i.v. glucocorticoid; withdraw when emergency is over.
- Acute asthma exacerbation: short-course of high dose oral corticoid, followed by gradual withdrawal.
- Severe chronic asthma not controlled by inhaled steroids and bronchodilators: add low dose prednisolone daily or on alternate days.

6. *Other lung diseases* Corticosteroids benefit aspiration pneumonia and pulmonary edema from drowning. Given during late pregnancy, corticoids accelerate lung maturation and surfactant production in the foetal lung and prevent respiratory distress syndrome at birth. Two doses of betamethasone or dexamethasone 12 mg i.m. at 24-hour interval may be administered to the mother if premature delivery is contemplated. Betamethasone or dexamethasone are preferred because of their higher placental transfer.

7. *Infective diseases* Administered under effective chemotherapeutic cover, corticosteroids are indicated only in serious infective diseases to tideover crisis or to prevent complications. They are indicated in conditions like severe forms of tuberculosis (miliary, meningeal, renal, etc.), severe lepra reaction, certain forms of bacterial meningitis and *Pneumocystis carinii* pneumonia with hypoxia in AIDS patients.

8. *Eye diseases* Corticoids are used in a large number of inflammatory ocular diseases. In certain severe conditions, they may prevent blindness. Topical instillation as eye drops or ointment is effective in diseases of the anterior chamber, e.g. allergic conjunctivitis, iritis, iridocyclitis, keratitis, etc. Ordinarily, steroids should not be used in infective conditions. But if inflammation is severe, they may be applied in conjunction with an effective antibiotic. Steroids are contraindicated in herpes simplex keratitis and in ocular injuries. Posterior segment afflictions like retinitis, optic neuritis, uveitis require systemic steroid therapy. Retrobulbar injection is occasionally given to avoid systemic side effects.

9. *Skin diseases* (*see* Ch. 66) Topical corticosteroids are widely employed and are highly effective in many eczematous skin diseases. Systemic therapy is needed (may be life-saving) in pemphigus vulgaris, exfoliative dermatitis, Stevens-Johnson syndrome and other severe afflictions.

10. *Intestinal diseases* Ulcerative colitis, Crohn's disease, coeliac disease are inflammatory bowel diseases with exacerbations and remissions. Corticoids are indicated during acute phases—may be used orally or as retention enema (for colonic involvement). They are particularly valuable for patients with systemic manifestations, and are given in addition to sulfasalazine/mesalazine ± other measures (*see* Ch. 49). Some specialists advocate small maintenance doses to prevent relapses.

11. *Neurological conditions* Cerebral edema due to tumours, tubercular meningitis, etc., responds to corticoids. Dexa- or betamethasone are preferred because they donot have Na^+ retaining activity. Their value in traumatic and poststroke cerebral edema is questionable. Large doses given i.v. soon after spinal injury may reduce the resulting neurological sequelae.

A short course (2–4 weeks) of oral prednisolone can hasten recovery from Bell's palsy and acute exacerbation of multiple sclerosis. In the latter, methyl prednisolone 1 g i.v. daily for 2–3 days may be given in the beginning.

Neurocysticercosis: When albendazole/praziquantel is used to kill cysticerci lodged in the brain, prednisolone 40 mg/day or equivalent is given for 2–4 weeks to suppress the reaction to the dying larvae.

12. *Nausea and vomiting* Dexamethasone 8–20 mg i.v. is frequently used to augment the antiemetic effect of ondansetron or metoclopramide against highly emetogenic cancer chemotherapy. High dose glucocorticoids by themselves afford modest protection from chemotherapy induced as well as general anaesthesia associated nausea and vomiting, probably due to their anti-inflammatory action.

13. *Malignancies* Corticoids are an essential component of combined chemotherapy of acute lymphatic leukaemia, Hodgkin's and other lymphomas, because of their marked lympholytic action in these conditions. They have a secondary place in hormone responsive breast carcinoma—act probably by causing HPA suppression so as to reduce production of adrenal androgens which are converted to estrogens in the body (*see* Ch. 64).

Corticoids also afford symptomatic relief in other advanced malignancies by improving appetite and controlling secondary hypercalcaemia. For hypercalcaemia, however, bisphosphonates are more effective and have superseded corticosteroids.

14. *Organ transplantation and skin allograft* High dose corticoids are given along with other immunosuppressants to prevent the rejection reaction. Low maintenance doses may be continued over long term ± maintenance doses of companion drugs (*see* Ch. 65).

15. *Septic shock* High-dose corticosteroid therapy for septic shock has been abandoned, because it worsens the outcome. However, many such patients have relative adrenal insufficiency. Recent studies have documented beneficial effects of low-dose (hydrocortisone 100 mg 8 hourly i.v. infusion for 5–7 days) therapy in patients who are adrenal deficient and who do not respond adequately to fluid replacement and vasopressors.

16. *Thyroid storm* Many patients in thyroid storm have concomitant adrenal insufficiency. Moreover, corticosteroids reduce peripheral T_4 to T_3 conversion. Hydrocortisone 100 mg i.v. 8 hourly may improve the outcome.

17. *To test pituitary-adrenal axis function* Dexamethasone suppresses pituitary-adrenal axis at doses which do not contribute to steroid metabolites in urine. Responsiveness of the axis can be tested by measuring daily urinary steroid metabolite excretion after dosing with dexamethasone.

ADVERSE EFFECTS

These are extension of the pharmacological action which become prominent with prolonged therapy, and are a great limitation to the use of corticoids in chronic diseases.

A. Mineralocorticoid Sodium and water retention, edema, hypokalaemic alkalosis and a progressive rise in BP. These are now rare due to availability of highly selective glucocorticoids.

Gradual rise in BP occurs due to excess glucocorticoid action as well.

B. Glucocorticoid

1. Cushing's habitus: characteristic appearance with rounded face, narrow mouth, supraclavicular hump, obesity of trunk with relatively thin limbs.
2. Fragile skin, purple striae—typically on thighs and lower abdomen, easy bruising, telangiectasis, hirsutism. Cutaneous atrophy localized to the site occurs with topical application as well.
3. Hyperglycaemia, which may lead to glycosuria, precipitation of diabetes.
4. Muscular weakness: proximal (shoulder, arm, pelvis, thigh) muscles are primarily affected. Myopathy occurs occasionally, warrants withdrawal of the corticoids.
   To offset the catabolic state, patients receiving corticosteroid therapy longer than 2 weeks should be put on high protein, high potassium diet.
5. Susceptibility to infection: this is nonspecific for all types of pathogenic organisms. Latent tuberculosis may flare; opportunistic infections with low grade pathogens (*Candida,* etc.) set in.

6. Delayed healing: of wounds and surgical incisions.
7. Peptic ulceration: risk is doubled; bleeding and silent perforation of ulcers may occur. Dyspeptic symptoms are frequent with high dose therapy.
8. Osteoporosis: especially involving vertebrae and other flat spongy bones. Compression fractures of vertebrae and spontaneous fracture of long bones can occur, especially in the elderly. Radiological evidence of osteoporosis is an indication for withdrawal of corticoid therapy. Corticosteroid induced osteoporosis can be prevented/arrested to some extent by calcium supplements + vit D, but bisphosphonates are the most effective drugs in this regard.

   Avascular necrosis of head of femur, humerous, or knee joint is an occasional abrupt onset complication of high dose corticosteroid therapy.
9. Posterior subcapsular cataract may develop after several years of use, especially in children.
10. Glaucoma: may develop in susceptible individuals after prolonged topical therapy.
11. Growth retardation: in children occurs even with small doses if given for long periods. Large doses do inhibit GH secretion, but growth retardation may, in addition, be a direct cellular effect of corticoids. Recombinant GH given concurrently can prevent growth retardation, but risk/benefit of such use is not known.
12. Foetal abnormalities: Cleft palate and other defects are produced in animals, but have not been encountered on clinical use in pregnant women. The risk of abortion, still-birth or neonatal death is not increased, but intrauterine growth retardation can occur after prolonged therapy, and neurological/behavioral disturbances in the offspring are feared. Prednisolone appears safer than dexa/beta methasone, because it is metabolized by placenta, reducing foetal exposure. There is no evidence of foetal growth retardation occurring after short term use in the mother.

    Prolonged corticosteroid therapy during pregnancy increases the risk of gestational diabetes, pregnancy induced hypertension and preeclampsia.
13. Psychiatric disturbances: mild euphoria frequently accompanies high dose steroid treatment. This may rarely progress to manic psychosis. Nervousness, decreased sleep and mood changes occur in some patients. Rarely a depressive illness may be induced after long-term use.
14. Suppression of hypothalamo-pituitary-adrenal (HPA) axis: occurs depending both on dose and duration of therapy. In time, the adrenal cortex atrophies. Stoppage of exogenous steroid precipitates withdrawal syndrome consisting of malaise, fever, anorexia, nausea, postural hypotension, electrolyte imbalance, weakness, pain in muscles and joints and reactivation of the disease for which the steroid was used. Subjected to stress, these patients may go into acute adrenal insufficiency leading to cardiovascular collapse.

Any patient who has received > 20–25 mg/day hydrocortisone, or ≥ 5 mg prednisolone/day or equivalent for longer than 2–3 weeks should be put on a scheme of gradual withdrawal: 20 mg hydrocortisone/day reduction every week and then still smaller fractions once this level has been achieved. Such patients may need protection with a corticosteroid (oral or i.v.) if a stressful situation develops up to one year after withdrawal. Administration of ACTH during withdrawal does not hasten recovery because it has been found that adrenals recover earlier than pituitary and hypothalamus.

If a patient on corticosteroid therapy develops an infection—the *steroid should not be discontinued* despite its propensity to weaken host defence and delay healing. Rather, the dose may have to be increased to meet the stress of infection. Surgery in such a patient should be covered by intraoperative and postoperative i.v. hydrocortisone till the condition stabilizes, followed by oral prednisolone.

Measures that minimise HPA axis suppression are:

(a) Use shorter acting steroids (hydrocortisone, prednisolone) at the lowest possible dose.

(b) Use steroids for the shortest period of time possible.

(c) Give the entire daily dose at one time in the morning.

(d) Switch to alternate-day therapy if the condition does not deteriorate on the 'off' day.

It has been found that moderate dose of a short acting steroid (e.g. prednisolone) given at 48 hr interval did not cause HPA suppression, whereas the same total amount given in 4 divided 12 hourly doses produced marked HPA suppression. Alternate-day therapy also resulted in less immunological suppression—lower risk of infection. The longer acting steroids (dexamethasone, etc.) are not suitable for alternate-day therapy. Only problem with alternate-day therapy is that many steroid dependent patients are incapacitated on the 'off day'.

(e) If appropriate, use local (dermal, inhaled, ocular, nasal, rectal, intrasynovial) preparations of a steroid with poor systemic availability (beclomethasone dipropionate, triamcinolone acetonide, fluticasone, etc.).

CONTRAINDICATIONS

The following diseases are aggravated by corticosteroids. Since corticosteroids may have to be used as a life-saving measure, all of these are relative contraindications in the presence of which these drugs are to be employed only under compelling circumstances, and with due precautions.

1. Peptic ulcer
2. Diabetes mellitus
3. Hypertension
4. Viral and fungal infections
5. Tuberculosis and other infections
6. Osteoporosis
7. Herpes simplex keratitis
8. Psychosis
9. Epilepsy
10. CHF
11. Renal failure

Combination of any other drug with corticosteroids in fixed dose formulation for internal use is banned.

Metyrapone It inhibits 11-β hydroxylase in adrenal cortex and prevents synthesis of hydrocortisone so that its blood level falls → increased ACTH release → increased synthesis, release and excretion of 11-desoxycortisol in urine. Thus, it is used to test the responsiveness of pituitary and its ACTH producing capacity.

Aminoglutethimide, trilostane and high doses of the antifungal drug *Ketoconazole* also inhibit steroidogenic enzymes—can be used to treat Cushing's disease when surgery or other measures are not an option. Ketoconazole reduces gonadal steroid synthesis as well.

Glucocorticoid antagonist The antiprogestin *mifepristone* (*see* p. 345–46) acts as a glucocorticoid receptor antagonist as well. In Cushing's syndrome, it can suppress the manifestations of corticosteroid excess, but blockade of feedback ACTH inhibition leads to oversecretion of ACTH → more hydrocortisone is produced, which tends to annul the GR blocking action of mifepristone. It is indicated only for inoperable cases of adrenal carcinoma and in patients with ectopic ACTH secretion.

☞ PROBLEM DIRECTED STUDY

20.1 A 35-year female patient of inflammatory bowel disease was treated with prednisolone 40 mg/day and mesalazine 800 mg TDS. After 4 weeks, the symptoms subsided and prednisolone dose was tapered at the rate of 10 mg every 2 weeks. When she was taking 10 mg prednisolone/day, she met with a road-side accident and suffered compound fracture of both bones of the right leg. Internal fixation of the fracture and suturing of wounds under general anaesthesia is planned.

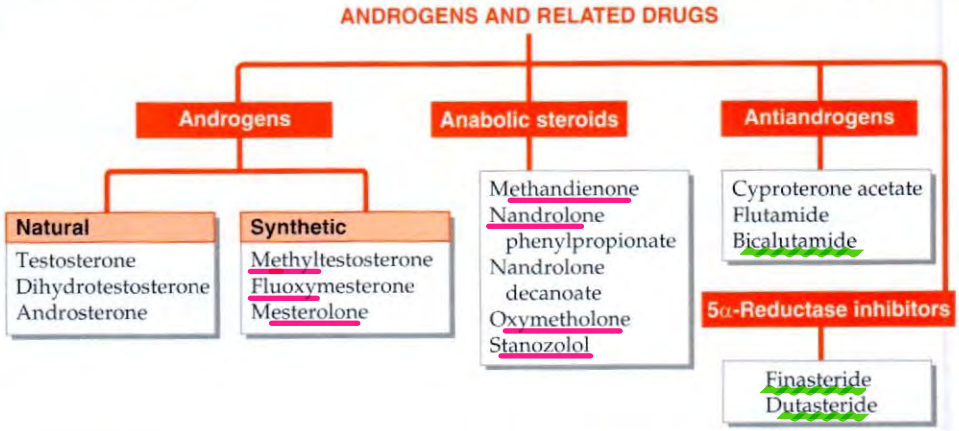
(a) Whether any additional measure needs to be taken during surgery in view of her corticosteroid therapy?

(b) Does the prednisolone therapy need discontinuation or any alteration in the postoperative period? Give reasons.

(see Appendix-1 for solution)

Chapter 21 Androgens and Related Drugs, Drugs for Erectile Dysfunction

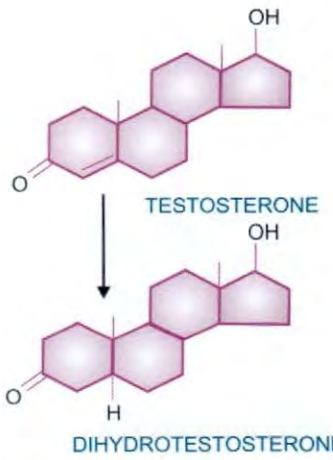
Drugs that have androgenic action or that modify androgen function can be grouped as follows:



ANDROGENS (Male Sex Hormones)

These are substances which cause development of secondary sex characters in the castrated male. That testes are responsible for the male characters is known since prehistoric times. Its endocrine function was established by Berthold in 1849. *Testosterone* was isolated as the testicular hormone, its structure was worked out and it was synthetically prepared by the year 1935.

Natural androgens Testes of adult male produce 5–12 mg of *testosterone* daily, a part of which is converted in extraglandular tissues to the more active *dihydrotestosterone* (DHT); by the enzyme steroid 5 α-reductase; cholesterol is the starting material and the same pathway depicted in Fig. 20.1 is utilized. Adrenal cortex produces small quantities of *dehydroepiandrosterone* and *androstenedione* which are called 'weak androgens' (potency 1/20 to 1/30), but are infact inactive as such, and derive their weak activity from partial conversion to testosterone



↦ sublingual

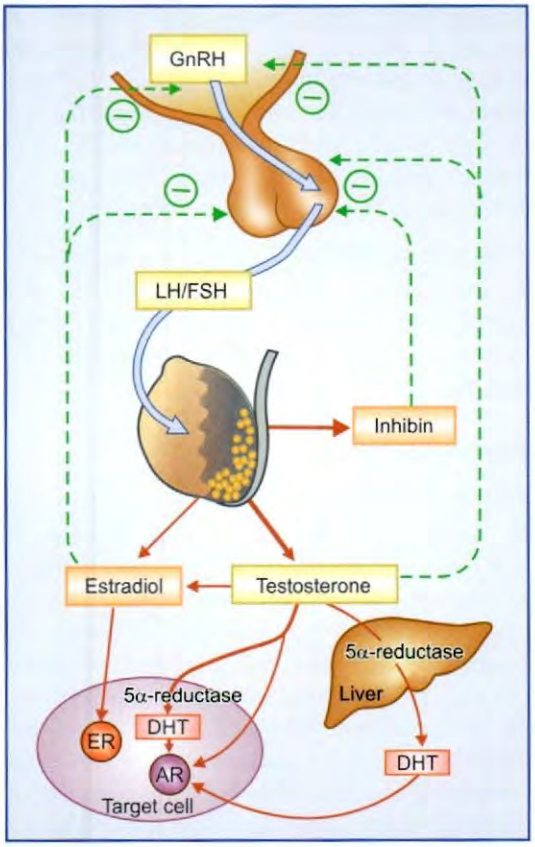


Fig. 21.1: Production of sex steroids and their regulation in the male
In liver and many target cells the 5α-reductase enzyme converts testosterone to the more potent androgen dihydrotestosterone (DHT) which combines more avidly with the androgen receptor (AR). The aromatase enzyme in testes, liver and adipose tissue converts some testosterone into estradiol which exerts certain actions in male target cells by combining with estrogen receptor (ER) and is probably important for feedback inhibition of gonadotropins (LH/FSH) as well as that of gonadotropin releasing hormone (GnRH) from hypothalamus.

in peripheral tissues. Adrenals themselves do not produce significant quantity of testosterone. In women ovary produces small quantity of testosterone; this together with that derived indirectly from adrenals amounts to 0.25–0.5 mg/day.

Androsterone It is a metabolite of testosterone which is excreted in urine. It has 1/10 the activity of testosterone.

Synthetic androgens *Methyltestosterone* and *fluoxymesterone* are 17-alkyl substituted derivatives of testosterone which are orally active because of resistance to first pass metabolism, but have submaximal androgenic efficacy and potential to cause cholestatic jaundice. Other orally active compounds are *testosterone undecanoate* which is administered as oily solution to be absorbed through lymphatics bypassing the liver, and *mesterolone*. A number of lipid-soluble esters of testosterone have been produced, suitable for injection in oily vehicle, from which they are absorbed slowly and exert prolonged action after deesterification in the body.

Regulation of secretion

Testosterone is secreted by the interstitial (Leydig) cells of the testes under the influence of pulsatile secretion of LH from pituitary. FSH is mainly responsible for promotion of spermatogenesis in tubular (Sertoli) cells. The mediator of feedback relationship with pituitary is uncertain. While relatively high concentration of testosterone inhibits LH secretion and in time causes atrophy of interstitial cells, it has only weak inhibitory action on FSH secretion. Estrogens are more potent inhibitors of Gn secretion even in males, and it is believed that the small amount of estradiol produced by testes as well as that generated from conversion of testosterone to estradiol in liver and fat plays a role in the feedback inhibition. *Inhibin* (a protein), produced by Sertoli cells, has strong FSH inhibitory action and may be mediating the feedback inhibition. Testosterone and estradiol act on hypothalamus to reduce GnRH as well as act directly on pituitary. The plasma level of testosterone in adult males ranges from 0.3 to 1 μg/dl. In women, small amounts of testosterone are produced by corpus luteum and adrenal cortex; blood levels remain low (20–60 ng/dl).

ACTIONS

1. Sex organs and secondary sex characters (Androgenic) Testosterone is responsible for all the changes that occur in a boy at puberty:

Growth of genitals—penis, scrotum, seminal vesicles, prostate.

Growth of hair—pubic, axillary, beard, moustache, body hair and male pattern of its distribution.

Thickening of skin which becomes greasy due to proliferation and increased activity of sebaceous glands—especially on the face. The duct often gets blocked and infection occurs resulting in acne. Subcutaneous fat is lost and veins look prominent.

Larynx grows and voice deepens.

Behavioural effects are—increased physical vigour, aggressiveness, penile erections. Male libido appears to be activated by testosterone directly, and probably to a greater extent by estradiol produced from testosterone.

Testosterone is also important for the intrauterine development of the male phenotype. Relatively large amounts of testosterone are produced by the foetal testes during the first half of intrauterine life.

2. Testes Moderately large doses cause testicular atrophy by inhibiting Gn secretion from pituitary. Still larger doses have a direct sustaining effect and atrophy is less marked. Testosterone is needed for normal spermatogenesis and maturation of spermatozoa. High concentration of testosterone is attained locally in the spermatogenic tubules by diffusion from the neighbouring Leydig cells and stimulates spermatogenesis.

3. Skeleton and skeletal muscles (Anabolic) Testosterone is responsible for the pubertal spurt of growth in boys and to a smaller extent in girls. There is rapid bone growth, both in thickness as well as in length. After puberty, the epiphyses fuse and linear growth comes to a halt. Estradiol produced from testosterone, and not testosterone itself, is responsible for fusion of epiphyses in boys as well as in girls. Moreover, estradiol largely mediates the effect of testosterone on bone mineralization. Testosterone also promotes muscle building, especially if aided by exercise. There is accretion of nitrogen, minerals (Na, K, Ca, P, S) and water—body weight increases rapidly, more protoplasm is built. Appetite is improved and a sense of well being prevails. The nitrogen retaining and muscle building effect of exogenous androgens is more marked in women and children than in adult men. Testosterone given to patients prone to salt and water retention may develop edema.

4. Erythropoiesis Testosterone accelerates erythropoiesis by increasing erythropoietin production and probably direct action on haeme synthesis. Men have higher hematocrit than women.

Mechanism of action

Testosterone can largely be regarded as the circulating prohormone. In most target cells, the 4–5 double bond is reduced producing *dihydrotestosterone*—which binds more avidly with the cytoplasmic androgen receptor (AR), and this complex is more active than testosterone-receptor complex in combining with DNA. No subtypes of AR are known; both genital and nongenital (muscle, bone) cells express the same AR. After combining with androgen response elements of the target genes, DNA transcription is enhanced/repressed with the help of coactivators or corepressors, which may be tissue specific. The effects are expressed through modification of protein synthesis.

The 5α-reductase enzyme exists in two isoforms: 5α-reductase-1 and 5α-reductase-2. The genital skin of both sexes and urogenital tract of male contains 5α-reductase-2 which is more sensitive to inhibition by finasteride. Genetic deficiency of this isoenzyme causes male pseudohermaphroditism because of inability of male genitalia to produce the active hormone dihydrotestosterone from circulating testosterone. 5α-reductase-1 has a wider distribution in the body including nongenital skin and liver; and is inhibited by finasteride to a lesser extent.

Testosterone itself appears to be the active hormone at certain sites, such as—

- foetal genital rudiments
- hypothalamus/pituitary site involved in feed back regulation
- erythropoietic cells
- spermatogenic cells in testes.

Principal androgen for different target tissue actions

Testosterone	*Dihydrotestosterone*
Pituitary: LH inhibition	• External genitalia (scrotum, penis, male urethra) formation in foetus and maturation during puberty
Testes: Spermatogenesis	• Pubertal changes, sexual maturity, male behaviour
Internal genitalia (epididymis, vas deferens, seminal vesicle) development in foetus	• Prostate growth; hypertrophy in elderly
Erythropoiesis	• Hair follicles: growth during puberty, scalp hair loss in adults
Bone and skeletal muscle: increase in mass and strength	

PHARMACOKINETICS

Testosterone is inactive orally due to high first pass metabolism in liver. The duration of action after i.m. injection is also very short. Therefore, slowly absorbed esters of testosterone are used by this route; they are hydrolysed to the active free form. While testosterone propionate is short acting, and needs daily injections, the enanthate, cypionate, isocaproate and decanoate esters are long acting; can be injected every 2–4 weeks depending on the dose. The latter are preferred for long term replacement therapy. Testosterone in circulation is 98% bound to sex hormone binding globulin (SHBG) and to albumin. The SHBG bound testosterone is unavailable for action due to tight binding.

The major metabolic products of testosterone are androsterone and etiocholanolone which are excreted in urine, mostly as conjugates with glucuronic acid and sulfate. Small quantities of estradiol are also produced from testosterone by aromatization of A ring in extraglandular tissues (liver, fat, hypothalamus). Plasma t½ of testosterone is 10–20 min.

Methyltestosterone and fluoxymesterone are metabolized slowly and have a longer duration of action, but are weaker androgens. Estrogens are not produced from fluoxymesterone and dihydrotestosterone.

Preparations and Dose

1. Testosterone (free): 25 mg i.m. daily to twice weekly; AQUAVIRON 25 mg in 1 ml inj.

2. Testosterone propionate: 25–50 mg i.m. daily to twice weekly: TESTOVIRON, PARENDREN, TESTANON 25, 50 mg/ml inj.

3. TESTOVIRON DEPOT 100: testo. propionate 25 mg + testo. enanthate 100 mg in 1 ml amp; 1 ml i.m. weekly.

4. TESTOVIRON DEPOT 250: testo. propionate 250 mg + testo. enanthate 250 mg in 1 ml amp; i.m. every 2–4 weeks.

5. SUSTANON '100': testo. propionate 20 mg + testo. phenyl propionate 40 mg + testo. isocaproate 40 mg in 1 ml amp; 1 ml i.m. every 2–3 weeks.

6. SUSTANON '250': testo. propionate 30 mg + testo. phenylpropionate 60 mg + testo. isocaproate 60 mg + testo. decanoate 100 mg in 1 ml amp; 1 ml i.m. every 3–4 weeks.

7. NUVIR, ANDRIOL; Testosterone undecanoate 40 mg cap, 1–3 cap daily for male hypogonadism, osteoporosis.

8. Mesterolone: Causes less feedback inhibition of Gn secretion and spermatogenesis, and has been promoted for treatment of male infertility PROVIRONUM, RESTORE, MESTILON 25 mg tab; 1–3 tab daily for androgen deficiency, oligozoospermia and male infertility.

Transdermal androgen Delivery of androgen across skin has been achieved by developing suitable solvents and absorption facilitators. By cutaneous delivery, testosterone/dihydrotestosterone circumvent hepatic first pass metabolism and uniform blood levels are produced round the clock. A gel formulation has been marketed for once daily application which has become the preferred method of androgen replacement for hypogonadism and impotence.

ANDRACTIM: Dihydrotestosterone 25 mg/g gel (100 g tube); 5–10 g gel to be applied over nonscrotal skin once daily.

Fixed dose combinations of testosterone with yohimbine, strychnine and vitamins are banned in India.

SIDE EFFECTS

1. Administered to women, androgens can cause virilization, excess body hair and menstrual irregularities. Many effects, e.g. voice change may be permanent after prolonged therapy.
2. Acne: in both males and females.
3. Frequent, sustained and often painful erections in males in the beginning of therapy; subside spontaneously after sometime.
4. Oligozoospermia can occur with moderate doses given for a few weeks to men with normal testosterone levels. Prolonged use may produce testicular atrophy.
5. Precocious puberty, premature sexual behaviour, and stunting of stature due to early closure of epiphysis—if testosterone is given continuously to young boys for increasing stature.
6. Salt retention and edema: especially when large doses are given to patients with heart or kidney disease. This is rare with the doses used for hypogonadism.
7. Cholestatic jaundice: occurs with methyltestosterone and other 17-alkyl substituted derivatives (fluoxymesterone and some anabolic steroids like oxymetholone, stanozolol) in a dose dependent manner, but not with parenterally used esters of testosterone. For this reason, the latter are preferred. However, the jaundice is reversible on discontinuation.
8. Hepatic carcinoma: incidence is higher in patients who have received long-term methyltestosterone or other oral androgens.
9. Gynaecomastia: may occur, especially in children and in patients with liver disease. This is due to peripheral conversion of testosterone to estrogens. Dihydrotestosterone does not cause gynaecomastia because it is not converted to estradiol.
10. Lowering of HDL and rise in LDL levels, especially with 17α-alkylated analogues.

Contraindications Androgens are contraindicated in carcinoma of prostate and carcinoma of male breast, as well as in liver and kidney disease and during pregnancy (masculinization of female foetus). They should not be given to men aged >65 years, and to those with coronary artery disease or CHF. Androgen therapy can worsen sleep apnoea, migraine and epilepsy.

USES

1. *Testicular failure* It may be primary, which is noticed during childhood, and results in delayed puberty. Treatment with parenteral testosterone esters or transdermal testosterone/dihydrotestosterone in courses of 4–6 months at a time may achieve satisfactory results/normal adult stature if administered judiciously to avoid acceleration of epiphyseal closure which occurs if the dose is high. Secondary testicular failure (hypogonadism) occurring later in life manifests mainly as loss of libido, muscle mass and energy, feminization, mild anaemia and impotence. These are corrected gradually over months by androgen treatment. However, impotence due to psychological and other factors, and not testosterone deficiency, does not respond.

2. *Hypopituitarism* Hypogonadism is one of the features of hypopituitarism. Androgens are added at the time of puberty in boys to other hormonal replacement.

3. *AIDS related muscle wasting* Testosterone therapy has been shown to improve weakness and muscle wasting in AIDS patients with low testosterone levels.

4. *Hereditary angioneurotic edema* This is a genetic disorder. The attacks can be prevented by 17α-alkylated androgens (methyltestosterone, stanozolol, danazol) but not by testosterone. These drugs act by increasing the synthesis of complement (C1) esterase inhibitor.

5. *Ageing* Because testosterone levels decline in old age, it has been administered to elderly males with the aim of improving bone mineralization and muscle mass. However, safety of such therapy in terms of metabolic, cardiovascular and prostatic complications is not known.

Occasionally small amount of androgen is added to postmenopausal hormone replacement.

6. *Idiopathic male infertility* Since high intratesticular level of testosterone is essential for spermatogenesis, it is presumed that exogenous androgens will stimulate spermatogenesis or improve sperm maturation in epididymis. On the other hand, androgens can adversely affect spermatogenesis by suppressing Gn secretion. Since mesterolone causes less feedback inhibition of Gn (probably due to restricted entry into brain) it is believed that moderate doses will predominantly stimulate testis directly.

A recent metaanalysis of 11 clinical trials has found that oral androgens (mesterolone and testosterone undecanoate) had no effect on sperm count or sperm motility as well as on subsequent pregnancy rate when given to oligo-astheno-spermic subfertile men. As such, use of these androgens for improving male fertility is not backed by objective evidence.

ANABOLIC STEROIDS

These are synthetic androgens with supposedly higher anabolic and lower androgenic activity. Drugs are *Nandrolone, Oxymetholone, Stanozolol* and *Methandienone.*

The anabolic: androgenic activity ratio is determined by injecting the drug in castrated rats and measuring the increase in weight of levator ani muscles to that of ventral prostate. The anabolic: androgenic ratio of testosterone is considered as 1; The anabolic selectivity of these steroids is modest with ratios between 1 to 3 in the rat model, and probably still lower in man. The anabolic effects are similar to that of testosterone and are mediated through the same receptor as the androgenic effects. For all practical purposes, they are androgens.

Preparations and dose

1. Methandienone: 2–5 mg OD–BD oral; children 0.04 mg/kg/day, 25 mg i.m. weekly; ANABOLEX 2, 5 mg tab, 2 mg/ml drops, 25 mg/ml inj.
2. Nandrolone phenyl propionate: 10–50 mg; children 10 mg; i.m. once or twice weekly; DURABOLIN 10, 25 mg/ml inj.
3. Nandrolone decanoate: 25–100 mg i.m. every 3 weeks, DECADURABOLIN, 25, 100 mg/ml inj.
4. Oxymetholone: 5–10 mg, children 0.1 mg/kg, OD; ADROYD 5 mg tab.
5. Stanozolol: 2–6 mg/day, MENABOL, NEURABOL, TANZOL 2 mg tab.

Combination of anabolic steroids with any other drug is banned in India.

Side effects Anabolic steroids were developed with the idea of avoiding the virilizing side effects of androgens while retaining the anabolic effects. But the same adverse effect profile applies to these compounds.

The 17-alkyl substituted compounds oxymetholone, stanozolol, can produce jaundice and worsen lipid profile.

Contraindications are same as for testosterone.

Uses

1. *Catabolic states* Acute illness, severe trauma, major surgery, etc. are attended by negative N balance. Anabolic steroids can reduce N_2 loss over short periods, but long-term benefits are questionable. They may cause a transient response in the elderly, under-nourished or debilitated individuals, but controlled studies have failed to demonstrate a difference in the total weight gained. However, short-term use may be made during convalescence for the sense of wellbeing and improvement in appetite caused by such treatment.

2. *Osteoporosis* In elderly males and that occurring due to prolonged immobilization may respond to anabolic steroids, but bisphosphonates are more effective and are the preferred drugs.

3. *Suboptimal growth in boys* Use of anabolic steroids for accelerating the growth rate is controversial; somatropin is a better option. Brief spurts in linear growth can be induced by anabolic steroids, but this probably does not make a difference in the final stature, except in hypogonadism. Use for more than 6 months is not recommended—premature closure of epiphyses and shortening of ultimate stature may result.

4. *Hypoplastic, haemolytic and malignancy associated anaemia* Majority of properly selected patients respond to anabolic steroids/androgens by an increase in RBC count and Hb%. However, erythropoietin therapy is more effective.

5. *To enhance physical ability in athletes* When administered during the period of training androgens/anabolic steroids can increase the strength of exercised muscles. However, effects are mostly short-lived and the magnitude of improvement in performance is uncertain except in women who may gain substantially. However, such use is considered illegal, and anabolic steroids are included in the list of 'dope test' performed on athletes before competitive games.

ANTIANDROGENS

Superactive GnRH agonists are the most potent inhibitors of gonadal function. Administered over a few days, they markedly inhibit LH and FSH release, resulting in loss of androgen secretion (*see* Ch. 17).

Ketoconazole at high doses inhibits steroidogenic CYP 450 enzymes: testosterone as well as adrenal steroid production is interfered. Plasma protein binding of testosterone is also reduced. However, toxicity of high doses precludes its use to suppress androgens.

Cimetidine and *spironolactone* have weak antiandrogenic action which manifests as side effects. *Progesterone* has weak androgen receptor blocking action.

Drugs that have been clinically used as antiandrogens are:

Cyproterone acetate This relatively weak AR antagonist is chemically related to progesterone. In contrast to flutamide which increases LH release by blocking feedback inhibition, cyproterone acetate inhibits LH release by its progestational activity. Lowering of serum testosterone (consequent to LH inhibition) supplements its direct antiandrogenic action.

Given to boys in relatively higher doses, it prevents pubertal changes, while in adult men libido and androgenic anabolism are suppressed. Its clinical indications are— precocious puberty in boys, inappropriate sexual behaviour in men, acne and hirsutism in women (in combination with an estrogen). Combined with ethinylestradiol (35 µg) cyclic (3 weeks on–1 week off) treatment with cyproterone has also been used as a contraceptive in women. Efficacy of cyproterone in metastatic prostate carcinoma is inferior to other forms of androgen deprivation. Hepatotoxicity limits its use.

Dose: 2 mg OD; GINETTE-35, DINAC-35; cyproterone acetate 2 mg + ethinyl estradiol 35 µg tab.

Flutamide A nonsteroidal AR antagonist with no other hormonal activity. Its active metabolite 2-hydroxyflutamide competitively blocks androgen action on accessory sex organs as well as on pituitary. Thus, it increases LH secretion by blocking feedback inhibition. Plasma testosterone levels increase in males which partially overcome the direct antiandrogenic action. This limits utility of monotherapy with antiandrogens in carcinoma prostate. They are now used only in conjunction with a GnRH agonist (to suppress LH and testosterone secretion) or after castration to block the residual action of adrenal androgens as *combined androgen blockade (CAB)* therapy of metastatic carcinoma prostate (also *see* p. 264). It is preferably started 3 days before the GnRH agonist to block the initial flare up that may occur due to excess release of LH and testosterone in the beginning (before GnRH receptors are desensitized). However, long-term benefit of CAB over GnRH agonist alone is not established. Along with oral contraceptives it has been tried in female hirsutism, but its hepatotoxic potential may not justify such use. Though gynaecomastia and breast tenderness occur frequently, libido and potency are largely preserved during flutamide treatment. Reports of liver damage have restricted its use.

Dose: 250 mg TDS

PROSTAMID, FLUTIDE, CYTOMID 250 mg tab.

Bicalutamide This more potent and longer acting (t½ 6 days) congener of flutamide is suitable for once daily administration in metastatic carcinoma of prostate as a component of CAB therapy. When used along with a GnRH agonist or castration, 50 mg OD affords marked relief in bone pain and other symptoms due to the metastasis. Side effects are hot flashes, chills, edema and loose stools, but it is better tolerated and less hepatotoxic than flutamide. Elevation of hepatic transaminase above twice normal is a signal for stopping the drug.

BIPROSTA, CALUTIDE, TABI 50 mg tab.

Nilutamide is another potent and long acting antiandrogen.

5 α-REDUCTASE INHIBITOR

Finasteride A competitive inhibitor of the enzyme 5 α-reductase which converts testosterone into the more active DHT responsible for androgen action in many tissues including the prostate gland and hair follicles. It is relatively selective for 5 α-reductase type 2 isoenzyme which predominates in male urogenital tract. Circulating and prostatic DHT concentration are lowered, but plasma LH and testosterone levels remain unchanged because testosterone itself mediates feedback pituitary LH inhibition.

Treatment with finasteride has resulted in decreased prostate size and increased peak urinary flow rate in ~50% patients with symptomatic benign hypertrophy of prostate (BHP). The beneficial effects are typically delayed needing ~6 months for maximum symptomatic relief. Patients with large prostate (volume > 40 ml) obtain greater relief than those with smaller gland. Upto 20% reduction in prostate size may be obtained.

Withdrawal of the drug results in regrowth of prostate, but with continued therapy benefit is maintained for 3 years or more. The relief of obstructive symptoms, however, is less marked compared to surgery and adrenergic α_1 blockers (*see* p. 157). It primarily reduces the static component of obstruction, while α_1 blockers overcome the dynamic component.

Concurrent treatment with both produces greater symptomatic relief.

Finasteride has also been found effective in male pattern baldness, though hair follicles have primarily type 1 enzyme. In such subjects it promotes hair growth and prevents further hair loss. Observable response takes 3 or more months therapy and benefit is reversed within 1 year of treatment cessation. However, 20–30% cases do not improve.

Finasteride is effective orally, extensively metabolized in liver—metabolites are excreted in urine and faeces; plasma t½ 4–8 hours (elderly 6–15 hours). It is well tolerated by most patients; side effects are decreased libido, impotence and decreased volume of ejaculate (each in 3–4% patients). Gynaecomastia, skin rashes, swelling of lips are rare.

Dose for BHP 5 mg OD, review after 6 months; for male pattern baldness 1 mg/day.

FINCAR, FINAST, FINARA 5 mg tab; FINPECIA, ASTIFINE 1 mg tab.

Dutasteride This newer congener of finasteride inhibits both type 1 and type 2 5α-reductase and reduces DHT levels. It is metabolized by CYP3A4 and is very long-acting (t½ is ~ 9 weeks). It is approved for use in BHP and can benefit male pattern baldness. In clinical trias, both finasteride and dutasteride have been found to reduce the risk of developing carcinoma prostate by upto 25%. Interactions with CYP3A4 inducers and inhibitors are possible.

Dose: 0.5 mg OD; DUPROST, DURIZE 0.5 mg tab.

DRUGS FOR ERECTILE DYSFUNCTION

Erectile dysfunction (ED) refers to the inability of men to attain and maintain an erect penis with sufficient rigidity to allow sexual intercourse. It occurs mainly past middle-age and is common after the age of 65 years. A variety of vascular, neurogenic, hormonal, pharmacologic or psychogenic causes may underlie the disorder.

Sexual arousal increases blood flow to the penis and relaxes the cavernosal sinusoids so that they fill up with blood, making the penis rigid, elongated and erect. Nitric oxide (NO) released from parasympathetic nonadrenergic noncholinergic (NANC) nerves and vascular endothelium is the major transmitter causing relaxation of smooth muscle in corpus cavernosum and the blood vessels supplying it; ACh and PGs also play a role. A variety of mechanical/prosthetic devices and surgery have been used for ED, but drug therapy has made a big impact now.

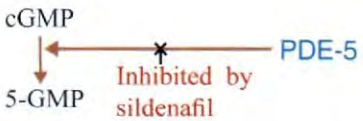
1. Androgens

Hypogonadism is an infrequent cause of ED. Parenteral testosterone esters or transdermal testosterone therapy is effective only when androgen deficiency is proven to be responsible for the loss of libido and ED.

2. Phosphodiesterase-5 (PDE-5) inhibitors

This class of drugs have become the first line therapy for ED.

Nitric oxide causes smooth muscle relaxation by generating cGMP intracellularly which then promotes dephosphorylation of myosin light chain kinase (MLCK) so that myosin fails to interact with actin (*see* Fig. 40.3). Inhibition of PDE-5, the cGMP degrading isoenzyme in cavernosal and vascular smooth muscle, results in accumulation of cGMP and marked potentiation of NO action. *Sildenafil, Tadalafil* and *vardenafil* are selective PDE-5 inhibitors found effective in a majority of patients with ED.



Sildenafil It is an orally active drug, marketed in the USA in 1998 and 2 years later in India, for treatment of ED. It became an instant hit, and evoked worldwide response. Sildenafil acts by selectively inhibiting PDE-5 and enhancing NO action in corpus cavernosum. Penile tumescence during sexual arousal is improved, but it has no such effect in the

absence of sexual activity. It does not cause priapism in most recipients.

Oral bioavailability of sildenafil is ~40%, peak blood levels are attained in 1–2 hr; it is metabolized largely by CYP3A4 and an active metabolite is produced; t½ in men <65 years averages 4 hours. It is recommended in a dose of 50 mg (for men > 65 years 25 mg), if not effective then 100 mg 1 hour before intercourse. Duration and degree of penile erection is increased in 74–82% men with ED including diabetic neuropathy cases. Over 20 controlled trials have confirmed its efficacy. However, sildenafil is ineffective in men who have lost libido or when ED is due to spinal injury or damaged nervi eregantes.

Adverse effects Side effects are mainly due to PDE-5 inhibition related vasodilatation—headache, nasal congestion, dizziness, facial flushing and fall in BP, loose motions. Relaxation of lower esophageal sphincter may cause gastric reflux and dyspepsia. Sildenafil, in addition, weakly inhibits the isoenzyme PDE-6 which is involved in photoreceptor transduction in the retina. As such, impairment of colour vision, especially blue-green discrimination, occurs in some recipients. Few cases of sudden loss of vision due to nonarteritic ischaemic optic neuropathy (NAION) among users of PDE-5 inhibitors have been reported.

Sildenafil markedly potentiates the vasodilator action of nitrates; precipitous fall in BP; MI can occur. After >6 million prescriptions dispensed in USA, the FDA received reports of 130 deaths related to sildenafil use by the year 2002. Most deaths occurred in patients with known risk factors, drug interactions or contraindications, and were timed either during or within 4–5 hours of sex. Sildenafil is contraindicated in patients of coronary heart disease and those taking nitrates. Though sildenafil remains effective for <8 hours, it is advised that nitrates be avoided for 24 hours. Caution is advised in presence of liver or kidney disease, peptic ulcer and bleeding disorders. Inhibitors of CYP3A4 like erythromycin, ketoconazole, verapamil, cimetidine potentiate its action. Caution is required also in patients of leukaemia, sickle cell anaemia or myeloma which predispose to priapism.

Sildenafil is erroneously perceived as an aphrodisiac. Men even without ED are going for it to enhance sexual satisfaction/pleasure.

PENEGRA, CAVERTA, EDEGRA 25, 50, 100 mg tabs.

Pulmonary arterial hypertension (PAH) Since NO is an important regulator of pulmonary vascular resistance, PDE-5 inhibitors lower pulmonary arterial pressure (*see* p. 547). Sildenafil is more selective for pulmonary circulation than vardenafil. Sildenafil has been shown to improve arterial oxygenation in pulmonary hypertension; exercise capacity is significantly imporved. Sildenafil 20 mg TDS has now become one of the drugs of choice for PAH.

Ambrisentan This endothelin receptor antagonist is a new drug for PAH.

Tadalafil It is a more potent and longer acting congener of sildenafil; t½ 18 hours and duration of action 24–36 hours. Peak plasma levels are attained between 30–120 min. Consequently time to onset of action may be longer. Side effects, risks, contraindications and drug interactions are similar to sildenafil. In addition, back pain is reported, which has been ascribed to some degree of PDE-2 inhibition by tadalafil. Because of its longer lasting action, nitrates are contraindicated for upto 3 days after tadalafil. Due to its lower affinity for PDE-6, visual disturbances occur less frequently. Tadalafil is also approved for use in PAH.

Dose: 10 mg at least 30 min before intercourse (max. 20 mg)

MEGALIS, TADARICH, TADALIS 10, 20 mg tabs, MANFORCE 10 mg tab.

Vardenafil Another congener of sildenafil with similar time-course of action; peak levels in 30–120 min and t½ 4–5 hours. Side effects, contraindications and interactions are also the same. It prolongs Q-T interval; should be avoided in hyperkalaemia and in patients with long Q-T or those receiving class IA and class III antiarrhythmics. *Dose:* 10 mg (elderly 5 mg), max 20 mg.

3. Papaverine/Phentolamine induced penile erection (PIPE) therapy

Injection of papaverine (3–20 mg) with or without phentolamine (0.5–1 mg) in the corpus cavernosum produces penile tumescence to permit intercourse. However, the procedure requires skill and training. Priapism occurs in 2–15% cases, which if not promptly treated leads to permanent damage. This is reversed by aspirating blood from the corpus cavernosum or by injecting phenylephrine locally. Repeated injections can cause penile fibrosis. Other complications are—local haematoma, infection, paresthesia and penile deviation. In view of the availability of PDE-5 inhibitors, it is rarely used now; only in cases not responding to sildenafil and alprostadil.

4. Prostaglandin E_1

Alprostadil (PGE_1) injected directly into the corpus cavernosum using a fine needle produces erection lasting 1–2 hours to permit intercourse. Alprostadil injections are less painful than papaverine, but local tenderness may occur. Penile fibrosis and priapism are rare. It is now the most commonly used drug in patients not responding to PDE-5 inhibitors, such as neurogenic and psychogenic ED.

A transurethral pellet termed 'medicated urethral system for erection' (MUSE) has been developed which avoids intracavernosal injection, but is less effective and may cause urethral burning.

☞ PROBLEM DIRECTED STUDY

21.1 A 65-year-old man presented with severe pain in the left shoulder region. The pain has progressively increased over the last 4 weeks, is not relieved by analgesics or NSAIDs and is worsened by pressure or movement. He also has increasing micturition difficulty for the last 6 months. Shoulder X-ray showed osteolytic lesion in the head of humerus. Rectal examination was consistent with prostate cancer which was confirmed by needle biopsy and raised serum PSA level (30 ng/ml). He refused orchidectomy and was prescribed injection triptorelin 3.75 mg i.m. to be repeated after one week and then every 4 weeks. After 1 week of 1st injection, he reported increased bone pain and greater bladder voiding difficulty. The serum PSA level was 34 ng/ml.

(a) What is the cause of the increase in bone pain and urinary obstructive symptoms? Is the choice of the drug incorrect?

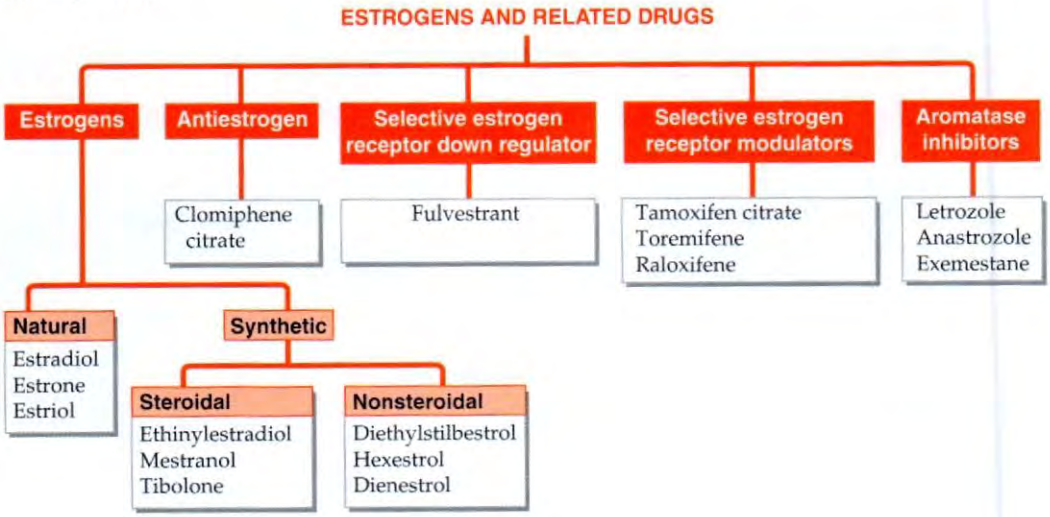
(b) Could this flaring of symptoms be avoided; if so how?

(c) Can any other drug be given to relieve the bone pain?

(see Appendix-1 for solution)

Chapter 22 Estrogens, Progestins and Contraceptives

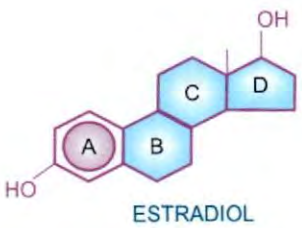
The estrogens, its receptor agonists and antagonists, and synthesis blockers are classified in the following chart:



ESTROGENS (Female Sex Hormones)

These are substances which can induce estrus in spayed (ovariectomized) animals.

It was established in the year 1900 that ovaries control female reproductive function through a hormonal mechanism. Allen and Doisy (1923) found that an alcoholic extract of ovaries was capable of inducing estrus in rodents, and devised a simple bioassay method. The active principle estradiol was obtained in pure form in 1929 and soon its chemical structure was worked out.



ESTRADIOL

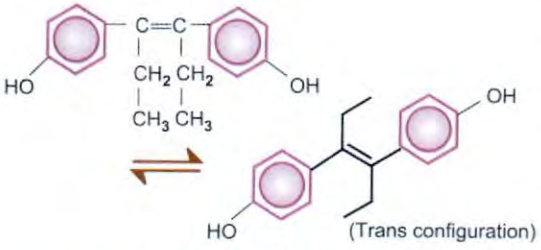
Natural estrogens *Estradiol* is the major estrogen secreted by the ovary. It is synthesized in the graafian follicle, corpus luteum and placenta from cholesterol. Steps depicted on the right hand side in Fig. 20.1 are carried out. Further steps are shown below.



Estradiol is rapidly oxidized in liver to *estrone* which is hydroxylated to form *estriol*. All three are active and circulate in blood, but estradiol is the most potent estrogen. Estrone and estriol have much lower affinity for the estrogen receptor (ER) than estradiol. Small quantity (2–20 µg/day) of estradiol is produced in human males also from aromatization of testosterone in the testes and extraglandular tissues. In the mare, large quantity of *equilin* is produced which has 1/5 estrogenic potency of estradiol.

Synthetic estrogens Natural estrogens are inactive orally and have a short duration of action due to rapid metabolism in liver. To overcome this, steroidal and nonsteroidal synthetic compounds have been produced (*see* chart).

The nonsteroidal compounds assume a trans configuration as depicted below and sterically resemble natural estrogens.



DIETHYLSTILBESTROL

Regulation of secretion The daily secretion of estrogens in menstruating women varies from 10–100 µg depending on the phase of the cycle. Its secretion starts from the graafian follicle under the influence of FSH and the blood level rises gradually during the follicular phase. Due to the modest preovulatory FSH surge, estrogens further rise transiently. After ovulation, corpus luteum continues to secrete estrogens till about two days before menstruation. Estrogens exercise feedback inhibition of FSH (also of LH at higher concentrations) by direct action on pituitary as well as through hypothalamus (*see* p. 262).

During pregnancy, placenta secretes large quantities of estrogens, (mainly estrone and estriol) reaching a peak of upto 30 mg/day at term. Their level declines sharply after delivery. In the postmenopausal women, daily production of estrogen has been estimated as 2–10 µg—derived primarily by extraglandular aromatization of adrenal androgens.

Actions

1. *Sex organs* The estrogens bring about pubertal changes in the female including growth of uterus, fallopian tubes and vagina. Vaginal epithelium gets thickened, stratified and cornified. They are responsible for the proliferation of endometrium in the preovulatory phase, and it is only in concert with estrogens that progesterone brings about secretory changes.

In the absence of progesterone (anovulatory cycles) withdrawal of estrogens alone produces menstruation. If modest doses of estrogen are given continuously without added progesterone—endometrium hypertrophies and menstruation is delayed, but breakthrough bleeding occurs at irregular intervals. However, the normal event which triggers menstruation is progesterone withdrawal. The progesterone withdrawal bleeding cannot be suppressed even by high doses of estrogens.

Estrogens augment rhythmic contractions of the fallopian tubes and uterus, and induce a watery alkaline secretion from the cervix. This is favourable to sperm penetration. They also sensitize the uterus to oxytocin. Deficiency of estrogens is responsible for atrophic changes in the female reproductive tract that occur after menopause.

2. *Secondary sex characters* Estrogens produced at puberty cause growth of breasts—proliferation of ducts and stroma, accumulation of fat. The pubic and axillary hair appear, feminine body contours and behaviour are influenced.

Acne is common in girls at puberty as it is in boys—probably due to small amount of androgens produced simultaneously. Administration of

estrogens to suppress pituitary-gonadal axis causes regression of acne.

3. *Metabolic effects* Estrogens are anabolic, similar to but weaker than testosterone. Therefore, small amount of androgen may be contributing to the pubertal growth spurt even in girls, as estrogens do in boys. Continued action of estrogen promotes fusion of epiphyses both in girls and boys.

Estrogen is important in maintaining bone mass primarily by retarding bone resorption. Osteoclast pit formation is inhibited and there is increased expression of bone matrix proteins such as osteonectin, osteocalcin, collagen and alkaline phosphatase. It promotes positive calcium balance, partly by inducing renal hydroxylase enzyme which generates the active form of Vit D_3.

Both osteoblasts and osteoclasts express estrogen receptors (ERs). The major action of estrogens is to reduce maturation and activity of osteoclasts by modifying regulatory cytokine signals from osteoblasts (*see* Ch. 24 for bone remodeling mechanisms).

Pharmacological doses of estrogens can cause mild salt and water retention—edema occurs in predisposed patients, but it can be treated with diuretics. BP may rise after prolonged use. Combination contraceptives containing higher doses of estrogens and progestins impair glucose tolerance. Normal blood sugar is not affected but diabetes may be precipitated or its control vitiated. However, amounts used for HRT and low dose contraception do not affect carbohydrate metabolism.

Estrogens decrease plasma LDL cholesterol while HDL and triglyceride levels are raised. The raised HDL : LDL ratio is probably responsible for rarity of atherosclerosis in premenopausal women. However, blood coagulability is increased due to induction of synthesis of clotting factors (factors II, VII, IX and X). Fibrinolytic activity in plasma also tends to increase due to lowering of plasminogen-activator inhibitor-1 (PAI-1).

Estrogens induce nitric oxide synthase and PGI_2 production in vascular endothelium. The increased availability of NO and PGI_2 could promote vasodilatation. They increase lithogenicity of bile by increasing cholesterol secretion and reducing bile salt secretion. Plasma levels of sex hormone binding globulin (SHBG), thyroxine binding globulin (TBG) and cortisol binding globulin (CBG) are elevated—but without any change in hormonal status.

Mechanism of action

Estrogens bind to specific receptors located normally within the nucleus of target cells and produce effects by regulating protein synthesis. Estrogen receptors (ERs) have been demonstrated in female sex organs, breast, pituitary, liver, bone, blood vessels, heart, CNS and in certain hormone responsive breast carcinoma cells. The ER is analogous to other steroid receptors: agonist binding to the ligand binding domain brings about receptor dimerization and interaction with 'estrogen response elements' (EREs) of target genes. Gene transcription is promoted through certain *coactivator proteins*. On binding an estrogen antagonist the receptor assumes a different conformation and interacts with other *corepressor proteins* inhibiting gene transcription.

Two distinct ERs designated ERα and ERβ have been identified, cloned and structurally characterized. Most tissues express both subtypes, but ERα predominates in uterus, vagina, breast, bone, hypothalamus and blood vessels, while ERβ predominates in prostate gland of males and ovaries in females. Estradiol binds to both ERα and ERβ with equal affinity, but certain ligands have differing affinities. More importantly ERα and ERβ may have a different pattern of interaction with coactivators and corepressors.

Few nongenomic rapid actions of estrogens in certain tissues (e.g. granulosa cells), mediated through the same ERs but which are located on the cell membrane, have also been observed.

Pharmacokinetics

Estrogens are well absorbed orally and transdermally, but natural estrogens are inactive by the oral route due to rapid metabolism in liver.

Estradiol esters injected i.m. are slowly absorbed and exert prolonged action. Natural estrogens in circulation are largely plasma protein bound—to SHBG as well as to albumin.

Estradiol is converted to estrone and *vice versa* in liver. Estriol is derived from estrone. All three are conjugated with glucuronic acid and sulfate, which are excreted in urine and bile. Considerable enterohepatic circulation occurs due to deconjugation in intestines and reabsorption; ultimate disposal occurs mostly in urine.

Ethinylestradiol is metabolized very slowly (t½ 12–24 hours). It is orally active and more potent.

Preparations and dose

All estrogen preparations have similar action. Their equivalent *parenteral* doses are—Estradiol 0.1 mg = Ethinylestradiol 0.1 mg = Mestranol 0.15 mg = Conjugated estrogens 10 mg = Estriol succinate 16 mg = Diethylstilbestrol 10 mg.

The *oral* potencies differ from the above due to differing extents of first pass metabolism. Estradiol is inactive orally, conjugated estrogens and estriol succinate undergo partial presystemic metabolism, while in case of ethinylestradiol, mestranol and diethylstilbestrol the oral and parenteral doses are practically the same.

The preferred route of administration of estrogens is oral. Intramuscular injection is resorted to only when large doses have to be given.

1. Estradiol benzoate/cypionate/enanthate/valarate: 2.5–10 mg i.m.; OVOCYCLIN-P 5 mg inj, PROGYNON DEPOT 10 mg/ml inj.
2. Conjugated estrogens: 0.625–1.25 mg/day oral; PREMARIN 0.625 mg, 1.25 mg tab (for HRT), 25 mg inj (for dysfunctional uterine bleeding), 0.625 mg/g vaginal cream (for atrophic vaginitis).
3. Ethinylestradiol: for menopausal syndrome 0.02–0.2 mg/day oral; LYNORAL 0.01, 0.05, 1.0 mg tab, PROGYNON-C 0.02 mg tab.
4. Mestranol: acts by getting converted to ethinylestradiol by demethylation in the liver: 0.1–0.2 mg/day oral; in OVULEN 0.1 mg tab, with ethynodiol diacetate 1 mg.
5. Estriol succinate: 4–8 mg/day initially, maintenance dose in menopause 1–2 mg/day oral: EVALON 1, 2 mg tab, 1 mg/g cream for vaginal application in atrophic vaginitis 1–3 times daily.
6. Fosfestrol tetrasodium: (For carcinoma prostate) initially 600–1200 mg slow i.v. inj for 5 days, maintenance 120–240 mg/day oral or 300 mg 1–3 times a week i.v. HONVAN 120 mg tab, 300 mg/mL
7. Dienestrol: 0.01% topically in vagina: DIENESTROL 0.01% vaginal cream.

Transdermal estradiol A transdermal patch (Estradiol-TTS) is available in 3 sizes, *viz.* 5, 10 and 20 cm^2 delivering 0.025 mg, 0.05 mg and 0.1 mg respectively in 24 hours for 3–4 days. The usual dose in menopause is 0.05 mg/day which produces plasma estradiol levels seen in premenopausal women in the early or mid follicular phase. Cyclic therapy (3 weeks on, 1 week off) with estradiol-TTS is advised with an oral progestin added for the last 10–12 days. Beneficial effects of estradiol-TTS on menopausal symptoms, bone density, vaginal epithelium and plasma Gn levels are comparable to those of oral therapy, but improvement in serum lipid profile is less marked.

Systemic side effects of estradiol-TTS are the same as with oral estrogens, but are milder. Oral therapy delivers high dose of the hormone to the liver and increases synthesis of several proteins which may have undesirable consequences. Estradiol-TTS avoids high hepatic delivery: consequently plasma levels of TBG, CBG, angiotensinogen and clotting factors are not elevated—risk of thromboembolic phenomena may not be increased or is low.

ESTRADERM-MX: Estradiol 25, 50 or 100 µg per 24 hr transdermal patches; apply to nonhairy skin below waist, replace every 3–4 days using a different site; add an oral progestin for last 10–12 days every month.

Recently a combined estradiol 50 µg + norethisterone acetate 0.25 mg patch has become available in some countries (ESTRAGEST-TTS). Two weeks of estraderm-TTS followed by 2 weeks estragest-TTS with patches changed twice weekly is used for total transdermal HRT.

A gel formulation of estradiol for application over skin is also available. OESTRAGEL, E_2 GEL 3 mg/5 g in 80 g tube, SANDRENA1 mg/g gel; apply over the arms and spread to cover a large area once daily for HRT.

Adverse effects

Most of the adverse effects of estrogens are described with HRT and with oral contraceptives (*see* p. 350).

In addition, dose dependent adverse effects noted when use is made for other indications are—

1. Suppression of libido, gynaecomastia and feminization when given to males.
2. Fusion of epiphyses and reduction of adult stature when given to children.
3. In postmenopausal women, estrogens can increase the risk of irregular bleeding and endometrial carcinoma (5–15 fold). A progestin given concurrently blocks the risk.
4. Estrogens can accelerate the growth of existing breast cancer, but low-dose estrogen only HRT does not appear to increase the risk of developing new breast cancer (*see* p. 335).
5. Long-term estrogen therapy doubles the incidence of gallstones. Benign hepatomas are more common in women taking estrogens in their teens and twenties.
6. Migraine, epilepsy and endometriosis may be worsened by estrogens.

Estrogens are contraindicated during pregnancy.

Uses

Currently, the two most common uses of estrogens are as *contraceptives* and for *hormone replacement therapy* (HRT) in postmenopausal women, but there are some other indications as well.

1. Hormone replacement therapy (HRT)

Due to cessation of ovarian function at menopause women suffer a number of physical, psychological and emotional consequences.

Medical problems related to menopause are:

- *Vasomotor disturbances* Hot flashes, chilly sensation, inappropriate sweating, faintness, paresthesias, aches and pains.
- *Urogenital atrophy* Change in vaginal cytology and pH, vaginal dryness, vulval shrinkage, dyspareunia, vaginitis, itching, urinary urgency, predisposition to urinary tract infection.
- *Osteoporosis* Loss of osteoid as well as calcium → thinning and weakening of bone → minimal trauma fractures especially of femur, hip, radius, vertebrae.
- *Dermatological changes* Thinning, drying and loss of elasticity of skin, wrinkles, thin and listless hairs.
- *Psychological/Cognitive disturbances* Irritability, depressed mood, loss of libido and self confidence, anxiety and dementia.
- *Increased risk of cardiovascular diseases* Coronary artery disease, myocardial infarction, stroke.

The vasomotor symptoms tend to subside over a few years, but the other changes progress continuously.

Estrogen ±progestin HRT or 'menopausal hormone therapy' (MHT) is highly efficacious in suppressing the perimenopausal syndrome of vasomotor instability, psychological disturbances as well as in preventing atrophic changes and osteoporosis. However, several recent findings have emphasized a number of risks and limitations of long-term HRT, so that HRT is now generally restricted to limited duration for control of hot flashes and other symptoms in women below 60 years or within 10 years after menopause.*

The *dose* of estrogen used in HRT is substantially lower than that for contraception. Typically, conjugated estrogens are used at 0.625 mg/day dose (equivalent to ethinylestradiol 10 μg) cyclically (3 weeks treatment 1 week gap), but there is a trend now to use lower doses (0.3–0.45 mg/day). A progestin (preferably micronized oral progesterone 100 mg/day, or medroxy progesterone acetate/norethisterone 2.5 mg daily) is added for the last 10–12 days each month. Though the progestin may attenuate the metabolic and cardiovascular benefits of estrogen, it is needed to block the increased risk of dysfunctional uterine bleeding and endometrial carcinoma due to continuous estrogenic stimulation of endometrium. Estrogen alone is used in hysterectomised women and when a progestin is not tolerated or is contraindicated. Low-dose estrogen alone may be tried, if it can control the symptons. Transdermal estradiol appears to have certain advantages (*see* above) and is preferred by many.

The benefits and risks of HRT are considered below:

a. *Menopausal symptoms and atrophic changes* The vasomotor symptoms respond promptly and almost completely. They are the primary indication for using HRT which also improves sleep disturbances, bodyache, general

* Global consensus statement on Menopausal Hormone Therapy.

physical, mental and sexual well being. Estrogen therapy tends to mitigate perimenopausal depression, but combining it with a progestin may nullify this benefit. HRT should be discontinued once the vasomotor symptoms abate. Estrogens also arrest genital and dermal atrophic changes; vulval and urinary problems resolve. Vaginal application of estrogen is effective in relieving local symptoms as well as dyspareunia and should be preferred when this is the only aim of HRT.

b. *Osteoporosis and fractures* HRT restores Ca^{2+} balance; further bone loss is prevented and the excess fracture risk is nullified. When used for this purpose, HRT should be initiated before significant bone loss has occurred, because reversal of osteoporosis is none or slight. Calcium + vit D supplements and exercise aid the beneficial effect of HRT. However, accelerated bone loss starts again on cessation of HRT. The 'Women's health, osteoporosis, progestin-estrogen' trial (2002) has shown that even lower doses of conjugated estrogens (0.3, 0.45 mg/day) increased bone mineral density in postmenopausal women, though 0.625 mg/day was more effective.

Not withstanding the above, appreciation of the other risks of HRT (*see* below) has dislodged estrogen from its prime position in the treatment of osteoporosis. Bisphosphonates are more effective and the drugs of choice. If prevention and treatment of osteoporosis is the goal, HRT is not the best option, and is not recommended beyond 5 years of use or in women over 60 years of age.

c. *Cardiovascular events* Since hypertension and cardiovascular disease are rare in premenopausal women, and estrogens improve HDL:LDL ratio, retard atherogenesis, reduce arterial impedance, increase NO and PGI_2 production and prevent hyperinsulinaemia, it was believed that estrogen therapy in postmenopausal women will have a protective cardiovascular influence.

In the past two decades many large scale placebo controlled randomized interventional trials and cohort studies have yielded opposite results. The 'Heart and estrogen/progestin replacement study' (HERS and HERS II) conducted in older women with preexisting cardiovascular disease found that HRT triples the risk of venous thromboembolism, increases risk of MI in the 1st year and affords no secondary prophylaxis of CAD in the long-term. The larger 'women's health initiative' (WHI) study conducted in over 16000 younger women without CAD found 24% increase in CAD, 40% increase in stroke and doubling of venous thromboembolism with the use of combined HRT. The study was terminated prematurely in 2002. The increased risk of MI was attributed to the progestin component, since women who took estrogen alone had no increase in the incidence of MI. Reexamination of the data has revealed ~30% reduction in incidence of MI among women who took HRT within 10 years of menopause. As such, a few years of HRT just after menopause and before 60 years of age may be protective.

d. *Cognitive function and dementia:* Contrary to earlier belief, the 'women's health initiative memory study' (WHIMS) conducted among older women (65–79 years) has failed to detect any protection against cognitive decline by either estrogen alone or combined HRT. There was in fact a slight global deterioration. Surprisingly, incidence of dementia (Alzheimer's) was doubled.

e. *Cancer:* That estrogens enhance the growth of *breast cancer* has been well recognized. However, it was contended that small replacement doses of estrogens will not induce new cancer. This appears to be supported by the estrogen alone arm of WHI study in hysterectomized women, as the occurrence of breast cancer was actually lower (but insignificantly). On the other hand, another longer term 'California Teachers study' found a slightly higher risk. In the combined HRT group, a significantly higher incidence of cancer breast occurred, indicating that medroxyprogesterone was the culprit. The prospective observational cohort 'Million women study' (MWS) in the UK found a marginally higher incidence of breast cancer with estrogen alone, but a clearly higher one with estrogen + progestin. Some other studies have also implicated the progestin, and the CSM of UK has drawn similar conclusions. Thus, the protective effect of progestin on endometrial cancer appears to be counter balanced by the procarcinogenic effect on the breast.

Estrogen is well known to induce endometrial hyperplasia and its continuous use unopposed by progestin results in irregular uterine bleeding. In the long-term it predisposes to *endometrial carcinoma*. The MWS has supported this contention. The standard practice is to give combined HRT to women with an intact uterus. However, a Cochrane Database Review has concluded that lower dose unopposed estrogen does not increase endometrial carcinoma risk. Thus, low-dose estrogen alone may be used for HRT in women with intact uterus when a progestin is contraindicated.

A small protective effect of combined HRT on *colorectal carcinoma* has been detected by the WHI study, but this needs to be confirmed.

f. *Gallstone, migraine:* Estrogens slightly increase the risk of developing gallstones, while progestins may trigger migraine.

Tibolone It is a 19-norsteroid developed specifically to be used for HRT. It is converted into 3 metabolites which exert estrogenic, progestational and weak androgenic actions in specific tissues. In a dose of 2.5 mg daily, it suppresses menopausal symptoms and lowers the raised Gn levels. No endometrial stimulation has been noted. Urogenital atrophy, psychological symptoms, libido and osteoporosis are improved similar to other forms of HRT. Contraindications are the same as for conventional HRT, but long term benefits and risks are not defined.

Weight gain, increased facial hair and occasional vaginal spotting may be noted. After the initial response, tibolone has failed to gain popularity.

Current conclusions regarding HRT

1. The main indication of HRT is vasomotor and other symptoms in women before the age of 60 years or within 10 years after menopause. It should be used at the smallest effective dose and for the shortest duration.
2. Young women with premature menopause clearly deserve HRT at least till the age of natural menopause.
3. Hysterectomized women should receive estrogen alone, while those with intact uterus be given estrogen + progestin. The option of low-dose estrogen alone may be tried, if symptomatically effective.
4. Perimenopausal women should be given cyclic HRT rather than continuous HRT.
5. HRT is not the best option to prevent osteoporosis and fractures, but may be used in women <60 years of age.
6. HRT affords protection against coronary artery disease only in early postmenopausal women. Combined HRT at conventional dose may increase the risk of venous thromboembolism, MI and stroke in elderly women.
7. HRT does not protect against cognitive decline; may increase the risk of dementia.
8. Combined HRT increases the risk of breast cancer, gallstones and migraine.
9. Transdermal HRT may have certain advantages over oral HRT.
10. The need for HRT should be assessed in individual women, and not prescribed routinely.

LIVIAL 2.5 mg tab, one tab daily without interruption; institute therapy only after the woman has been menopausal for at least 12 months.

2. *Senile vaginitis* Estrogens change vaginal cytology to the premenopausal pattern and are effective in preventing as well as treating atrophic vaginitis that occurs in elderly women. Oral therapy can be given but more commonly a topical preparation is used; an antibacterial may be combined. Estrogens help in overcoming vaginal infection and relieve symptoms of *Kraurosis vulvae*.

3. *Delayed puberty in girls (primary hypogonadism)* This may be due to ovarian agenesis (Turner's syndrome) or hypopituitarism. In both cases pubertal changes are brought about by cyclic estrogen treatment started at the age of 12–13 years, building up gradually to adult doses and then cyclic progestin is added. For rapid gain in height growth hormone and/or a small dose of androgen may be added. This treatment will have to be continued till the age of menopause (~ 50 yrs).

4. *Dysmenorrhoea* While PG synthesis inhibitors are the first line drugs, cyclic estrogen therapy (with added progestin to ensure withdrawal bleeding) benefits by inhibiting ovulation (anovular cycles are painless) and decreasing prostaglandin synthesis in endometrium. However, hormonal treatment should be reserved for severe cases.

5. *Acne* It occurs at puberty due to increased androgen secretion in both boys and girls. Estrogens benefit by suppressing ovarian production of androgen by inhibiting Gn release from pituitary. Cyclic treatment (with added progestin) is quite effective. Use of estrogen in boys is out of question. Even in girls, topical therapy with antimicrobials, tretinoin and other drugs is preferred over estrogens (*see* Ch. 66).

6. *Dysfunctional uterine bleeding* A progestin given cyclically is the rational and effective therapy. Estrogens have adjuvant value.

7. *Carcinoma prostate* Estrogens are palliative; produce relief in primary as well as metastatic carcinoma prostate by suppressing androgen production (through pituitary). GnRH agonists with or without androgen antagonist are preferred over estrogens for this purpose.

ANTIESTROGEN

Clomiphene citrate It binds to both ERα and ERβ and the *trans* isomer (*enclomiphene*) acts as a pure estrogen antagonist in all human tissues, but the *cis* isomer (*zuclomiphene*) and the racemate display weak agonistic action in rats. Clomiphene induces Gn secretion in women by blocking estrogenic feedback inhibition of pituitary. The amount of LH/FSH released at each secretory pulse is increased. In response, the ovaries enlarge and ovulation occurs if the ovaries are responsive to Gn. Antagonism of peripheral actions of estrogen results in hot flashes. Endometrium and cervical mucus may be modified.

The chief use of clomiphene is for infertility due to failure of ovulation: 50 mg once daily for 5 days starting from 5th day of cycle. Treatment is given monthly. Conception occurs in many women who previously were amenorrhoeic or had anovular cycles. If 1–2 months treatment does not result in conception—the daily dose may be doubled for 2–3 cycles.

No more than 6 treatment cycles should be tried. The antiestrogenic effect of clomiphene on developing follicle, endometrium or cervical mucus can be counterproductive. Luteal phase dysfunction has also been blamed for therapeutic failures. Addition of menotropins or chorionic gonadotropin on the last 2 days of the course improves the success rate.

Clomiphene is well absorbed orally, gets deposited in adipose tissue and has long t½ of ~6 days. It is largely metabolized and excreted in bile.

Adverse effects Clomiphene can produce polycystic ovaries, multiple pregnancy, hot flashes, gastric upset, vertigo, allergic dermatitis. Risk of ovarian tumour may be increased. Cautious use with lower dose is advised in women with enlarged ovaries.

Other uses *To aid in vitro fertilization* Clomiphene given with Gns causes synchronous maturation of several ova—improves their harvesting for *in vitro* fertilization.

Oligozoospermia: Clomiphene increases Gn secretion in men as well. This promotes spermatogenesis and testosterone secretion if the same have been deficient. For male infertility—25 mg daily given for 24 days in a month with 6 days rest for upto 6 months has been recommended. However, success rates are low.

CLOMID, FERTOMID, CLOFERT, CLOME 25, 50, 100 mg tab.

SELECTIVE ESTROGEN RECEPTOR DOWN-REGULATOR

Fulvestrant It is the first member of a distinct class of ER ligands called 'selective estrogen receptor down-regulators' (SERDs) or 'pure estrogen antagonists' that has been introduced for the treatment of locally advanced or metastatic ER positive breast cancer in postmenopausal women which has stopped responding to tamoxifen. In contrast to tamoxifen, it inhibits ER dimerization so that ER interaction with DNA is prevented and receptor degradation is enhanced. The ER is thus down regulated resulting in more complete suppression of ER responsive gene function. This feature along with its higher affinity for the ER probably accounts for its efficacy in tamoxifen resistant cases.

Fulvestrant is administered as (250 to 500 mg) monthly i.m. injections in the buttock. It is slowly absorbed and has an elimination t½ of more than a month.

FULVENAT 250 mg/vial inj.

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)

These are drugs which exert estrogenic as well as antiestrogenic actions in a tissue selective manner.

That ligand binding could change the configuration of ER in multiple ways allowing interaction with different coactivators and corepressors in a tissue specifie manner has paved the way for development of compounds with unique profile of agonistic and antagonistic actions in different tissues. These drugs have been designated '*selective estrogen receptor modulators*' (SERMs), and three SERMs *Tamoxifen citrate*, *Raloxifene* and *Toremifene* are in clinical use. It has been demonstrated that the conformation of ER after binding tamoxifen or raloxifene is different from that after binding estradiol.

Tamoxifen citrate Though chemically related to clomiphene, it has complex actions, *viz* acts as potent estrogen antagonist in breast carcinoma cells, blood vessels and at some peripheral sites, but as partial agonist in uterus, bone, liver and pituitary. Inhibition of human breast cancer cells and hot flashes reflect antiestrogenic action, while the weak estrogen agonistic action manifests as stimulation of endometrial proliferation, lowering of Gn and prolactin levels in postmenopausal women as well as improvement in their bone density.

A decrease in total and LDL cholesterol without any change in HDL and triglyceride level reflects estrogenic action. Similar to estrogen HRT, it increases the risk of deep vein thrombosis by 2–3 times.

Tamoxifen and aromatase inhibitors (AIs), e.g. letrozole, are the established hormonal

treatment options for breast cancer. In early cases tamoxifen is given as postmastectomy adjuvant therapy, while in advanced cases, it is a constituent of palliative treatment. Response rates are high in ER-positive breast carcinomas, but some ER-negative tumours also respond. However, use of tamoxifen for ER negative breast carcinoma (primary as well as metastatic) is usually not recommended. Tamoxifen is the only drug approved for primary as well as metastatic breast carcinoma in premenopausal women. However, two recent trials (SOFT and TEXT) have shown that exemestane (an AI) given along with ovarian suppression reduced chances of relapse of high-risk ER positive breast cancer in premenopausal women, and was a more effective option than tamoxifen plus ovarian suppression. Tamoxifen is also effective in surgically treated cancer of male breast.

Based on large epidemiological studies which have shown 45% reduction in the incidence of ER-positive breast cancer, tamoxifen has been approved for primary prophylaxis of breast cancer in high-risk women. Recurrence rate in ipsilateral as well as contralateral breasts is reduced by tamoxifen. Traditionally, benefit of tamoxifen prophylaxis was considered to be limited to 5 years, but recently the ATLAS trial comparing 5 years *vs* 10 years of adjuvant tamoxifen, and the 'aTTom' study have shown that disease free survival was higher in women who were treated for 10 years. However, due to greater reduction of risk of contralateral breast cancer by AIs, as well as increased risk of endometrial carcinoma and thromboembolic events, tamoxifen adjuvant therapy of breast carcinoma in postmenopausal women is generally replaced after 2 years by an AI, while in premenopausal women, tamoxifen itself is continued till 5 years postmastectomy.

Improvement in bone mass due to antiresorptive effect, and in lipid profile are the other benefits of tamoxifen therapy.

Tamoxifen is effective orally; has a biphasic plasma t½ (10 hours and 7 days) and a long duration of action. Some metabolites of tamoxifen are more potent antiestrogens. The drug is excreted primarily in the bile.

Dose 20 mg/day in 1 or 2 doses, max. 40 mg/day; TAMOXIFEN, MAMOFEN, TAMODEX 10, 20 mg tabs.

Male infertility: May be used as alternative to clomiphene.

Side effects Hot flashes, vomiting, rashes, vaginal bleeding, vaginal discharge and menstrual irregularities are the side effects. Increased risk of venous thromboembolism is due to estrogenic action on clotting mechanism.

Infrequent side effects are dermatitis, anorexia, depression, mild leucopenia and ocular changes. Tamoxifen is much less toxic than other anticancer drugs.

Toremifene It is a newer congener of tamoxifen with similar actions, but is a weaker ER agonist. Uses and adverse effects are also similar.

Raloxifene This SERM has a different pattern of action than tamoxifen. It is an estrogen partial agonist in bone, on lipid metabolism and cardiovascular system, but an antagonist in endometrium and breast. It has high affinity for both ERα and ERβ, and has a distinct DNA target the *'raloxifene response element'* (RRE).

Several long-term multicentric studies have shown that raloxifene prevents bone loss in postmenopausal women; bone mineral density (BMD) may even increase by 0.9–3.4% over years in different bones, particularly the lumbar vertebrae. However, accelerated bone loss occurs when raloxifene is stopped. The risk of vertebral fracture is reduced to half, but not that of long bones. Reloxifene is less efficacious than bisphosphonates in preventing fractures.

In postmenopausal women raloxifene reduces LDL cholesterol, probably by upregulating hepatic LDL receptors. In contrast to estrogen HRT there is no increase in HDL and triglyceride levels. Follow up studies have shown that raloxifene reduces the risk of breast cancer by 65%, though the protection was confined to ER-positive breast cancer.

Raloxifene does not stimulate endometrial proliferation and there is no increase in the risk of endometrial carcinoma. No relief of

menopausal vasomotor symptoms occurs; rather hot flashes may be induced in some women.

Raloxifene is absorbed orally but has low bioavailability due to extensive first pass glucuronidation. The t½ is 28 hours and major route of excretion is faeces.

Side effects Hot flashes, leg cramps are generally mild; vaginal bleeding is occasional. The only serious concern is 3-fold increase in risk of deep vein thrombosis and pulmonary embolism. However, similar risk attends estrogen HRT.

Use Raloxifene is a second line drug for prevention and treatment of osteoporosis in postmenopausal women; Ca^{2+} and vit D supplements enhance the benefit. According to British guidelines, raloxifene is not recommended for primary prophylaxis of osteoporotic fractures in postmenopausal women, but is an alternative option for secondary prevention and treatment of vertebral fractures, *i.e.* in those who have already suffered a fracture. It is also approved for prevention of breast cancer in women with risk factors.

Dose: 60 mg/day;
BONMAX, RALOTAB, ESSERM 60 mg tab.

AROMATASE INHIBITORS

Aromatization of 'A' ring of testosterone and androstenedione is the final and key step in the production of estrogens (estradiol/estrone) in the body. In addition to the circulating hormone, locally produced estrogens appear to play an important role in the development of breast cancer. Though some aromatase inhibitors (AIs) were produced in the past, three newer 'third generation' AIs *Letrozole*, *Anastrozole* and *Exemestane* have demonstrated clinical superiority and are widely used now in the treatment of breast cancer.

Properties of AIs are compared with that of tamoxifen in Table 22.1.

Letrozole It is an orally active nonsteroidal (type 2) compound that reversibly inhibits aromatization including that within the breast cancer cells, resulting in nearly total estrogen deprivation in postmenopausal women. However

Table 22.1: Comparative properties of tamoxifen (SERM) and letrozole/anastrozole (AIs)

Tamoxifen	*Letrozole/Anastrozole*
1. Estrogen antagonist in breast and blood vessels, but agonist in uterus, bone, liver and pituitary.	1. Inhibits production of estrogens in all tissues. Nearly total estrogen deprivation.
2. Can be used for breast Ca. in premenopausal women as well.	2. Not to be used in premenopausal women.
3. Less effective in delaying recurrence when used as adjuvant therapy after surgery.	3. More effective in delaying recurrence of early stage breast Ca. (adjuvant therapy).
4. Prophylactic use for breast Ca. recurrence usually limited to 5 years.	4. Continues to exert prophylactic effect beyond 5 years.
5. Less delay in disease progression and lower survival advantage in advanced/metastatic breast Ca. than AIs.	5. Greater delay in disease progression and greater survival advantage in palliative treatment of advanced/ metastatic breast Ca.
6. Not effective in failure cases.	6. Effective in tamoxifen failure cases of advanced breast Ca.
7. Causes endometrial hyperplasia, predisposes to endometrial carcinoma.	7. No endometrial hyperplasia/cancer predisposition.
8. No bone losss, no increase in fractures or arthritic sympoms.	8. Accelerates bone loss, predisposes to fractures, arthritic symptoms.
9. Increases risk of venous thromboembolism.	9. No increase in thromboembolic risk.
10. Improves lipid profile; small lowering of LDL Ch.	10. No effect on lipid profile.

SERM—Selective estrogen receptor modulate; AIs—Aromatase inhibitors; Ca.—Carcinoma; LDL Ch—Low density lipoprotein cholesterol

in those with functioning ovaries, estrogen production is not totally blocked. As such, AIs are not recommended in premenopausal women, unless ovaries are removed, or Gn secretion from pituitary is suppressed. Proliferation of estrogen dependent breast carcinoma cells is suppressed to a greater extent than with tamoxifen. Letrozole is rapidly absorbed with 100% oral bioavailability, large volume of distribution, slow metabolism and a t½ of ~40 hours. Randomized clinical trials have established its utility in:

(a) *Early breast cancer:* Letrozole is a first line drug for adjuvant therapy after mastectomy in ER+ive postmenopausal women. Extended adjuvant therapy with letrozole beyond the standard 5 year tamoxifen treatment continues to afford protection. Replacement of tamoxifen by an AI is now recommended after 2 years (sequential therapy) because AIs do not predispose to thromboembolism and endometrial cancer. Survival is prolonged in patients who have positive axillary lymph nodes.

(b) *Advanced breast cancer:* Current guidelines recommend letrozole as first line therapy because of longer time to disease progression and higher response rate obtained with it compared to tamoxifen. It is also effective as second line treatment when tamoxifen has failed.

Adverse effects Hot flashes, vaginal dryness, nausea, diarrhoea, dyspepsia and thinning of hair are the side effects. Joint pain and stiffness are common; bone loss may be accelerated. However, there is no endometrial hyperplasia or increased risk of endometrial carcinoma. Risk of venous thromboembolism is also not increased, and there is no deterioration of lipid profile.

Dose: 2.5 mg OD oral.

LETOVAL, LETROZ, FEMARA, ONCOLET 2.5 mg tab.

Though contraindicated in premenopausal women, letrozole was clandestinely promoted and tested as an ovulation inducing fertility drug. Use of letrozole for inducing ovulation in infertile women has been banned in India since Oct. 2011.

Anastrozole Another nonsteroidal and reversible (Type 2) AI, more potent than letrozole and suitable for single daily dosing. It accumulates in the body to produce peak effect after 7–10 days. Anastrozole is useful as adjuvant therapy in early ER+ive breast cancer as well as for palliation of advanced cases in postmenopausal women. In early cases, tumor recurrence time was found to be longer than with tamoxifen. Risk of new tumor appearing in the contralateral breast was also lower with anastrozole. A longer time to disease progression compared to tamoxifen has been obtained in advanced ER+ive breast cancer. Many tamoxifen resistant cases responded with increased survival. Like letrozole, it is also a first line drug for early as well as advanced breast carcinoma in postmenopausal women. Side effects are similar to those with letrozole.

Dose: 1 mg OD.

ALTRAZ, ARMOTRAZ, ANABREZ 1 mg tab.

Exemestane: This steroidal and irreversible (Type 1) inhibitor of aromatase acts like a suicide substrate by covalent binding to the enzyme. As a result >90% suppression of estradiol production is obtained. However, it has weak androgenic activity similar to androstenedione. Exemestane has been found beneficial in early breast cancer by reducing the risk of disease progression when it was substituted for tamoxifen as adjuvant therapy. In advanced breast cancer, longer survival, increased time to disease progression and fewer treatment failures have been obtained with exemestane. It is administered orally and is well tolerated. Adverse effects are similar to other AIs.

Dose: 25 mg OD oral after meals; those receiving CYP3A4 inducer 50 mg OD.

EXMASIN, XTANE 25 mg tab.

PROGESTINS

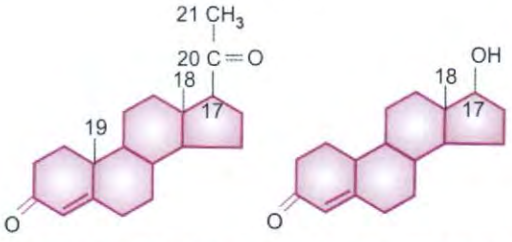
These are substances which convert the estrogen primed proliferative endometrium to secretory and maintain pregnancy in animals spayed after conception (*Progestin* = favouring pregnancy).

At the turn of the last century it became apparent that ovaries secrete two hormones, and that corpus luteum was essential for maintenance of pregnancy. Progesterone was isolated in 1929, but its full therapeutic potential has been

exploited only after the 1950s when a large number of orally active synthetic progestins were developed.

Natural progestin Progesterone, a 21 carbon steroid, is the natural progestin and is derived from cholesterol (*see* Fig. 20.1). It is secreted by the corpus luteum (10–20 mg/day) in the later half of menstrual cycle under the influence of LH. Its production declines a few days before the next menstrual flow. If the ovum gets fertilized and implants—the blastocyst immediately starts producing chorionic gonadotropin which is absorbed into maternal circulation and sustains the corpus luteum in early pregnancy. Placenta starts secreting lots of estrogens and progesterone from 2nd trimester till term. Men produce 1–5 mg progesterone per day from adrenals and testes; its role if any, in males is not known.

Synthetic progestins A number of synthetic progestins with high oral activity have been produced. These are either progesterone derivatives (21 C) or 19-nortestosterone derivatives, also called *'estranes'* (18C).



PROGESTERONE 19-NORTESTOSTERONE

The progesterone derivatives are almost pure progestins, have weaker antiovulatory action and are used primarily as adjuvants to estrogens for HRT in postmenopausal women, threatened abortion, endometriosis, etc. for selective progestational effect. The older 19-nortestosterone derivatives, e.g. *norethindrone* and *lynestrenol* developed in the 1950-60s have additional weak estrogenic, androgenic, anabolic and potent antiovulatory action. They are used primarily in combined contraceptive pills. Estranes with a 13-ethyl substitution are called '*gonanes*', e.g. *norgestrel*. Gonanes are more potent (especially the levoisomers, e.g. *levonorgestrel*) and have reduced androgenic activity.

In the 1980-90s a number of other gonane compounds were introduced, of which *desogestrel* has been marketed in India. Desogestrel and *norgestimate* are prodrugs. In addition to being very potent progestins they have strong antiovulatory action (*gestodene* inhibits ovulation at as low as 40 µg/day dose), and little or no androgenic property. Therefore, they do not antagonise the beneficial action of estrogens on lipid profile and are preferable in women with hyperandrogenemia. High antiovulatory potency allows reduction of ethinylestradiol dose when these are combined in oral contraceptives.

The newer 19-norprogesterone derivative *nomegestrol* has weak antiandrogenic property, is less antiovulatory, but has strong antiestrogenic effect on endometrium. Adverse effects on lipid profile and glucose tolerance appear to be lacking.

PROGESTERONE DERIVATIVES
Medroxyprogesterone acetate
Megestrol acetate
Dydrogesterone
Hydroxyprogesterone caproate
Newer compound
Nomegestrol acetate

19-NORTESTOSTERONE DERIVATIVES	
Estranes	*Gonanes*
Norethindrone (Norethisterone)	Levonorgestrel
Lynestrenol (Ethinylestrenol)	Desogestrel
Allylestrenol	Norgestimate
	Gestodene

Actions

The main function of progesterone is preparation of the uterus for nidation and maintenance of pregnancy. The latter is due to prevention of endometrial shedding, decreased uterine motility and inhibition of immunological rejection of the foetus, since progesterone depresses T-cell function and cell-mediated immunity (CMI).

1. *Uterus* Progesterone brings about secretory changes in the estrogen primed endometrium:

hyperemia, tortuocity of glands and increased secretion occurs while epithelial proliferation is halted. It is lack of progestational support which causes mucosal shedding during menstruation.

Continued action of progesterone (when pregnancy occurs) brings about decidual changes in endometrium—stroma enlarges and becomes spongy, glands atrophy, and sensitivity of myometrium to oxytocin is decreased.

2. *Cervix* Progesterone converts the watery cervical secretion induced by estrogens to viscid, scanty and cellular secretion which is hostile to sperm penetration.

3. *Vagina* Progesterone induces pregnancy like changes in the vaginal mucosa: leukocyte infiltration of cornified epithelium occurs.

4. *Breast* Progesterone causes proliferation of acini in the mammary glands. Cyclic epithelial proliferation and turnover occurs during luteal phase, but continuous exposure to progesterone during pregnancy halts mitotic activity and stabilizes mammary cells. Acting in concert with estrogens, it prepares the breast for lactation. Withdrawal of these hormones after delivery causes release of prolactin from pituitary and milk secretion starts.

5. *CNS* High circulating concentration of progesterone (during pregnancy) appears to have a sedative effect. It can also affect mood.

6. *Body temperature* A slight (0.5°C) rise in body temperature by resetting the hypothalamic thermostat and increasing heat production is induced. This is responsible for the higher body temperature seen during the luteal phase.

7. *Respiration* Progestins in relatively higher doses stimulate respiration, as occurs during pregnancy.

8. *Metabolism* Prolonged use of oral contraceptives impairs glucose tolerance in some women. This has been ascribed to the progestational component. Progestins, especially those with androgenic activity (19-nortestosterone derivatives) tend to raise LDL and lower HDL cholesterol levels. This may counteract the beneficial effect of estrogen used concurrently for HRT or in contraceptives. Micronized oral progesterone formulation (referred to as *'natural progesterone'*) does not affect the beneficial effect of estrogen on LDL and HDL cholesterol.

9. *Pituitary* Progesterone is a weak inhibitor of Gn secretion from pituitary. It exerts negative feedback primarily at the level of hypothalamic pulse generator—reducing the frequency of GnRH pulses. However, the amount of LH at each pulse may increase. Administration of progestin during the follicular phase suppresses the preovulatory LH surge and prevents ovulation. It synergises with estrogen for the antiovulatory action. The gonanes markedly suppress GnRH and are potent antiovulatory drugs.

Mechanism of action

Unlike other steroid receptors, the progesterone receptor (PR) has a limited distribution in the body: confined mostly to the female genital tract, breast, CNS and pituitary. The PR is normally present in the nucleus of target cells. Analogous to ER, upon hormone binding the PR undergoes dimerization, attaches to progesterone response element (PRE) of target genes and regulates transcription through coactivators. The antiprogestins also bind to PR, but the conformation assumed is different from agonist bound receptor and opposite effects are produced by interaction with corepressors.

The PR exists in a short (PR-A) and a longer (PR-B) isoforms. The two have differing activities, but because the ligand binding domain of both is identical, all agonists and antagonists display similar binding properties for them. Tissue selective modulation of PR has not yet been possible, as has been in the case of ER. Progesterone also acts on cell membrane receptors in certain tissues and produces rapid effects, like Ca^{2+} release from spermatozoa and oocyte maturation, but the physiological significance of these receptors is not clear.

Estrogens have been shown to increase PR density, whereas progesterone represses ER and enhances local degradation of estradiol.

Pharmacokinetics

Progesterone, unless specially formulated, is inactive orally because of high first-pass metabolism in liver. It is mostly injected i.m. in oily solution. Even after an i.m. dose it is rapidly

cleared from plasma and has a short t½ (5–7 min). Nearly complete degradation occurs in the liver—major product is pregnanediol which is excreted in urine as glucuronide and sulfate conjugates. However, effects of progesterone last longer than the hormone itself.

A micronized formulation of progesterone has been developed for oral administration. Microfine particles of the drug are suspended in oil and dispensed in gelatin capsules. Absorption occurs through lymphatics bypassing the liver. Though bioavailability is low, effective concentrations are attained in the body.

Most of the synthetic progestins are orally active and are metabolized slowly; have plasma t½ ranging from 8–24 hours.

Preparations and dose

1. Progesterone: 10–100 mg i.m. (as oily solution) OD; PROGEST, PROLUTON, GESTONE 50 mg/ml inj., 1 and 2 ml amp; 100–400 mg OD oral: NATUROGEST, DURAGEST, OGEST 100, 200, 400 mg caps containing micronized oily suspension.
2. Hydroxyprogesterone caproate: 250–500 mg i.m. at 2–14 days intervals; PROLUTON DEPOT, MAINTANE INJ, PROCAPRIN 250 mg/ml in 1 and 2 ml amp.
3. Medroxyprogesterone acetate: 5–20 mg OD–BD oral, 50–150 mg i.m. at 1–3 month interval; FARLUTAL 2.5, 5, 10 mg tab., PROVERA, MEPRATE, MODUS 2.5, 10 mg tab, DEPOT-PROVERA 150 mg in 1 ml inj. (as contraceptive). Has weak androgenic and antiestrogenic property.
4. Dydrogesterone: 5–10 mg OD/TDS oral; DUPHASTON 5 mg tab. It has poor antiovulatory action: may be preferred when contraceptive effect is not required.
5. Norethindrone (Norethisterone): 5–10 mg OD–BD oral; PRIMOLUT-N, STYPTIN, REGESTRONE, NORGEST 5 mg tab; REGESTRONE HRT, NORETA HRT 1 mg tab (for HRT); NORISTERAT 200 mg/ml inj (as enanthate) for contraception 1 ml i.m every 2 months; has androgenic, anabolic and antiestrogenic activity.
6. Lynestrenol (Ethinylestrenol): 5–10 mg OD oral; ORGAMETRIL 5 mg tab. Has additional androgenic, anabolic and estrogenic activity.
7. Allylestrenol: 10–40 mg/day; GESTANIN, FETUGARD, MAINTANE 5 mg tab. Has been especially used for threatened/habitual abortion, PROFAR 25 mg tab.
8. Levonorgestrel: 0.1–0.5 mg/day; DUOLUTON-L, OVRAL 0.25 mg+ ethinylestradiol 0.05 mg tab. Has androgenic, anabolic and antiestrogenic property.
9. Desogestrel 150 µg + ethinylestradiol 30 µg (NOVELON) tab, 1 tab OD 3 week on 1 week off cyclic therapy. (Other preparations are given with oral contraceptives).

Adverse effects

- Breast engorgement, headache, rise in body temperature, edema, esophageal reflux, acne and mood swings may occur with higher doses.
- Irregular bleeding or amenorrhoea can occur if a progestin is given continuously.
- The 19-nortestosterone derivatives lower plasma HDL levels—may promote atherogenesis, but progesterone and its derivatives have no such effect.
- Long-term use of progestin in HRT may increase the risk of breast cancer.
- Blood sugar may rise and diabetes may be precipitated by long-term use of potent agents like levonorgestrel.
- Intramuscular injection of progesterone is painful.
- Given in early pregnancy, progestins can cause masculinization of female foetus and other congenital abnormalities.

Use of a progestin for diagnosis of pregnancy is contraindicated.

Uses

1. *As contraceptive* Most common use (*see* later).

2. *Hormone replacement therapy (HRT)* In nonhysterectomised postmenopausal women estrogen therapy is supplemented with a progestin for 10–12 days each month to counteract the risk of inducing endometrial carcinoma. Micronized oral progesterone lacking androgenic activity is preferred. Progesterone may be omitted if very low dose estrogen is used.

3. *Dysfunctional uterine bleeding* Frequent or heavy irregular menstrual bleeding is often associated with anovular cycles occurring near menopause. Continued estrogenic action on endometrium (causing hyperplasia) without progesterone induction and withdrawal resulting in incomplete sloughing leads to irregular, often profuse bleeding. A progestin in relatively large doses (medroxyprogesterone acetate 10–20 mg/day or norethindrone 5–10 mg/day or equivalent) promptly stops bleeding and keeps it in abeyance as long as given, followed by bleeding on

stoppage. Subsequently cyclic treatment at lower doses regularizes and normalizes menstrual flow. A progestin with inherent estrogenic action is preferred; often supplemental dose of estrogen is combined, or a combination oral contraceptive pill is given cyclically for 3–6 months.

4. *Endometriosis* This condition results from presence of endometrium at ectopic sites. Manifestations are dysmenorrhoea, painful pelvic swellings and infertility. Continuous administration of progestin induces an anovulatory, hypoestrogenic state by suppressing Gn release. The direct action on endometrium prevents bleeding in the ectopic sites by suppressing menstruation. Treatment for a few months may cause atrophy and regression of the ectopic masses. Therapy can be withdrawn in many cases after 6 months without reactivation, but return of fertility is not certain. Progestin treatment of endometriosis is inexpensive and generally well tolerated, but not all cases respond and recurrences are frequent. Initial progestin therapy is often replaced by cyclic tratment with an estrogen-progestin contraceptive pill given for 3–6 months. GnRH agonist and danazol are alternatives used in nonresponsive cases. Intrauterine levonorgestrel system has also been used in refractory cases. Aromatase inhibitors have been tried in resistant cases, but their beneficial role is not established.

5. *Premenstrual syndrome/tension* Some women develop headache, irritability, fluid retention, distention and breast tenderness a few days preceding menstruation. When depression predominates, it has been labelled 'premenstrual dysphoric disorder'. Fluoxetine and other SSRIs given daily on symptom days dampen irritability and mood changes in majority of women. Severe premenstrual syndrome requires suppression of ovulation by combined estrogen-progesterone treatment given cyclically. Relatively higher dose of progestin is generally used. Ovarian suppression with GnRH agonist may be required in nonresponsive cases. Progestins are added to estrogen when it is used for severe dysmenorrhoea.

6. *Threatened/habitual abortion* In most such patients there is no progesterone deficiency, and administration of excess hormone is of no benefit. Progestin therapy may be considered in those patients who have established deficiency. However, progestins are briskly promoted and almost routinely prescribed in India. There is some evidence of its efficacy in preventing premature delivery in high risk pregnancy. If such use is made—a pure progestin without estrogenic or androgenic activity should be employed.

7. *Endometrial carcinoma* Progestins are palliative in about 50% cases of advanced/metastatic endometrial carcinoma. High doses are needed.

IMPEDED ANDROGEN / PROGESTIN

Danazol It is an orally active isoxazol derivative of ethisterone which has weak androgenic, anabolic, progestational and glucocorticoid activities. However, the most prominent action is suppression of Gn secretion from pituitary in both men and women → inhibition of testicular/ovarian function. In mensturating women, the midcycle surge of FSH and LH is suppressed, but basal level of these Gns is not much affected. In addition, danazol suppresses gonadal function directly by inhibiting steroidogenic CYP enzymes, but not the aromatase needed for estrogen production. In women, endometrial atrophy occurs over few a weeks and amenorrhoea may supervene. Danazol has also been labelled as an impeded/attenuated androgen, because it binds to the androgen receptor and translocates it into the nucleus to induce production of some androgen-specific RNA. Danazol is metabolized with a t½ of 12–18 hours. *Dose:* 200–600 mg/day;
DANAZOL, LADOGAL, DANOGEN, GONABLOK 50, 100, 200 mg cap.

Uses

1. *Endometriosis* Danazol causes improvement in ~75% cases by inhibiting ovarian function. Relief of dysmenorrhoea is prompt. Pain, dyspareunia and excessive bleeding regress slowly. Estrogen-progestin combination contraceptive is the first line drug. Non-responsive cases are treated by a high dose progestin alone. The Gn RH agonists given by intranasal spray daily or by monthly injection for 6–12 months are another option (*see* Ch. 17). Danazol is infrequently used now because of androgenic side effects and risk of liver damage.

2. *Menorrhagia* Danazol reduces menstrual blood loss. Usually complete amenorrhoea does not occur with 200 mg/day. It is a second line drug to an oral progestin.

3. *Fibrocystic breast disease* (chronic cystic mastitis): 3–6 months danazol treatment causes improvement with decrease in pain, nodularity and engorgement in ~75% cases.

4. *Hereditary angioneurotic edema* Danazol is a 17α alkylated steroid. Like other such compounds, it has prophylactic effect in this condition by inducing complement (C1) esterase inhibitor (*see* p. 324).

Side effects are frequent and dose related. Complete amenorrhoea occurs with higher doses. Androgenic side effects are acne, hirsutism, decreased breast size, deepening of voice, edema and weight gain. Loss of libido in men, hot flashes in women and night sweats, muscle cramps, g.i. upset, elevation of hepatic enzymes are the other problems.

ANTIPROGESTIN

Mifepristone It is a 19-norsteroid with potent antiprogestational and significant antiglucocorticoid, antiandrogenic activity.

Given during the follicular phase, its antiprogestin action results in attenuation of the midcycle Gn surge from pituitary. This causes slowing of follicular development and delay/failure of ovulation. If given during the luteal phase, it prevents secretory changes by blocking progesterone action on the endometrium. Later in the cycle, it blocks progesterone support to the endometrium, unrestrains PG release from it—this stimulates uterine contractions. Mifepristone also sensitizes the myometrium to PGs and induces menstruation. If implantation has occurred, it blocks decidualization, so that the conceptus is dislodged, HCG production falls, secondary luteolysis occurs—endogenous progesterone secretion decreases and cervix is softened. All these effects lead to abortion.

Mifepristone is a partial agonist and competitive antagonist at both A and B forms of PR. In the absence of progesterone (during anovulatory cycles or after menopause) it exerts weak progestational activity and induces predecidual changes. Therefore, it is now regarded as 'progesterone receptor modulator' rather than 'pure antagonist.' The weak agonistic action is not manifest in the presence of progesterone.

The antiglucocorticoid action of usual doses is also not manifest in normal individuals because blockade of the negative feedback at hypothalamic-pituitary level elicits ACTH release, so that plasma cortisol rises and overcomes the direct antiglucocorticoid action. Amelioration of Cushing's symptoms has been obtained with large doses (*see* p. 319).

Pharmacokinetics Mifepristone is active orally, but bioavailability is only 25%. It is largely metabolized in liver by CYP 3A4 and excreted in bile; some enterohepatic circulation occurs; t½ is 20–36 hr.

Interaction with CYP 3A4 inhibitors (erythromycin, ketoconazole) and inducers (rifampin, anticonvulsants) has been reported.

Uses

1. *Termination of pregnancy* of up to 7 weeks: 600 mg as single oral dose causes complete abortion in 60–85% cases. To improve the success rate, current recommendation is to follow it up 48 hours later by a single 400 μg oral dose of misoprostol. This achieves >90% success rate and is the accepted nonsurgical method of early first trimester abortion. In place of oral misoprostol, a 1 mg gemeprost pessary can be inserted intravaginally. Mifepristone administered within 10 days of a missed period results in an apparent late heavy period (with dislodged blastocyst) in upto 90% cases.

This procedure is generally safe, but prolonged bleeding and failed abortion are the problems in some cases. Anorexia, nausea, tiredness, abdominal discomfort, uterine cramps, loose motions are the other side effects.

2. *Cervical ripening* 24–30 hours before attempting surgical abortion or induction of labour, mifepristone 600 mg results in softening of cervix; the procedure is facilitated.

3. *Postcoital contraceptive* Mifepristone 600 mg given within 72 hr of intercourse interferes with implantation and is a highly effective method of emergency contraception. The subsequent menstrual cycle, however, is disturbed.

4. *Once-a-month contraceptive* A single 200 mg dose of mifepristone given 2 days after midcycle each month causes luteolysis and prevents conception on most occasions. Administering mifepristone in late luteal phase to

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dislodge the embryo (if present) and to ensure menstruation irrespective of conception, has also been tried. These alternative methods of contraception, though attractive, may prolong/disrupt the next menstrual cycle, and thus cannot be used continuously. There is little experience and little justification to use these methods on regular basis.

5. *Induction of labour* By blocking the relaxant action of progesterone on uterus of late pregnancy, mifepristone can promote labour. It may be tried in cases with intrauterine foetal death and to deliver abnormal foetuses.

6. *Cushing's syndrome* Mifepristone may have palliative effect due to glucocorticoid receptor blocking property, but efficacy is low. It may be tried in case the causative tumour is nonresectable.

Other proposed uses are—in endometriosis, uterine fibroid, certain breast cancers and in meningioma.

MIFEGEST, MIFEPRIN 200 mg tab.

T-PILL + MISO, ABORTOM: Mifepristone 200 mg (3 tabs) + Misoprostol 200 µg (2 tabs); for medical termination of pregnancy of upto 49 days: take 3 tablets of T-PILL on day 1, followed on day 3 by 2 tablets of MISO.

Ulipristal It is a recently approved 'selective progesterone receptor modulator' (SPRM) for use as emergency contraceptive. It inhibits ovulation by suppressing LH surge as well as by direct effect on follicular rupture. In addition, its action on endometrium can interfere with implantation. In clinical trials the efficacy of ulipristal (30 mg) as emergency contraceptive has been rated equal to that of levonorgestrel (1.5 mg) when taken within 72 hours of unprotected intercourse, and to be more effective when taken between 72–120 hours. Thus, it may have an advantage, if the woman misses to take the drug within 72 hours.

Headache, nausea, vomiting, abdominal pain and menstrual delay are the side effects, as they are with levonorgestrel. Few cases of ovarian cysts are reported.

The antiglucocorticoid activity of ulipristal is weaker than that of mifepristone.

Onapristone (a pure progesterone antagonist) and *Gestinone* (more efficacious in endometriosis) are the other antiprogestins.

HORMONAL CONTRACEPTIVES

These are hormonal preparations used for reversible suppression of fertility. Because of our alarming population trends, antifertility drugs are a growing need. In developing countries particularly, the mortality rate has declined and birth rate has increased due to urbanization. In the earlier part of the 20th century, methods of contraception used (condoms, diaphragms, spermicidal creams, foam tablets, etc.) were intimately related to sexual intercourse, therefore, despised by most couples. These devices have a higher failure rate as well. Rock and Pincus (1955) announced the successful use of an oral progestin for contraception, separating fertility control from coitus.

It was soon discovered that addition of a small quantity of an estrogen enhanced their efficacy; combined pills have become the most popular method of contraception, particularly because the hormone content of the pills has been reduced, minimizing the potential harm and affording other health benefits.

FEMALE CONTRACEPTION

Over 100 million women worldwide are currently using hormonal contraceptives. With these drugs, fertility can be suppressed at will, for as long as desired, with almost 100% confidence and complete return of fertility on discontinuation. The efficacy, convenience, low cost and overall safety of oral contraceptives (OCs) has allowed women to decide whether and when they want to become pregnant and to plan their activities. A variety of oral and parenteral preparations are now available offering individual choices.

TYPES OF METHODS

Oral

1. *Combined pill* It contains an estrogen and a progestin in fixed dose for all the days of a treatment cycle (monophasic). With accumulated experience, it has been possible to reduce the amount of estrogen and progestin in the 'second generation' OC pills without compromising efficacy, but reducing side effects and complications. 'Third generation'pills containing newer progestins like desogestrel with

Table 22.2: Oral contraceptive preparations

PROGESTIN		ESTROGEN		TRADE NAME
COMBINED PILLS				
1. Norgestrel	0.3 mg	Ethinylestradiol	30 µg	MALA–D (21 tabs + 7 ferrous sulfate 60 mg tabs.)
2. Norgestrel	0.5 mg	Ethinylestradiol	50 µg	OVRAL-G 20 tabs.
3. Levonorgestrel	0.25 mg	Ethinylestradiol	50 µg	OVRAL, DUOLUTON-L 21 tabs.
4. Levonorgestrel	0.15 mg	Ethinylestradiol	30 µg	OVRAL-L, OVIPAUZ 21 tabs.
5. Levonorgestrel	0.1 mg	Ethinylestradiol	20 µg	LOETTE, OVILOW, COMBEE 21 tabs
6. Desogestrel	0.15 mg	Ethinylestradiol	30 µg	NOVELON 21 tabs.
7. Desogestrel	0.15 mg	Ethinylestradiol	20 µg	FEMILON 21 tabs.
PHASED PILL				
1. Levonorgestrel	50–75 –125 µg	Ethinylestradiol	30–40 –30 µg	TRIQUILAR (6 + 5 + 10 tablets)
2. Norethindrone	0.5–0.75 –1.0 mg	Ethinylestradiol	35–35 –35 µg	ORTHONOVUM 7/7/7 (7+7+7 tabs)
POSTCOITAL PILL				
1. Levonorgestrel	0.25 mg	Ethinylestradiol	50 µg	OVRAL, DUOLUTON-L (2+2 tabs)
2. Levonorgestrel	0.75 mg 1.5 mg	-Nil -Nil-	—	NORLEVO, ECEE2 (1+1 tab)— iPILL, NOFEAR-72, OH GOD (1 tab)
MINI PILLS				
1. Norethindrone	0.35 mg	-Nil-	—	MICRONOR*, NOR-QD*
2. Norgestrel	75 µg	-Nil-	—	OVRETTE*

*Not marketed in India.

improved profile of action have been introduced in the 1990s. Ethinylestradiol 30 µg daily is considered threshold but can be reduced to 20 µg/day if a progestin with potent antiovulatory action is included. The progestin is a 19-nortestosterone because these compounds have potent antiovulatory action. Used alone the ovulation inhibitory dose (per day) of the currently used progestins is estimated to be—levonorgestrel 60 µg, desogestrel 60 µg, norgestimate 200 µg, gestodene 40 µg, but the amount in the pill is 2–3 times higher to attain 100% certainty. While both estrogens and progestins synergise to inhibit ovulation, the progestin ensures prompt bleeding at the end of a cycle and blocks the risk of developing endometrial carcinoma due to the estrogen. One tablet is taken daily for 21 days, starting on the 5th day of menstruation. The next course is started after a gap of 7 days in which bleeding occurs. Thus, a cycle of 28 days is maintained. Calendar packs of pills are available (Table 22.2). This is the most popular and most efficacious method.

2. Phased pill Triphasic regimens have been introduced to permit reduction in total steroid dose without compromising efficacy by mimicking the normal hormonal pattern in a menstrual cycle. The estrogen dose is kept constant (or varied slightly between 30–40 µg), while the amount of progestin is low in the first phase and progressively higher in the second and third phases.

Phasic pills are particularly recommended for women over 35 years of age and for those with no withdrawal bleeding or breakthrough bleeding while on monophasic pill, or when other risk factors are present. However, evidence of superiority of triphasic pills over monophasic pills is insufficient.

3. *Progestin-only pill (Minipill)* It has been devised to eliminate the estrogen, because many of the long-term risks have been ascribed to this component. A low-dose progestin-only pill is an alternative for women in whom an estrogen is contraindicated. It is taken daily continuously without any gap. The menstrual cycle tends to become irregular and ovulation occurs in 20–30% women, but other mechanisms (hostile cervical mucus and interference with implantation) contribute to the contraceptive action. The efficacy is lower (96–98%) compared to 98–99.9% with combined pill. Pregnancy should be suspected if amenorrhoea of more than 2 months occurs. This method is not popular.

4. *Emergency (postcoital) pill* These are for use in a woman not taking any contraceptive who had a sexual intercourse risking unwanted pregnancy. The most commonly used and standard regimen is—

- Levonorgestrel 0.75 mg two doses 12 hours apart, or 1.5 mg single dose taken as soon as possible, but before 72 hours of unprotected intercourse.

  Trials conducted globally by a WHO task force on postovulatory methods of fertility control have found this regimen to be 2–3 times more effective and better tolerated than the earlier 'Yuzpe method' which used levonorgestrel 0.5 mg + ethinylestradiol 0.1 mg, two doses at 12 hours interval within 72 hours of exposure. Incidence of nausea and vomiting is ~6% in the progestin only regimen compared to 20–50% with the estrogen+progestin regimen. Headache and other side effects are also milder. However, the next period may be delayed or disrupted with either regimens.

  Recently (2010) a SPRM ulipristal has been approved for emergency contraception.
- Ulipristal 30 mg single dose as soon as possible, but within 120 hours of intercourse.

  It is an equally effective (failure rate 1–3% compared to levonorgestrel 2–4%) and equally well tolerated alternative method now available with an extended window of protective action (*see* p. 346).

  Another antiprogestin that has been used, particularly in Europe and China, with high success rate and few side effects is—
- Mifepristone 600 mg single dose taken within 72 hours of intercourse.

Emergency postcoital contraception should be reserved for unexpected or accidental exposure (rape, condom rupture) only, because all emergency regimens have higher failure rate and side effects than regular low-dose combined pill.

Injectable

These contraceptives have been developed to obviate the need for daily ingestion of pills. They are given i.m. as oily solution; are highly effective; over 50 million women have used them so far. Their major limitations are:

(a) Animal data has indicated carcinogenic potential, but there is no proof from human studies despite >30 years of experience. No increase in overall risk of cervical, ovarian or hepatic cancer has been noted by a WHO sponsored study. Breast cancer risk may be slightly increased in younger women (< 35 yr). The logistics of administration and supervision for mass use are considered inadequate in developing countries and use–effectiveness in field conditions is low. In India approval has been granted for use only under close supervision, but not on mass scale under the National Programme.

(b) Menstrual irregularities, excessive bleeding or amenorrhoea are very common; incidence of amenorrhoea increases with increasing duration of use. Return of fertility may take 6–30 months after discontinuation; permanent sterility may occur in some women. Weight gain and headache occur in >5% subjects. Bone mineral density may decrease after 2–3 years of use (especially with DMPA) due to low estrogen levels caused by Gn suppression. This may also produce menopause-like symptoms (hot flashes, vaginal dryness, reduced libido).

Only the *long-acting progestin alone* injections are in use now. They are injected once in

2–3 months depending on the steroid and its dose. Two compounds have been marketed:

(a) Depot medroxyprogesterone acetate (DMPA) 150 mg at 3-month intervals. After i.m. injection peak blood levels are reached in 3 weeks and decline with a t½ of ~ 50 days.
DEPOT-PROVERA 150 mg in 1 ml vial for deep i.m. injection during first 5 days of menstrual cycle. Repeat every 3 months.

(b) Norethindrone (Norethisterone) enanthate (NEE) 200 mg at 2-month intervals.
NORISTERAT 200 mg in 1 ml vial for deep i.m. injection during first 5 days of menstrual cycle. Repeat every 2 months.

The most important drawback is complete disruption of menstrual bleeding pattern or total amenorrhoea (more common with DMPA). It is not suitable for adolescent girls and lactating mothers. Use of DMPA is generally restricted to women who are unlikely to use other contraceptives effectively. NEE is shorter acting and failure rates have been higher than with DMPA. All fixed dose combination injectable preparations of synthetic estrogens and progestins are not allowed in India and discontinued in most countries.

Implants These are drug delivery systems implanted under the skin, from which the steroid is released slowly over a period of 1–5 years. They consist of either—
(a) Biodegradable polymeric matrices—do not need to be removed on expiry.
(b) Non-biodegradable rubber membranes—have to be removed on expiry.
NORPLANT: A set of 6 capsules each containing 36 mg levonorgestrel (total 216 mg) for subcutaneous implantation is available in some countries, but has been discontinued in the USA. It works for up to 5 years.

A progestin impregnated intrauterine insert (PROGESTASERT) has been introduced in some countries. It contains 52 mg of levonorgestrel which primarily acts locally on endometrium. The device remains effective for 5 years, but efficacy is rated lower.

Transdermal contraceptive A transdermal patch containing a progestin norelgestromin and ethinylestradiol for once weekly application for 3 weeks followed by one week gap is available in some countries.

MECHANISM OF ACTION

Hormonal contraceptives interfere with fertility in many ways; the relative importance depends on the type of method. This is summarized in Table 22.3.

1. Inhibition of Gn release from pituitary by reinforcement of normal feedback inhibition. The progestin reduces frequency of LH secretory pulses (an optimum pulse frequency is required for triggering ovulation) while the estrogen primarily reduces FSH secretion. Both synergise to inhibit midcycle LH surge. When the combined pill is taken both FSH and LH are reduced and the midcycle surge is abolished. As a result, follicles fail to develop and fail to rupture. *Suppression of ovulation* is the primary mode of action of combined oral pill.

The low dose progestin- only pill and progestin-only injectable regimen also attenuate LH surge but less consistently—ovulation may occur irregularly in ~ 1/3 cycles. Postcoital pill when taken before ovulation can dampen LH surge and inhibit ovulation in some cases. However, pregnancy is still prevented by direct actions on the genital tract.

CHAPTER 22

Table 22.3: Effects of different forms of hormonal contraception

	Oral pills			*Injections*
	Combined E + P	*Progestin-only P*	*Postcoital only P*	*Progestin-only*
1. FSH inhibition	++	–	–	+
2. LH inhibition	+++	+	+	+++
3. Antiovulatory effect	+++	+	+,–	++
4. Hostile cervical mucus	+++	+++	–	+++
5. Endometrium	Hypersecretory	Out of phase	Unfavourable	Atrophic
6. Failure rate (on perfect use)	0.3%	2–3%	2–4%	< 0.5%
7. Contraceptive efficacy	++++	+++	++	++++

E—Estrogen; P—Progestin

2. Thick *cervical mucus* secretion *hostile to sperm penetration* is evoked by progestin action. As such, this mechanism can operate with all methods except postcoital pill.
3. Even if ovulation and fertilization occur, the blastocyst may fail to implant because *endometrium* is either hyperproliferative or hypersecretory or atrophic and in any case *out of phase* with fertilization—not suitable for nidation. This action appears to be the most important in case of minipills and postcoital pill.
4. *Uterine and tubal contractions* may be modified to disfavour fertilization. This action is uncertain but probably contributes to the efficacy of minipills and postcoital pill.
5. The postcoital pill may *dislodge* a just implanted blastocyst or may interfere with fertilization/implantation.

Practical considerations

1. Discontinuation of all OCs results in full return of fertility within 1–2 months. There may even be a rebound increase in fertility—chances of multiple pregnancy are more if conception occurs within 2–3 cycles. With injectable preparations, return of fertility is delayed. The cycles take several months to normalize or may not do so at all. They are to be used only if the risk of permanent infertility is acceptable.
2. If a woman on combined pills misses to take a tablet, she should be advised to take two tablets the next day and continue as usual. If more than 2 tablets are missed, then the course should be interrupted, an alternative method of contraception used and next course started on the 5th day of bleeding.
3. If pregnancy occurs during use of hormonal contraceptives—it should be terminated by suction-aspiration, because the risk of malformations, genital carcinoma in female offspring and undescended testes in male offspring is increased.
4. While for most women a pill containing 30 µg ethinylestradiol is sufficient, the obese may require a pill containing 50 µg, and only 20 µg may be appropriate/sufficient for those with cardiovascular risk factor, as well as for those above 40 years age.
5. If breakthrough bleeding occurs—switch over to a pill containing higher estrogen dose.
6. In women with contraindications for estrogen (*see* below), a progestin only contraceptive may be used.

ADVERSE EFFECTS

Since contraceptives are used in otherwise healthy and young women, adverse effects, especially long-term consequences, assume great significance. The adverse effects are dose dependent; most of the early data with high-dose preparations cannot be directly extrapolated to the present-day low-dose preparations which carry relatively minor risk. The following applies primarily to combined oral pill which has been most extensively used.

A. Nonserious side effects These are frequent, especially in the first 1–3 cycles, and then disappear gradually.

1. Nausea and vomiting: similar to morning sickness of pregnancy.
2. Headache is generally mild; migraine may be precipitated or worsened.
3. Breakthrough bleeding or spotting: especially with progestin-only preparations. Shift to triphasic pill may overcome the breakthrough bleeding. Rarely bleeding fails to occur during the gap period. Prolonged amenorrhoea or cycle disruption occurs in few women taking injectables or minipill.
4. Breast discomfort.

B. Side effects that appear later

1. Weight gain, acne and increased body hair may be noted due to androgenic action of older 19-nortestosterone progestins. The newer ones like desogestrel are relatively free of this effect.
2. Chloasma: pigmentation of cheeks, nose and forehead, similar to that occurring in pregnancy.
3. Pruritus vulvae is infrequent.
4. Carbohydrate intolerance and precipitation of diabetes in few subjects taking high dose preparations; but this is unlikely with the present pills. Many large studies have found no link between OC use and development of diabetes.

5. Mood swings and mental depression can occur in some women. Abdominal distention is occasional, especially reported with progesterone-only contraceptives.

C. Serious complications

1. *Leg vein thrombosis and pulmonary embolism:* The older preparations increased the incidence of venous thromboembolism, but this is found to be less marked (only 2–3 patients per 1000 women years) with the newer reduced steroid content pills. However, even low-dose pills pose significant risk in women >35 years of age, diabetics, hypertensives and in those who smoke. The excess risk is due to the estrogen component of the OC, and normalizes shortly after stopping the OC.

2. *Coronary and cerebral thrombosis* resulting in *myocardial infarction or stroke:* A 2 to 6-fold increase in risk was estimated earlier, but recent studies have demonstrated only small increase in incidence with the low dose pills in the absence of other risk factors. Women above 35-year age are particularly at risk.

The estrogen component of OC has been mainly held responsible for venous thromboembolism, while both estrogen and progestin have been blamed for the arterial phenomena. The mechanisms involved may be:

- Increase in blood clotting factors (coagulability is enhanced).
- Decreased antithrombin III.
- Decreased plasminogen activator in endothelium.
- Increased platelet aggregation.

3. *Rise in BP*: Occurred in 5–10% women taking the earlier pills. This again is less frequent and smaller in magnitude with the low-dose pills of today. If the BP rises, best is to stop OCs: the BP normalizes in the next 3–6 months. Both the estrogen and progestin components are responsible for this effect, probably by increasing plasma angiotensinogen level and renin activity which have been found to be raised during OC use. Aldosterone secretion is enhanced resulting in salt and water retention.

4. Estrogen tends to raise plasma HDL/LDL ratio (beneficial), but the progestin nullifies this benefit. Lipid profile is not significantly altered by low dose OCs, except that triglyceride level may rise marginally which poses no excess risk.

5. *Genital carcinoma:* An increased incidence of vaginal, cervical, and breast cancers was feared on the basis of animal data, but extensive epidemiological data over the past 30 years has repeatedly shown that oral as well as injected contraceptives do not increase the occurrence of these cancers in the general population. However, risk is increased in predisposed individuals. Growth of already existing hormone dependent tumour may be hastened.

Epidemiological data has recorded minor increase in breast cancer incidence among current OC users, but not among past users. Since breast cancer is rare in young women, this finding is considered inconsequential.

A protective effect against endometrial carcinoma has been shown for the progestin component. Prolonged suppression of gonadotropic stimulation of ovary may account for the lower incidence of ovarian malignancy noted in contraceptive users.

6. *Benign hepatomas:* which may rupture or turn malignant; incidence of this rare tumour appears to be slightly higher in OC users.

7. *Gallstones:* Estrogens increase biliary cholesterol excretion; incidence of gallstones is slightly higher in women who are taking OCs, or after long-term use.

Contraindications

The combined oral contraceptive pill is absolutely contraindicated in:

1. Thromboembolic, coronary and cerebrovascular disease or a history of it.
2. Moderate-to-severe hypertension; hyperlipidaemia.
3. Active liver disease, hepatoma or h/o jaundice during past pregnancy.
4. Suspected/overt malignancy of genitals/ breast.
5. Prophyria.
6. Impending major surgery—to avoid excess risk of postoperative thromboembolism. Estrogen

containing contraceptive should be stopped 4 weeks before surgery.

Relative contraindications (requiring avoidance/ cautious use under supervision)

1. Diabetes: control may be vitiated.
2. Obesity
3. Smoking
4. Undiagnosed vaginal bleeding
5. Uterine leiomyoma: may enlarge with estrogenic preparations; progestin only pills can be used.
6. Mentally ill
7. Age above 35 years
8. Mild hypertension
9. Migraine
10. Gallbladder disease.

Interactions Contraceptive failure may occur if the following drugs are used concurrently:
(a) *Enzyme inducers:* phenytoin, phenobarbitone, primidone, carbamazepine, rifampin, ritonavir. Metabolism of estrogenic as well as progestational component is increased.
(b) *Suppression of intestinal microflora:* tetracyclines, ampicillin, etc. Deconjugation of estrogens excreted in bile fails to occur → their enterohepatic circulation is interrupted → blood levels fall.

With both types of interacting drugs, it is wise to switch over to a preparation containing 50 µg of ethinylestradiol or to use alternative method of contraception. Rifampin is usually taken for a long time and is such a potent enzyme inducer that alternative contraception should be advised.

Other health benefits Apart from benefits due to prevention of unwanted pregnancy and the risks during delivery, use of oral contraceptives affords certain other beneficial effects as a bonus:

- Lower risk of developing endometrial and ovarian carcinoma; probably colorectal cancer as well.
- Reduced menstrual blood loss and associated anaemia; cycles if irregular become regular; premenstrual tension, dysmenorrhoea and menorrhagia are ameliorated.
- Endometriosis and pelvic inflammatory disease tend to subside.
- Reduced incidence as well as symptomatic relief of fibrocystic breast disease and ovarian cysts.

Ormeloxifene (Centchroman) It is a nonsteroidal SERM developed at CDRI India as an oral contraceptive. It has predominant estrogen antagonistic action in uterus and breast with little action on vaginal epithelium and cervical mucus. Endometrial proliferation is suppressed by down regulation of endometrial ER. Contraceptive action is probably due to utero-embyonic asynchrony and failure of implantation. Pituitary, ovarian and other endocrine functions remain practically unaffected. Menstrual cycle is not disrupted, but in some women it may be lengthened irregularly. Excessive bleeding attending anovulatory cycles (that generally occurs near menopause) is diminished; ormeloxifene is also approved for use in dysfunctional uterine bleeding.

The plasma t½ of ormeloxifene is long (~1 week). It prevents conception as long as taken with return of fertility few months after stoppage. Failure rate is considered acceptable, but it has failed to gain popularity for use as contraceptive. Side effects are nausea, headache, fluid retention, weight gain, rise in BP and prolongation of menstrual cycles.

Dose: For contraception—30 mg twice a week for 12 weeks followed by once a week.
For dysfunctional uterine bleeding—60 mg twice a week for 12 weeks, then once a week for 12 weeks.
CENTRON 30 mg tab, SAHELI 60 mg tab.

MALE CONTRACEPTION

The only way to suppress male fertility by drugs is to inhibit spermatogenesis. Though considerable effort has been made in this direction and effective drugs have been found, no satisfactory/acceptable solution is yet tangible. Reasons are—

1. Complete suppression of spermatogenesis is relatively difficult without affecting other tissues: millions of spermatozoa are released at

each ejaculation *vs* a single ovum per month in women.

2. Spermatogenesis takes 64 days. A drug which even completely inhibited spermatogenesis will take a long latent period to produce infertility. Accordingly, return of fertility will be slow.

3. Gonadotropin suppression inhibits testosterone secretion as well, resulting in loss of libido and impotence, which is unacceptable to all men and to most spouses.

4. Risk of adverse effects.

5. Most importantly—men don't get pregnant: few would be ready to bear the contingency of regular medication so that their sexual partners do not become pregnant.

Drugs and approaches tried are—

1. *Antiandrogens* Depress spermatogenesis, but raise Gns; cause unacceptable loss of libido.

2. *Estrogens and progestins* Act by suppressing Gns—cause unacceptable feminization.

3. *Androgens* They inhibit Gns but have poor efficacy. Even combination with progestin is not reliable.

4. *Superactive Gn RH analogues* They inhibit Gn release by continuous action; inhibit testosterone secretion as well; produce impotence, loss of libido.

5. *Cytotoxic drugs* Cadmium, nitrofurans and indoles suppress spermatogenesis, but are toxic.

6. *Gossypol* It is a nonsteroidal compound, obtained from cotton seed which has been studied in China. It is effective orally—causes suppression of spermatogenesis and reduces sperm motility—infertility develops after a couple of months. Fertility is restored several months after discontinuation. However, about 10% men remain oligozoospermic. During treatment serum LH and testosterone levels do not change: ~~libido and potency~~ are not affected. The mechanism of action though not clearly known, appears to involve direct toxicity on seminiferous epithelium.

Most important adverse effect of gossypol is hypokalaemia (due to renal loss of K^+) with its attendant muscular weakness (even paralysis). Other side effects are—edema, diarrhoea, breathlessness and neuritis. Its use has now been dropped.

☞ PROBLEM DIRECTED STUDY

22.1 A 55-year-old postmenopausal woman developed a cancerous lump in the left breast for which radical mastectomy was performed. The tumour was ER positive and only one of the excised axillary lymph nodes had metastasis. She was put on adjuvant therapy with tamoxifen 20 mg per day. On her checkup visit one year later, she was found to be asymptomatic with no sign of local recurrence or lymph node enlargement, but ultrasound examination of the uterus revealed thickening of endometrium.

(a) What could be the cause and implication of the increase in endometrial thickness?

(b) Should the same adjuvant therapy continue, or should it be stopped altogether, or be replaced by another drug? Give reasons.

22.2 A 28-year-old mother with a 9 month baby wants to space out her next child and consults you for taking oral contraceptive.

(a) What questions will you ask, what physical examination will you perform and what investigations will you order before advising her whether she should take oral contraceptive or not, as well as for selecting the contraceptive preparation most suitable for her?

(see Appendix-1 for solutions)

Chapter 23 Oxytocin and Other Drugs Acting on Uterus

Drugs acting on uterus can primarily affect the endometrium or the myometrium. The most important drugs affecting endometrium are estrogens, progestins and their antagonists. Myometrium receives both sympathetic and parasympathetic innervation. As such, autonomic drugs can affect its motility. However, the directly acting drugs are more important and have more selective action. The responsiveness of myometrium to drugs is markedly affected by the hormonal and gestational status.

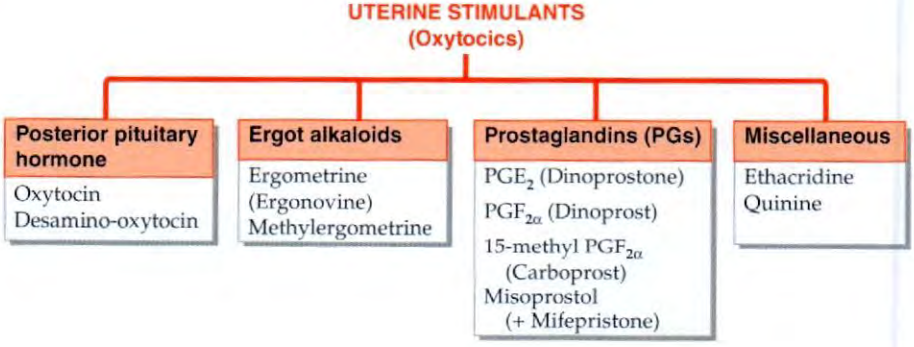
UTERINE STIMULANTS (Oxytocics, Abortifacients)

These drugs increase uterine motility, especially at term.

OXYTOCIN

Oxytocin is a nonapeptide secreted by the posterior pituitary along with argenine vasopressin (AVP or ADH). Pituitary extract was first used in labour in 1909. Controversy as to whether the antidiuretic and uterine stimulating activities were due to one substance or two separate substances was finally resolved by du Vigneaud in 1953 when he separated *Oxytocin* and *Vasopressin*, determined their chemical structure and synthesized them. Both have 9 amino acids, and differ at positions 3 and 8.

Both oxytocin and AVP are synthesized within the nerve cell bodies in supraoptic and paraventricular nuclei of hypothalamus; are transported down the axon and stored in



the nerve endings within the neurohypophysis. They are stored in separate neurones as complexes with their specific binding proteins (neurophysins) to form granules. Both are released by stimuli appropriate for oxytocin, i.e. coitus, parturition, suckling; or for ADH, i.e. hypertonic saline infusion, water deprivation, haemorrhage, etc., or nonspecific, i.e. pain and apprehension. However, the proportion of oxytocin to ADH can vary depending upon the nature of the stimulus.

ACTIONS

1. Uterus Oxytocin increases the force and frequency of uterine contractions. With low doses, full relaxation occurs inbetween contractions; basal tone increases only with high doses. Estrogens sensitize the uterus to oxytocin. They increase oxytocin receptors. Nonpregnant uterus and that during early pregnancy is rather resistant to oxytocin; sensitivity increases progressively in the third trimester, and there is a sharp increase near term. A quick fall in sensitivity occurs during puerperium. Progestins decrease the sensitivity, but this effect is not marked *in vivo*.

At term the enhancement of contractility is restricted to the fundus and body; lower segment is not contracted; may even be relaxed.

Mechanism of action Action of oxytocin on myometrium is independent of innervation. There are specific G-protein coupled oxytocin receptors on the myometrium which mediate the response mainly by depolarization of muscle fibres and influx of Ca^{2+} ions as well as through phosphoinositide hydrolysis and IP_3 mediated intracellular release of Ca^{2+} ions. The number of oxytocin receptors increases markedly during later part of pregnancy. Oxytocin also increases PG synthesis and release by the endometrium which may contribute to the contractile response. Distinct subtypes of oxytocin receptors have been shown on the myometrium and the endometrium.

2. Breast Oxytocin contracts the myoepithelium of mammary alveoli and forces milk into the bigger milk sinusoids. Oxytocin mediates the 'milk ejection reflex' (milk letdown in cattle) which is initiated by suckling, so that milk may be easily sucked by the infant. Oxytocin has been used in milch cattle to facilitate milking.

3. CVS Conventional doses of oxytocin used in obstetrics have no effect on BP, but higher doses cause vasodilatation producing brief fall in BP, reflex tachycardia and flushing. This action is most marked in chicken and is used for bioassay of oxytocin. The umbilical vessels are markedly constricted; oxytocin may help in their closure at birth.

4. Kidney Oxytocin in high doses exerts ADH-like action—urine output is decreased: pulmonary edema can occur if large amounts of i.v. fluids and oxytocin are infused together. Conventional doses are without any effect.

Physiological role

1. *Labour* Oxytocin is released during labour and the uterus is highly sensitive to it at this time. However, it does not appear to be obligatory for initiating parturition. Delivery occurs even in hypophysectomized animals and humans, though labour may be prolonged in its absence. A facilitatory role is more plausible. PGs and PAF are complementary to oxytocin.

2. *Milk ejection reflex* Suckling reflexly induces oxytocin release from pituitary and it contracts the myoepithelial cells. These cells in breast are more sensitive than the myometrium to oxytocin. Milk ejection reflex is absent in the hypophysectomized animal.

3. *Neurotransmission* Oxytocin appears to function as a peptide neurotransmitter of oxytocinergic neurones in the hypothalamus and brainstem which serves to regulate autonomic outflow.

PHARMACOKINETICS

Being a peptide, oxytocin is inactive orally and is generally administered by i.m. or i.v.

routes, rarely by intranasal spray. It is rapidly degraded in liver and kidney; plasma t½ 6–12 min. This is further shortened at term. Pregnant uterus and placenta elaborate a specific aminopeptidase called *oxytocinase*. This enzyme can be detected in maternal plasma.

Unitage and preparations 1 IU of oxytocin = 2 µg of pure hormone. Commercially available oxytocin is produced synthetically.

OXYTOCIN, SYNTOCINON 2 IU/2 ml and 5 IU/ml inj., PITOCIN 5 IU/0.5 ml inj.

USE

1. *Induction of labour* Labour needs to be induced in case of postmaturity or even prematurely in toxaemia of pregnancy, diabetic mother, erythroblastosis, ruptured membranes or placental insufficiency. For this purpose oxytocin is given by slow i.v. infusion: 5 IU is diluted in 500 ml of glucose or saline solution (10 milli IU/ml)—infusion is started at a low rate and progressively accelerated according to response (0.2–2.0 ml/min). Before starting the infusion, it should be made certain that:

- presentation is correct
- foetal lungs are adequately mature
- there is no cephalopelvic disproportion
- no placenta previa
- no foetal distress and
- no uterine scar (due to previous surgery).

Uterine contractions are then closely monitored: the drug is discontinued when they are strong enough. Usually a total of 2–4 IU is needed.

2. *Uterine inertia* When uterine contractions are feeble and labour is not progressing satisfactorily—oxytocin can be infused i.v. (as described above) to augment the contractions. It should not be used to hasten normally progressing labour. Before deciding to use an oxytocic for strengthening uterine contractions, all the conditions as setout above (for induction of labour) must be fulfilled. Too strong contraction can be catestrophic: use should only be made in selected cases and by experienced people.

Oxytocin is the drug of choice and is preferred over ergometrine/PGs for the above two purposes:

(a) Because of its short t½ and slow i.v. infusion, intensity of action can be controlled and action can be quickly terminated.

(b) Low concentrations allow normal relaxation inbetween contractions—foetal oxygenation does not suffer.

(c) Lower segment is not contracted: foetal descent is not compromised.

(d) Uterine contractions are consistently augmented.

3. *Postpartum haemorrhage, Caesarean section* Oxytocin 5 IU may be injected i.m. or given by i.v. infusion for an immediate response, especially in hypertensive women in whom ergometrine is contraindicated. It acts by forcefully contracting the uterine muscle which compresses the blood vessels passing through its mesh work to arrest haemorrhage from the inner surface exposed by placental separation.

4. *Breast engorgement* It may occur due to inefficient milk ejection reflex. Oxytocin is effective only in such cases but not when milk secretion is deficient. An intranasal spray may be given few minutes before suckling. Oxytocin does not increase milk production.

5. *Oxytocin challenge test* It is performed to determine uteroplacental adequacy in high risk pregnancies. Oxytocin is infused i.v. at very low concentrations till uterine contractions are elicited every 3–4 mins. A marked increase in foetal heart rate indicates uteroplacental inadequacy. The test is risky and is rarely performed.

Adverse effects

- Injudicious use of oxytocin during labour can produce too strong uterine contractions forcing the presenting part through incompletely dilated birth canal, causing maternal and foetal soft tissue injury, rupture of uterus, foetal asphyxia and death.
- Water intoxication: This occurs due to ADH like action of large doses given along with i.v. fluids, especially in toxaemia of pregnancy and renal insufficiency. It is a serious (may be fatal) complication.

Desamino-oxytocin It has been developed as a buccal formulation. The action is similar to injected oxytocin, but less consistent. Its indications are:

Induction of labour: 50 IU buccal tablet repeated every 30 min, max 10 tabs.
Uterine inertia: 25 IU every 30 min.
Promotion of uterine involution 25–50 IU 5 times daily for 7 days.
Breast engorgement 25–50 IU just before breast feeding.
BUCTOCIN 50 IU tab.

Carbetocin It is a long-acting analogue of oxytocin that has been introduced recently for prevention of uterine atony after caesarean section and to control PPH.

ERGOMETRINE, METHYLERGOMETRINE

The pharmacology of ergot alkaloids is described in Ch. 12. Only the amine ergot alkaloid ergometrine (ergonovine) and its derivative methylergometrine are used in obstetrics. Both have similar pharmacological property.

1. *Uterus* These alkaloids increase force, frequency and duration of uterine contractions. At low doses, contractions are phasic with normal relaxation in between, but only moderate increase in dose raises the basal tone, contracture occurs with high doses. Gravid uterus is more sensitive. Marked increase in sensitivity occurs at term and in early puerperium. Their stimulant action involves the lower segment of uterus as well. The uterotonic action is believed to result from partial agonistic action on 5-HT_2 and α adrenergic receptors.

2. *CVS* Ergometrine and methylergometrine are much weaker vasoconstrictors than ergotamine and have low propensity to cause endothelial damage. Though they can raise BP, this is not significant at doses used in obstetrics.

3. *CNS* No overt effects occur at usual doses. However, high doses produce complex actions—partial agonistic/antagonistic interaction with adrenergic, serotonergic and dopaminergic receptors in the brain have been shown.

4. *GIT* High doses can increase peristalsis.

Methylergometrine is 1½ times more potent than ergometrine on the uterus, but other actions are less marked. It has thus replaced ergometrine at many obstetric units.

Pharmacokinetics In contrast to the amino acid ergot alkaloids, ergometrine and methyl ergometrine are rapidly and nearly completely absorbed from the oral route. The onset of uterine action is: Oral—15 min; i.m.—5 min; i.v.—almost immediate.

They are partly metabolized in liver and excreted in urine. Plasma $t_{½}$ is 1–2 hours. Effects of a single dose last 3–4 hours.

Adverse effects Ergometrine and methylergometrine are less toxic than ergotamine. When correctly used in obstetrics—hardly any complications arise. Nausea, vomiting and rise in BP occur occasionally. They can decrease milk secretion if higher doses are used for many days postpartum. This is due to inhibition of prolactin release (dopaminergic action). Ergometrine should be avoided in—

- patients with vascular disease, hypertension, toxaemia.
- presence of sepsis—they may cause gangrene.
- liver and kidney disease.

They are contraindicated during pregnancy and before 3rd stage of labour.

Use

1. The primary indication for ergometrine/methylergometrine is to control and prevent postpartum haemorrhage (PPH): 0.2–0.3 mg i.m. at delivery of anterior shoulder reduces blood loss attending delivery and prevents PPH. However, routine use in all cases is not justified. They should be employed only in patients prone to bleed more, e.g. grand multipara, uterine inertia. Multiple pregnancy should be excluded before injecting.

If PPH is occurring—0.5 mg i.v. is recommended. A combination of 0.5 mg ergometrine with oxytocin 5 IU i.m./i.v. may be used in severe bleeding.
These drugs produce sustained tonic uterine contraction: perforating uterine arteries are compressed by the myometrial meshwork—bleeding stops.
2. After caesarean section/instrumental delivery these alkaloids serve to prevent uterine atony.
3. To ensure normal involution: A firm and active uterus involutes rapidly. To ensure this:

0.125 mg of ergometrine or methylergometrine has been given TDS orally for 7 days. However, routine use in all cases is not justified because normal involution is not hastened. Multipara and others in whom slow involution is apprehended, these drugs may be given prophylactically.

4. Diagnosis of variant angina: A small dose of ergometrine injected i.v. during coronary angiography causes prompt constriction of reactive segments of coronary artery that are responsible for variant angina.

ERGOMETRINE 0.25, 0.5 mg tab, 0.5 mg/ml inj.
Methylergometrine: METHERGIN, METHERONE, ERGOMET 0.125 mg tab, 0.2 mg/ml inj.

PROSTAGLANDINS

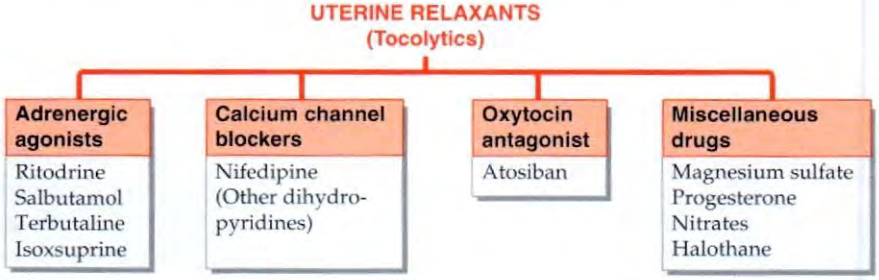
PGE_2, $PGF_{2\alpha}$ and 15-methyl $PGF_{2\alpha}$ are potent uterine stimulants, especially in the later part of pregnancy. They also promote ripening of cervix. Their actions and use in obstetrics is described in Ch. 13. Since misoprostol (a PG analogue) produces less side effects, it is being used for obstetric indications as well.

Ethacridine Available as 50 mg/50 ml solution (EMCREDIL, VECREDIL) for extra-amniotic infusion: 150 ml (containing 150 mg) is injected slowly for medical termination of pregnancy in the 2nd trimester. This is an alternative method used occasionally.

UTERINE RELAXANTS (Tocolytics)

These are drugs which decrease uterine motility. They have been used to delay or postpone labour, arrest threatened abortion and in dysmenorrhoea. Prevention of premature labour in those at higher risk due to past history or short cervix has been attempted by administration of high dose *progesterone* in the later half of pregnancy, with some success demonstrated in prospective controlled trials. Suppression of premature labour may be needed to allow the foetus to mature, to allow time for initiating glucocorticoid therapy for foetal lung maturation (*see* p. 316) or to transfer the mother in labour to a centre with proper facilities. However, no clearly satisfactory drug is available since none of them has been shown to improve foetal outcome. An attempt to delay premature labour is likely to succeed only if cervical dilatation is < 4 cm and 'taking up' of lower segment is minimal. Measures to delay labour should not be undertaken if membranes have ruptured, antepartum haemorrhage is occurring, in severe toxaemia of pregnancy, intrauterine infection or foetal death.

1. Adrenergic agonists (*see* Ch. 9) *Ritodrine*, the β_2 selective agonist having more prominent uterine relaxant action is approved to suppress premature labour and to delay delivery in case of some exigency or acute foetal distress. For dependable action it is started as 50 µg/min i.v. infusion, the rate is increased every 10 min till uterine contractions cease or maternal HR rises to 120/min. Contractions are kept suppressed by continuing i.v. infusion or by 10 mg i.m. 4–6 hourly followed by 10 mg oral 4–6 hourly. However, treatment beyond 48 hours is not recommended, since risk to mother increases and benefit is uncertain. Delivery can be postponed in about 70% cases by few hours to few weeks. However, cardiovascular (hypotension, tachycardia, arrhythmia, pulmonary edema) and metabolic (hyperglycaemia, hyperinsulinaemia, hypokalaemia) complications and anxiety, restlessness, headache occur frequently. Use of ritodrine to arrest labour has been found to increase maternal morbidity.



Foetal pulmonary edema can develop; volume of i.v. infusion should be kept to a minimum to avoid fluid overload. The neonate may develop hypoglycaemia and ileus. It should not be used if mother is diabetic, having heart disease, or receiving β-blockers or steroids.

Ritodrine has been discontinued in the USA, but is still available in UK and India.

YUTOPAR, RITROD 10 mg/ml inj (5 ml amp), 10 mg tab. RITODINE 10 mg tab, 10 mg in 1 ml inj.

Salbutamol and terbutaline can be used as alternatives to ritodrine. *Isoxsuprine* oral/i.m. has been used to stop threatened abortion, but efficacy is uncertain.

2. Calcium channel blockers Because influx of Ca^{2+} ions plays an important role in uterine contractions, Ca^{2+} channel blockers (*see* Ch. 40) reduce the tone of myometrium and oppose contractions. These drugs, especially nifedipine, which has prominent smooth muscle relaxant action, can postpone labour if used early enough. Efficacy comparable to β_2 adrenergic agonists has been demonstrated and side effects are fewer. Oral *nifedipine* 10 mg repeated once or twice after 20–30 min, followed by 10 mg 6 hourly has been used. Tachycardia and hypotension are prominent at doses which suppress uterine contractions. Reduced placental perfusion causing foetal hypoxia is apprehended. However, fewer babies delivered after nifedipine needed intensive care.

3. Oxytocin antagonist *Atosiban* is a peptide analogue of oxytocin that acts as antagonist at the oxytocin receptors. In clinical trials, i.v. infusion of atosiban has been found to suppress premature uterine contractions and postpone preterm delivery with fewer cardiovascular and metabolic complications than β_2 adrenergic agonists. In Europe and UK it is available for inhibition of labour between 24–33 weeks of gestation, and may offer better benefit: risk ratio than other tocolytics. However, it is not approved in USA and India.

4. Magnesium sulfate Infused i.v. it is a first line drug for prevention and treatment of seizures in preeclampsia and eclampsia. It also acts as a tocolytic by competing with Ca^{2+} ions for entry into myometrium through both voltage sensitive as well as ligand gated Ca^{2+} channels. However, its use to delay premature labour is risky, may increase perinatal mortality and is not recommended now.

5. Miscellaneous drugs Ethyl alcohol, nitrates, progesterone, general anaesthetics and indomethacin (PG synthesis inhibitors) are the other drugs, which can depress uterine contractions. However, their effect is not dependable and they are not used clinically as tocolytics.

Halothane is an efficacious uterine relaxant that has been used as the anaesthetic when external or internal version is attempted.

CHAPTER 23

☞ PROBLEM DIRECTED STUDY

23.1 A full term primigravida aged 26 years is brought to the hospital with the complaint of having labour pains for the past 24 hours without making much progress. Two hours ago she had passed meconium stained liquor. The lady is in distress, mildly dehydrated and looks exhausted. The presentation is vertex and head is engaged, but cervix is incompletely dilated and uterine contractions are relatively weak. Foetal tachycardia is noted with irregularity during contractions.

(a) What course of action is appropriate?

(b) Can she be administered a uterine stimulant to strengthen the contractions? If yes, which drug should be given and how? If no, then why?

(see Appendix-1 for solution)

Chapter 24 Hormones and Drugs Affecting Calcium Balance

CALCIUM

After C, O, H and N, calcium is the most abundant body constituent, making up about 2% of body weight, or 1–1.5 kg in an adult. About 98% of this is stored in bones, the rest being distributed in plasma and all tissues and cells. Calcium serves important physiological roles in several cellular functions.

Physiological roles

1. Calcium controls excitability of nerves and muscles and regulates permeability of cell membranes. It also maintains integrity of cell membranes and regulates cell adhesion.
2. Ca^{2+} ions are essential for excitation-contraction coupling in all types of muscle and excitation-secretion coupling in exocrine and endocrine glands, release of transmitters from nerve ending and other release reactions.
3. Ca^{2+} is an intracellular messenger for hormones, autacoids and transmitters.
4. Ca^{2+} controles impulse generation in heart; determines level of automaticity and A-V conduction.
5. Ca^{2+} is essential for coagulation of blood.
6. Calcium serves structural function in bone and teeth.

Plasma calcium level It is precisely regulated by 3 hormones almost exclusively devoted to this function, *viz. parathormone* (PTH), *calcitonin* and *calcitriol* (active form of vit D). These regulators control its intestinal absorption, exchange with bone and renal excretion as summarized in Fig. 24.1. In addition, several other hormones, *viz.* glucocorticoids, sex steroids, thyroid hormone, growth hormone affect calcium homeostasis, and can be considered its secondary regulators. Many other signal molecules and drugs also influence calcium handling (*see* box).

Influences affecting bone turnover

↑ *Resorption*	↓ *Resorption*
Corticosteroids	Androgens/Estrogens
Parathormone	Calcitonin
Thyroxine (excess)	Growth hormone
Hypervitaminosis D	Bisphosphonates
Prostaglandin E_2	Fluoride
Interleukin 1 & 6	Gallium nitrate
Alcoholism	Mithramycin
Loop diuretics	Thiazide diuretics

Normal plasma calcium is 9–11 mg/dl. Of this about 40% is bound to plasma proteins—chiefly to albumin; 10% is complexed with citrate, phosphate and carbonate in an undissociable form; the remaining (about 50%) is ionized and physiologically important. For example, in hypoalbuminemia, total plasma calcium may be low but the concentration of Ca^{2+} ion is usually normal. Acidosis favours and alkalosis disfavours ionization of calcium. As such, hyperventilation (by raising plasma pH) precipitates tetany and laryngospasm in calcium deficiency by reducing ionization.

Calcium turnover Major fraction of calcium in the bone is stored as crystalline hydroxyapatite deposited on the organic bone matrix *osteoid*, while a small labile pool is in dynamic equilibrium with plasma. Even the fully laid down parts of the bone undergo constant *remodeling* by way

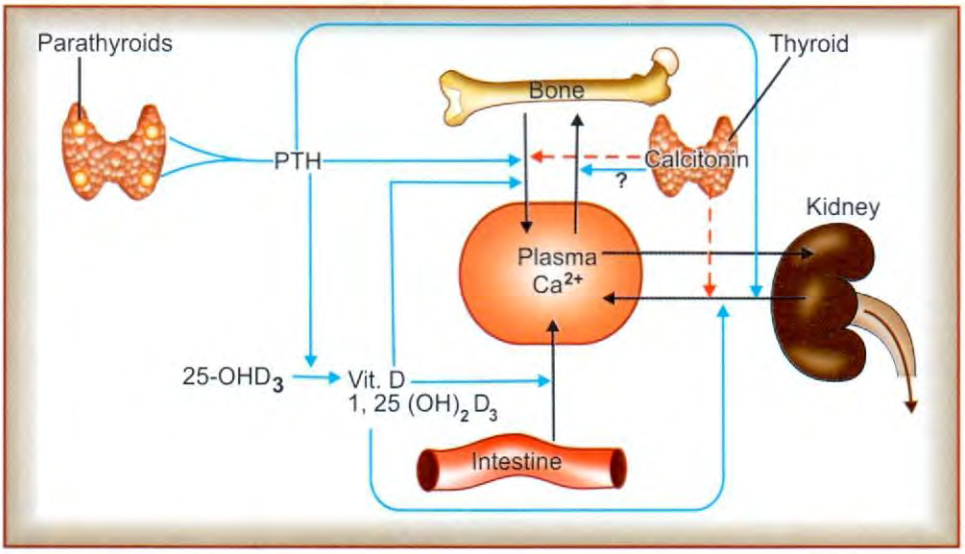


Fig. 24.1: Regulation of plasma level of calcium
——→ stimulation, - - - - → Inhibition; Bold arrow indicates—major action.
PTH—Parathormone; 25-OHD_3—Calcifediol; 1,25 $(OH)_2D_3$—Calcitriol.

of two closely coupled but directionally opposite processes of resorption and new bone formation (Fig. 24.2). Millions of tiny remodeling units are working on the surface of bone trabeculae and Haversian canals to dig micropits by osteoclastic activity and then repair by osteoblastic activity in which first collagen and other proteins (osteoid) are deposited followed by mineralization; the full cycle taking 4–6 months. Diet, exercise, several hormones and drugs regulate the number and efficiency of bone remodeling units at any given time. Remodeling deficits accumulate over life-time to account for age related bone loss, the pace of which can be retarded or accelerated by modulating the above listed influences. Estrogen lack after menopause mainly causes loss of trabecular bone, particularly affecting vertebrae, wrist bones and femoral neck. Minimal trauma/compression fractures are most common at these sites.

Absorption and excretion Calcium is absorbed by facilitated diffusion from the entire small intestine. In addition, a carrier-mediated active transport under the influence of vit D occurs in the duodenum. Calcium is secreted as well in the ileum, limiting net absorption. Phytates, phosphates, oxalates and tetracyclines complex with Ca^{2+} in an insoluble form in the intestines and interfere with its absorption. Glucocorticoids and phenytoin also reduce calcium absorption.

Ionized calcium is totally filtered at the glomerulus and most of it is reabsorbed in the tubules. Vit D and PTH increase, while calcitonin decreases tubular reabsorption of Ca^{2+}. About 300 mg of endogenous calcium is excreted daily: half in urine and half in faeces. To maintain calcium balance, the same amount has to be absorbed in the small intestine from the diet. Because normally only 1/3rd of ingested calcium is absorbed, the dietary allowance for calcium is 0.8–1.5 g per day. However, fractional calcium absorption is greater in presence of calcium deficiency and low dietary calcium.

Thiazide diuretics impede calcium excretion by facilitating its tubular reabsorption.

Preparations

1. *Calcium carbonate* (40% Ca): It is an insoluble, tasteless and nonirritating salt. Reacts with gastric HCl to form chloride, and can be used as antacid. It is the most common salt present in calcium supplements, but gastric acid is required for converting it into the absorbable form. Calcium availability from it is poor in patients taking proton pump inhibitors (PPIs), H_2 blockers, and in elderly.
2. *Calcium citrate* (as tetrahydrate, 21% Ca^{2+}): Slightly soluble in water, but dissolves well in presence of HCl. It is nonirritating and is used in supplements. Absorption in patients taking PPIs/H_2 blockers and elderly is lower, but satisfactory.
3. *Calcium gluconate* (9% Ca): is available as 0.5 g and 1 g tablets and 10% injection (5 ml amp.). It is nonirritating to g.i.t. and mildly irritating to the vascular endothelium.

A sense of warmth is produced on i.v. injection; extravasation should be guarded. It is the preferred injectable salt.

4. *Calcium lactate:* (13% Ca) is given orally, nonirritating and well tolerated.

5. *Calcium dibasic phosphate* (23% Ca): is insoluble, reacts with HCl to form soluble chloride in the stomach. It is bland; used orally as antacid and to supplement calcium. Availability of calcium from it is reduced by PPIs and H_2 blockers.

6. *Calcium chloride* (27% Ca): It is freely soluble in water, but highly irritating to gastric mucosa and to tissues; therefore not given orally. However, very dilute solution can be infused i.v.

Side effects Calcium supplements are usually well tolerated; only g.i. side effects like constipation, bloating and excess gas (especially with cal. carbonate) have been reported.

Some combined formulations

CALCINOL-RB: Cal. carb 0.375 g, Cal. Phos 75 mg + vit D_3 250 IU tab.

MILICAL: Cal. citrate 1 g + vit D_3 200 IU tab.

CALCIBONE: Cal. citrate 1 g + vit D_3 200 IU tab and susp.

CALSHINE: Cal. citrate 0.5 g + vit D_3 500 IU tab.

CALCIUM-SANDOZ: Cal. gluco-bionate 137.5 mg/ml inj. 10 ml amp., also tabs containing cal. carbonate 650 mg.

KALZANA: Cal. dibasic phos 430 mg + Vit C and D3 200 IU tab, also syrup: Cal. gluconate 300 mg, Cal. lactobionate 1.1 g, Cal. phos. 75 mg per 5 ml, containing Vit A, C, niacinamide and D3 200 IU.

OSTOCALCIUM: Cal. phos 380 mg + Vit D_3 400 IU tab, also syrup: Cal. phos 240 mg per 5 ml containing Vit D_3 200 IU and B_{12}.

SHELCAL: Cal. carb. 625 mg (eq 250 mg elemental cal), Vit D_3 125 IU tab and per 5 ml syr.

MACALVIT: Cal. carb. 1.25 g, cholecalciferol 250 IU tab; Cal. gluconate 1.18 g, Cal. lactobionate 260 mg + Vit D_3 100 IU per 5 ml syr.

CALCIMAX: Cal. carb. (150 mg cal), dibasic cal. phos. (23.3 mg cal) with magnesium, zinc and vit D_3 200 IU tab.; also syrup cal. carb. (150 mg cal) with magnesium, zinc and vit D_3 200 IU per 5 ml syrup.

Uses

1. *Tetany* For immediate treatment of severe cases 10–20 ml of Cal. gluconate (elemental calcium 90–180 mg) is injected i.v. over 10 min, followed by slow i.v. infusion. A total of 0.45-0.9 g calcium (50 to 100 ml of cal. gluconate solution) over 6 hours is needed for completely reversing the muscle spasms. Supportive treatment with i.v. fluids and oxygen inhalation may be required. Long-term oral treatment to provide 1–1.5 g of calcium daily is instituted along with vit. D. Milder cases need oral therapy only.

2. *As dietary supplement* especially in growing children, pregnant, lactating and menopausal women. The dietary allowance recommended by National Institute of Health (1994) is—

- Children 1–10 yr : 0.8–1.2 g
- Young adult 11–24 yr, pregnant and lactating women : 1.2–1.5 g
- Men 25–65 yr, women 25–50 yr and 51–65 yr if taking HRT : 1.0 g
- Women 51–65 yr not taking HRT, every one > 65 yr : 1.5 g

Calcium supplement can reduce bone loss in predisposed women as well as in men. It is often given to fracture patients, but if diet is adequate this does not accelerate healing.

3. *Osteoporosis* In the prevention and treatment of osteoporosis with alendronate/HRT/raloxifene, it is important to ensure that calcium deficiency does not occur. Calcium + vit D_3 have adjuvant role to these drugs in the prevention and treatment of osteoporosis.

However, the efficacy of calcium ± vit D supplements alone in increasing bone mass or preventing fractures among menopausal women/elderly men is controversial. It does not appear to reduce fracture risk in otherwise healthy subjects taking adequate diet. In the 7 year prospective WHI study involving >36000 postmenopausal women (51–79 years), the overall risk of fractures was the same in the calcium (1 g/day) + vit D (400 IU/day) group as in the placebo group, though the bone mineral density at the hip was 1% higher in the treated group. Certain subgroups of osteoporotic subjects may benefit from calcium supplements, but the benefit appears to be marginal and limited to cortical bone loss only. On the other hand, a metaanalysis has shown that subjects receiving calcium supplements had a 27% higher incidence of MI. Thus, calcium supplements should be given only to subjects taking diet low in calcium.

4. Empirically, Cal. gluconate i.v. has been used in dermatoses, paresthesias, weakness and other vague complaints. Any benefit is probably

psychological due to warmth and other subjective effects produced by the injection.
5. As antacid (*see* Ch. 47).

PARATHYROID HORMONE (Parathormone)

Vassale and Generali (1900) were the first to perform selective parathyroidectomy (without removing thyroids) and found that it produced tetany and death. MacCallum and Voegtlin in 1909 established this to be due to fall in plasma calcium levels; parathormone (PTH) was isolated in 1925.

Parathyroid hormone (PTH) is a single chain 84 amino acid polypeptide, MW 9500. It is synthesized as prepro-PTH; the excess amino acids are split off in two steps and PTH is then stored in intracellular vesicles. Secretion of PTH is regulated by plasma Ca^{2+} concentration through a calcium-sensing receptor (CaSR), that is a G-protein coupled receptor on the surface of parathyroid cells. There is no trophic hormone for it. Fall in plasma Ca^{2+} induces PTH release and rise inhibits secretion by decreasing cAMP in the parathyroid cells. Agents that increase cAMP cause PTH release, but direct activation of protein kinase C triggered by fall in Ca^{2+} concentration is more important physiologically. Prolonged hypocalcaemia causes hypertrophy and hyperplasia of parathyroids, while sustained hypercalcaemia has the opposite effect. Changes in phosphate concentration in plasma affect PTH secretion indirectly by altering Ca^{2+} concentration. The active form of vit. D calcitriol inhibits expression of PTH gene in parathyroid cells reducing PTH production. PTH is rapidly degraded in liver and kidney; its plasma $t_{1/2}$ is 2–5 min.

Actions

PTH increases plasma calcium levels by:

1. *Bone* PTH promptly increases resorption of calcium from bone. This is the most prominent action of PTH—exerted by increasing the number of bone remodeling units and activating osteoclasts when high concentrations are present continuously. Since bone resorption is followed by new bone deposition, this is also promoted by PTH: increased bone formation occurs when PTH is given intermittently and in low doses.

2. *Kidney* PTH increases calcium reabsorption in the distal tubule and provides moment to moment regulation of calcium excretion. It also promotes phosphate excretion which tends to supplement the hypercalcaemic effect. However, grossly increased plasma calcium level occurring in hyperparathyroidism overrides the direct action on tubules and calcium excretion in urine is actually increased. The converse occurs in hypoparathyroidism. In the kidney, PTH also promotes 1α-hydroxylation of 25-OHD_2 to generate calcitriol, the active form of vit D.

3. *Intestines* PTH has no direct effect on calcium absorption but increases it indirectly by enhancing the formation of calcitriol (active form of vit D) in the kidney by activating 1α-hydroxylase. Calcitriol then promotes intestinal absorption of calcium.

4. PTH decreases calcium levels in milk, saliva and ocular lens. This may be responsible for development of cataract in hypoparathyroidism.

Mechanism of action The PTH receptor is a G protein coupled receptor which on activation increases cAMP formation and intracellular Ca^{2+} in target cells. In bone, the target cell is the osteoblast because PTH receptors are not expressed on the surface of osteoclasts. Acting on the osteoblast, PTH induces a factor 'Receptor for activation of nuclear factor-κB-ligand' (RANKL) which diffuses and combines with RANK on osteoclast precursors and transforms them into osteoclasts as well as activates the osteoclasts (Fig. 24.2). In addition, birth rate of bone remodeling units into which osteoclasts are recruited is enhanced. Formation of the remodeling pit is followed by osteoblastic deposition of new bone into it. PTH enhances proliferation and differentiation of preosteoblasts and deposition of osteoid as well. Bone resorption predominates when high concentrations of PTH are present continuously, but intermittent exposure to low concentrations has the opposite effect.

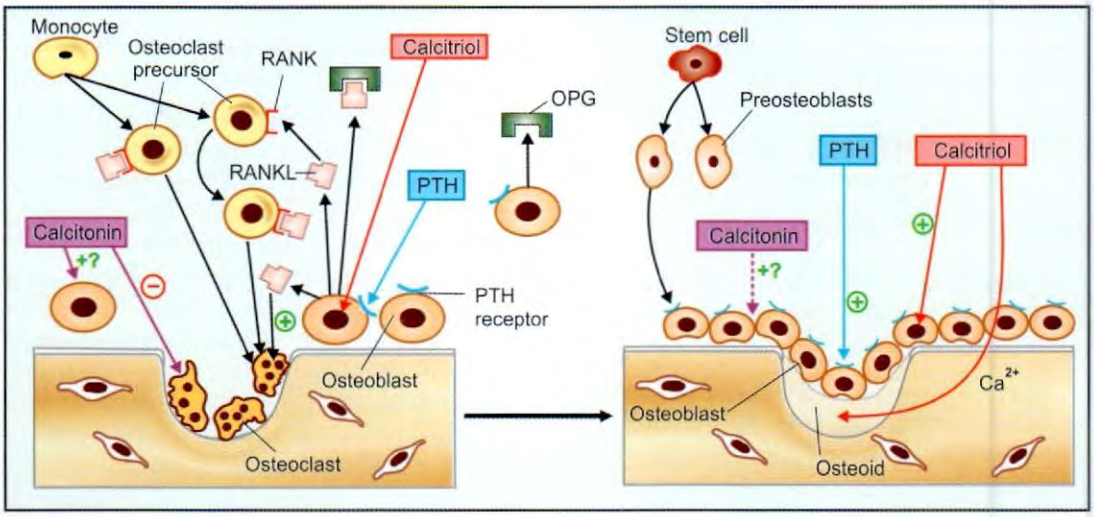


Fig. 24.2: Hormonal regulation of bone remodeling unit

The monocyte osteoclast precursor cells in the marrow near the bony surface are activated to proliferate and fuse to form multinucleated osteoclasts. The osteoclast-precursors express a 'receptor for activation of nuclear factor-κ B' (RANK) on their surface. The osteoblasts on activation release a protein RANK-ligand (RANKL). When RANKL is bound to RANK on the surface of osteoclast-precursors they are transformed into mature osteoclasts and develop bone lysing ruffled surface. A bone resorption pit is dug out by secretion of acid and proteolytic acid hydrolases.

Osteoblasts produce another protein osteoprotegerin (OPG) as well, which can bind RANKL and prevent it from combining with RANK to activate osteoclasts. Thus, osteoblasts by producing RANKL and OPG regulate bone resorption.

After formation of the remodeling pit, preosteoblasts from bone marrow stem cells proliferate, migrate to the base of the pit, transform into mature osteoblasts and laydown new osteoid, which is later mineralized.

Parathormone (PTH) acts on PTH-receptor located on the osteoblast membrane and induces RANKL production—indirectly activating osteoclast differentiation and function. Subsequently PTH promotes new bone formation as well.

Calcitriol also induces RANKL in osteoblasts to indirectly activate osteoclasts. Similarly, it promotes laying of osteoid as well as bone mineralization.

Calcitonin directly inhibits osteoclast function and probably enhances osteoblastic new bone formation.

Hypoparathyroidism Manifestations are:
Low plasma calcium levels, tetany, convulsions, laryngospasm, paresthesias, cataract and psychiatric changes. Pseudohypoparathyroidism occurs due to reduced sensitivity of target cells to PTH caused by a mutant G protein that couples PTH receptor activation to cAMP generation in target cells.

PTH is not used to treat hypoparathyroidism because plasma calcium can be elevated and kept in the normal range more conveniently by vit D therapy. PTH has to be given parenterally, while vit D can be given orally. Vit D is inexpensive. However, recombinant human PTH (1–84 amino acid) has been produced and is being clinically evaluated for use in hypoparathyroidism.

Hyperparathyroidism It is mostly due to parathyroid tumour. It produces—
hypercalcaemia, decalcification of bone—deformities and fractures (osteitis fibrosa generalisata), metastatic calcification, renal stones, muscle weakness, constipation and anorexia.

Treatment is surgical removal of the parathyroid tumour. When this is not possible—low calcium, high phosphate diet with plenty of fluids is advised.

Cinacalcet It is an orally active calcimimetic fluorinated compound which allosterically activates the calcium sensing receptor (CaSR) on parathyroid cells and in other body tissues. The primary action is to inhibit PTH secretion and thus decrease plasma levels of PTH, Ca^{2+} and phosphate. The biological t½ of cinacalcet is 30–40 hours. It is indicated in secondary hyperparathyroidism due to renal

disease and in patients undergoing long-term dialysis. Cinacalcet can also be used to lower plasma Ca^{2+} in inoperable cases of parathyroid cancer. Hypocalcaemia is a risk, and dose has to be adjusted carefully.

Dose: 30 mg BD with meals, increase to 60 mg BD or 90 mg BD, if needed.

SETZ 30, 60, 90 mg tab; PTH-30, SENACEPT 30 mg tab.

Teriparatide This recombinant preparation of 1–34 residues of amino terminal of human PTH has been recently introduced for the treatment of severe osteoporosis. It duplicates all the actions of the long (1–84) PTH. Injected s.c. 20 µg once daily, it acts only for 2–3 hours, and has been found to increase bone mineral density in osteoporotic women. The effect was faster and more marked than that produced by estrogens and bisphosphonates (BPNs). Teriparatide is the only agent which stimulates new bone formation, whereas the other two only check bone resorption. In clinical trials it was found to be equally or more effective than estrogens and BPNs in reducing risk of vertebral as well as non-vertebral fractures in osteoporotic women as well as men. After s.c. injection its plasma t½ is 1 hr. When given only once daily, action produced is intermittent, and the bone forming action predominates over bone resorbing action. High cost and need for daily s.c. injections are the limitations. Its use may be justified in severely osteoporotic women, those who have already suffered osteoporotic fractures or have multiple risk factors for fracture. Treatment with teriparatide beyond 2 years is not recommended, but BPNs may be continued thereafter. Side effects include dizziness, headache and leg cramps. Pagets disease and hypercalcaemia are the contraindications.

TEREOS 750 µg/3 ml vial for inj.

Diagnostic use To differentiate pseudo from true hypoparathyroidism: teriparatide is given i.v.: if plasma calcium level fails to rise, then it is pseudohypoparathyroidism.

CALCITONIN

Calcitonin is the hypocalcaemic hormone discovered by Copp in 1962. It is a 32 amino acid single chain polypeptide (MW 3600) produced by parafollicular 'C' cells of thyroid gland. Parathyroids, thymus and cells of medullary carcinoma of thyroid also contain calcitonin.

Synthesis and secretion of calcitonin is regulated by plasma Ca^{2+} concentration itself: rise in plasma Ca^{2+} increases, while fall in plasma Ca^{2+} decreases calcitonin release. However, circulating level of calcitonin is low and its physiological role in regulating plasma Ca^{2+} appears to be minor. The plasma t½ of calcitonin is 10 min, but its action lasts for several hours.

Actions

The actions of calcitonin are generally opposite to that of PTH. It inhibits bone resorption by direct action on osteoclasts—decreasing their ruffled surface which forms contact with the resorptive pit. Whether it also promotes calcium deposition by osteoblasts is not certain. The hypocalcaemic action of calcitonin lasts ~8 hours.

Calcitonin inhibits proximal tubular reabsorption of calcium and phosphate by direct action on the kidney. However, hypocalcaemia overrides the direct action by decreasing the total calcium filtered at the glomerulus—urinary Ca^{2+} is actually reduced.

The actions of calcitonin are mediated through a G-protein coupled calcitonin receptor (CTR) and increase in cAMP formation, but its target cells are different from that of PTH.

Preparation and unitage Synthetic salmon calcitonin is used clinically, because it is more potent and longer acting due to slower metabolism. Human calcitonin has also been produced.

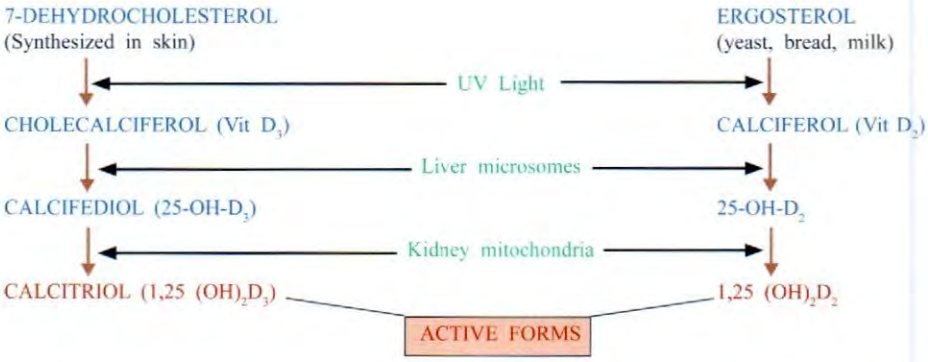
1 IU = 4 µg of the standard preparation.

CALSYNAR, ZYCALCIT: Synthetic salmon calcitonin 100 IU/ml amp. for i.m. or s.c. injection.

Nausea, flushing and tingling of fingers is frequent after calcitonin injection. Bad taste, flu-like symptoms, allergic reactions and joint pain are the other adverse effects.

Uses

1. *Hypercalcaemic states* Hyperparathyroidism, hypervitaminosis D, osteolytic bony metastasis and hypercalcaemia of malignancy; 4–8 IU/kg i.m. 6–12 hourly only for 2 days. It acts rapidly within 4 hours, the response peaks at 48 hours and then refractoriness develops. It also relieves bone pain.



For emergency treatment of hypercalcaemia 5–10 IU/kg may be diluted in 500 ml saline and infused i.v. over 6 hours. Calcitonin is a relatively weak hypocalcaemic drug. Therefore, used only to supplement BPNs initially, because BPNs take 24–48 hours to act.

2. *Postmenopausal osteoporosis* A nasal spray formulation delivering 200 IU per actuation has been employed in osteoporosis.

MIACALCIN NASAL SPRAY, OSTOSPRAY CALCINASE 2200 IU/ml metered dose nasal spray, 200 IU per actuation. One spray in alternate nostril daily has been shown to increase bone mineral density in menopausal women and to reduce vertebral, but not nonvertebral, fractures. It is less effective than BPNs/HRT. However, British guidelines no longer recommend use of calcitonin for postmenopausal osteoporosis, because of risk of malignancy associated with its long term use outweighs the benefit.

3. *Paget's disease* 100 IU i.m./s.c. daily or on alternate days produces improvement for few months. Later, resistance usually develops due to production of antibodies. Bisphosphonates are preferred; calcitonin may be used as adjuvant or 2nd line drug.

4. *Diagnosis of medullary carcinoma of thyroid* Detection of high blood level of calcitonin is diagnostic of this tumour, which arises from the calcitonin producing parafollicular cells of thyroid.

VITAMIN D

Vitamin D is the collective name given to antirachitic substances synthesized in the body and found in foods activated by UV radiation.

D3 : cholecalciferol — synthesized in the skin under the influence of UV rays.

D2 : calciferol—present in irradiated food—yeasts, fungi, bread, milk.

D1 : mixture of antirachitic substances found in food—only of historic interest.

In 1919 it was established that rickets was due to deficiency of a dietary factor as well as lack of exposure to sunlight. McCollum (1922) showed that this fat soluble dietary factor was different from vit A and its structure was determined in 1935. The interrelation between calciferol and cholecalciferol and their activation in the body has been fully understood only in the 1970s.

Activation of vit D It takes place in the following manner—

Ergosterol differs from 7-dehydrocholesterol in having an extra double bond between C22–23 and a methyl group at C24. In man vit D_2 and D_3 are equally active and *calcitriol* (active form of D_3) is more important physiologically; 25-OH D_3 is released in blood from the liver and binds loosely to a specific vit D binding globulin. The final 1α-hydroxylation in kidney is rate limiting and is controlled by many factors. This step is activated or induced by calcium deficiency, vit D deficiency as well as by PTH, estrogens and prolactin, while calcitriol inhibits it in a feedback manner.

Thus, vit D should be considered a hormone because:

(a) It is synthesized in the body (skin); under ideal conditions it is not required in the diet.
(b) It is transported by blood, activated and then acts on specific receptors in the target tissues.
(c) Feedback regulation of vit D activation occurs by plasma Ca^{2+} level and by the active form of vit D itself.

Actions

1. Calcitriol enhances absorption of calcium and phosphate from *intestine*. This is brought

about by increasing the synthesis of calcium channels and a carrier protein for Ca^{2+} called 'calcium binding protein' (Ca BP) or *Calbindin*. The action of calcitriol is analogous to that of steroid hormones. It binds to a cytoplasmic vitamin D receptor (VDR) and translocates to the nucleus where it increases synthesis of specific mRNA that in turn regulates protein synthesis. Another line of evidence suggests that activation of VDR promotes endocytotic capture of calcium, its transport across the duodenal mucosal cell and finally its active extrusion through the serosal membrane. At least part of vit D action is quick (within minutes) by affecting calcium flux across intestinal mucosal cell. This appears to be exerted by mechanisms not involving gene regulation.

2. Calcitriol enhances resorption of calcium and phosphate from *bone* by promoting recruitment and differentiation of osteoclast precursors in the bone remodeling units, but mature osteoclasts lack VDR. Like PTH, calcitriol induces RANKL in osteoblasts which may then activate the osteoclasts. Osteoblastic cells express VDR and respond to calcitriol by laying down osteoid, but it mainly appears to help bone mineralization indirectly by maintaining normal plasma calcium and phosphate concentration, as well as by inducing proteins like osteocalcin. The action is independent of but facilitated by PTH.

3. Calcitriol enhances tubular reabsorption of calcium and phosphate in the *kidney*, but the action is less marked than that of PTH. However, in hypervitaminosis D, influence of hypercalcaemia overrides the direct action and more calcium is excreted in urine.

4. *Other actions* Since VDR is expressed in many tissues, actions of calcitriol on immunological cells, lymphokine production, proliferation and differentiation of epidermal cells and certain malignant cells, neuronal and skeletal muscle function have also been demonstrated.

Vit D deficiency Plasma calcium and phosphate tend to fall in vit D deficiency due to inadequate intestinal absorption. As a consequence PTH is secreted and calcium is mobilized from bone in order to restore plasma Ca^{2+}. The bone fails to mineralize normally in the newly laid areas, becomes soft producing rickets in children and osteomalacia in adults. However, in contrast to *osteoporosis*, the organic matrix (osteoid) is normal in these conditions.

Hypervitaminosis D It may occur due to chronic ingestion of large doses (~50,000 IU/day) or due to increased sensitivity of tissues to vit D. Manifestations are due to elevated plasma calcium and its ectopic deposition. These are: hypercalcaemia, weakness, fatigue, vomiting, diarrhoea, sluggishness, polyuria, albuminuria, ectopic Ca^{2+} deposition (in soft tissues, blood vessels, parenchymal organs), renal stones or nephrocalcinosis, hypertension, growth retardation in children. Even coma has been reported.

Treatment: consists of withholding the vitamin, low calcium diet, plenty of fluids and corticosteroids. Recovery may be incomplete in many cases.

Pharmacokinetics

Vit D is well absorbed from the intestines in the presence of bile salts, mainly through lymphatics. Absorption of the D_3 form is somewhat better than that of D_2. Malabsorption and steatorrhoea interfere with its absorption.

In the circulation, vit D is bound to vit D binding protein (DBP), which is a specific α globulin, and is stored in the body, mostly in adipose tissues for many months. It is hydroxylated in the liver to active and inactive metabolites. The t½ of different forms of vit D varies from 1–18 days: 25-OHD_3, having the longest t½ , constitutes the primary circulating form. Calcitriol is cleared rapidly. Metabolites of vit D are excreted mainly in bile.

Unitage and preparations

1 µg of cholecalciferol = 40 IU of vit D.

The daily requirement varies, depending on exposure to sunlight. It is estimated that if no vit D3 is synthesized in the body, a dietary allowance of 400 IU/day will prevent deficiency symptoms. However, higher amounts (upto 1000 IU/day) are also recommended. The forms in which vit D is supplied are—

1. *Calciferol (Ergocalciferol, vit D2)* As solution in oil, filled in gelatin capsules 25,000 and 50,000 IU caps.
2. *Cholecalciferol (vit D3)* As granules for oral ingestion and oily solution for i.m. injection.

ARACHITOL 300,000 IU (7.5 mg) and 600,000 IU (15 mg) per ml inj.

CALCIROL 60,000 IU sachet/soft gel caps/chewable tabs, 1000 IU/5 ml syr, 800 IU/ml drops. CALCIBEST SACHET

60,000 IU in 1 g granules, to be suspended in milk/water and taken at 3–4 weeks intervals, and then every 2–6 months, LUMINA 60,000 IU caps.

3. *Calcitriol* 0.25–1 µg orally daily or on alternate days; CALTROL, ROLSICAL, ROCALTROL 0.25 µg cap. CALCIBEST 1 µg in 1 ml aqueous inj; 0.5–1 µg i.v. on alternate days.

Hypercalcaemia is the main adverse effect, which must be watched for and therapy promptly stopped if plasma Ca^{2+} rises.

4. *Alfacalcidol* It is 1 α-OHD_3—a prodrug that is rapidly hydroxylated in the liver to 1,25 $(OH)_2$ D_3 or calcitriol. Therefore, it does not require hydroxylation at position 1 which is the limiting step in the generation of active form of vit D, and which takes place in the kidney. As such, it is effective in renal bone disease, vit D dependent rickets, vit D resistant rickets, hypoparathyroidism, etc. i.e. indications for which calcitriol is needed. It is also being used in osteoporosis.

Alfacalcidol is orally active and clinically equally effective on long term basis to calcitriol. Its metabolic activation in liver does not pose a problem even in severe liver disease. *Dose*: 1–2 µg/day, children < 20 kg 0.5 µg/day. Repeated serum calcium measurements are essential for regulation of maintenance dose. Hypercalcaemia should be watched for and therapy promptly interrupted for few days when it develops.

ONE ALPHA, ALPHA D_3, ALPHADOL 0.25 and 1 µg caps, ALFACAL 0.25, 0.5 µg caps.

5. *Dihydrotachysterol* A synthetic analogue of vit D_2 that is much less active in antirachitic tests, but directly mobilizes calcium from bone after 25-hydroxylation in liver, and does not require PTH dependent activation in the kidney. It is particularly useful in hypoparathyroidism and renal bone disease.

Dose: 0.25–0.5 mg/day.

Combination preparations of vit D are listed on p. 362 and in Table 69.2.

Use

1. *Prophylaxis* (400 IU/day) *and treatment* (3000–4000 IU/day) *of nutritional vit D deficiency* Prophylactic dose or therapeutic dose of vit D is given to prevent or treat rickets in children and osteomalacia in adults. Alternatively 300,000–600,000 IU can be given orally or i.m. once in 2–6 months. Prophylaxis (oral or parenteral as appropriate) may be given in obstructive jaundice, steatorrhoea and other conditions which predispose to vit D deficiency.

2. *Metabolic rickets* These are a group of conditions in which tissues do not respond to normal doses of vit D.

(a) *Vit D resistant rickets:* X-linked hereditary disease in which vit D metabolism is normal but calcium and phosphate metabolism is deranged. Administration of phosphate with high dose of calcitriol or alfacalcidol is beneficial.

(b) *Vit D dependent rickets:* Another genetic disorder due to deficiency of renal hydroxylating mechanism which converts 25-OHD_3 into calcitriol. Administration of calcitriol or alfacalcidol is effective in normal doses.

(c) *Renal rickets:* Conversion of ~~25-OHD_3 into calcitriol~~ (which takes place in kidney) does not occur due to chronic renal disease. Calcitriol/alfacalcidol or dihydrotachysterol are needed in usual doses.

3. *Senile or postmenopausal osteoporosis* Age-related decrease in calcium absorption from gut has been noted. Vit D_3 + calcium have been shown to improve calcium balance in osteoporotic females and elderly males. However, benefit in terms of improved bone mass or reduced fracture risk is controversial or marginal (*see* p. 362). But this does not apply to active therapy with calcitriol/alfacalcidol for patients with established osteoporosis, treated with BPNs, etc. because calcitriol suppresses parathyroids and reduces bone remodeling. Vit D deficiency results in secondary hyperparathyroidism which contributes to osteoporosis. Calcitriol therapy carries the risk of hypercalcaemia, calcium stones and metastatic calcification which should be watched for.

4. *Hypoparathyroidism* Dihydrotachysterol or calcitriol or alfacalcidol are more effective than vit D_2 or D_3, because they act quickly and directly without requiring hydroxylation in kidney which needs PTH. Alternatively, conventional preparations of vit D_3 may be given in high doses (25000-100,000 IU/day).

5. *Fanconi syndrome* Vit D can raise the lowered phosphate levels that occur in this condition.

6. A nonhypercalcaemic analogue of vit D *Calcipotriol* (DAIVONEX 0.005% oint) is used locally in plaque type psoriasis, and has yielded

good results (*see* Ch. 66). Systemically it has been tried in skin cancer and immunological disorders.

Interactions

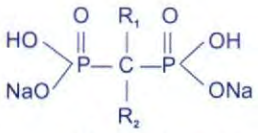
1. Cholestyramine and habitual use of liquid paraffine can reduce vit D absorption.
2. Phenytoin and phenobarbitone reduce the responsiveness of target tissues to calcitriol; their prolonged use (for epilepsy) can cause rickets/osteomalacia. It was believed earlier that these drugs enhance degradation of vit D. However, now it has been shown that plasma level of calcitriol is normal, but its effect on intestine and bone is diminished.

BISPHOSPHONATES

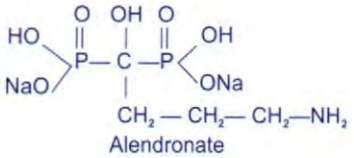
Bisphosphonates (BPNs) are analogues of pyrophosphate: carbon atom replacing oxygen in the P-O-P skeleton. They inhibit bone resorption and have attracted considerable attention because of their ability to prevent osteoporosis in addition to their usefulness in metabolic bone diseases and hypercalcaemia. They are the most effective antiresorptive drugs. Chronologically and according to their potency, the BPNs can be grouped into 3 generations (*see* box). The first generation compounds have simpler side chains, are the least potent and seldom used now. The second and third generation compounds have an amino or nitrogenous ring substitution in the side chain, are more potent, have higher efficacy and additional mode of action.

Bisphosphonate	Relative potency
First generation BPNs	
Etidronate	1
*Tiludronate	10
Second generation BPNs	
Pamidronate	100
Alendronate	100–500
Ibandronate	500–1000
Third generation BPNs	
Risedronate	1000
Zoledronate	5000

* Not marketed in India



Bisphosphonate



Alendronate

The mechanism of action of BPNs is not fully understood, but two facets of action have been delineated:

(a) BPNs have strong affinity for calcium phosphate and have selective action in calcified tissue. The two main components of bone are protein matrix and the solid mineral phase (hydroxyapatite). On the surface of resorptive pits, the mineral phase is solubilized in the clear acidic zone created at the ruffled border of osteoclasts, followed by resorption of protein matrix in this area by acid hydrolases secreted from osteoclasts. BPNs localise in the acidic zone under the osteoclasts due to their high affinity for Ca^{2+} ions. When Ca^{2+} ions are released from the bone surface due to high acidity, the BPNs are also released and are internalized into osteoclasts by endocytosis. This results in:

- Accelerated apoptosis of osteoclasts reducing their number.
- Disruption of cytoskeleton and ruffled border of osteoclasts.

In addition, BPNs appear to affect osteoclast precursors and inhibit their differentiation by suppressing IL-6.

(b) It has been shown now that the second and third generation potent amino-BPNs like alendronate, zoledronate have important metabolic effects in the mevalonate pathway for isoprenoid lipid synthesis. They inhibit prenylation of certain GTP-binding proteins involved in cytoskeletal organization, membrane ruffling and vesicle movement. The net result is inactivation of

osteoclasts, impaired vesicle fusion and enhanced apoptosis. Interference with mevalonate pathway may also impart antitumour activity on bony metastasis.

Pharmacokinetics All oral BPNs are poorly absorbed and produce gastric irritation, esophagitis as the major side effect. Alendronate, ibandronate and risedronate are administered orally. Oral BPNs are contraindicated in gastroesophageal reflux, peptic ulcer and renal impairment. The alternate route for BPNs is i.v. infusion, by which large amount of BPN can be made to enter the body. This also permits frequency of dosing to be reduced to as less as once a year, because about 50% of the absorbed/injected drug is sequestrated in the bone. The remaining 50% is excreted unchanged in the urine. Pamidronate and zoledronate are available for i.v. infusion.

Uses The BPNs are useful in conditions characterized by enhanced bone turnover.

1. *Osteoporosis* The second and third generation BPNs (e.g. alendronate, ibandronate, risedronate) are effective in preventing and treating postmenopausal osteoporosis in women as well as age related, idiopathic and steroid-induced osteoporosis in both men and women. Alendronate is equally or more effective than HRT or raloxifene in conserving bone mineral density and has reduced the risk of vertebral as well as hip fracture by 47–56%. However, BPNs do not directly stimulate bone formation.

Estrogens prevent vertebral but not other fractures. BPNs are more effective than calcitonin and continue to afford protection for at least 5 years of continuous use. Thus, they are the first choice drugs now for osteoporosis. Since the t½ of alendronate in bone is ~ 10 years, treatment beyond 5 years is considered unnecessary.

2. *Paget's disease* This disease due to abnormal osteoclast function producing disordered bone remodeling and honeycomb-like bone architecture is benefited by BPNs. They arrest osteolytic lesions, reduce bone pain and improve secondary symptoms. Long-lasting remissions may be induced. Alendronate, risedronate, ibandronate and zoledronate are used now. They are more convenient, more effective and cheaper than calcitonin. Combined use of BPNs and calcitonin further increases efficacy. Treatment with BPNs should not exceed 6 months; but courses may be repeated after a gap.

3. *Hypercalcaemia of malignancy* Severe hypercalcaemia, a common complication of malignancy, is a medical emergency with dehydration and altered consciousness. Rapid rehydration with i.v. saline infusion is the first step, which itself lowers serum Ca^{2+} to some extent. Pamidronate (60–90 mg i.v. over 2–4 hours) or zoledronate (4 mg i.v. over 15 min) are the most effective drugs, but take 24–48 hours to act. They may be supplemented by i.m. calcitonin 6–12 hourly for 2 days to achieve rapid action. Vigorous i.v. hydration is instituted first. After volume repletion, furosemide is added to enhance Ca^{2+} excretion and to prevent volume overload. This is followed by BPN infusion. This therapy reduces serum calcium within few hours and corrects the attending dehydration. Oral BPNs are not useful. Corticosteroids also lower plasma Ca^{2+}, but are slow to act, take 1–2 weeks.

4. *Osteolytic bone metastasis* Parenteral pamidronate/zoledronate arrests osteolytic lesions and reduces bone pain. Potent BPNs, especially zoledronate, have shown independent antitumour property. They have shown adjuvant value as add-on drugs in reducing breast carcinoma recurrences as well as in delaying skeletal events in women with bony metastasis.

Oral administration of BPNs All oral BPNs are to be taken on empty stomach in the morning with a full glass of water and the patient is instructed not to lie down or take food for at least 30 min. The tab/cap should not be chewed. These measures are needed to prevent contact of the drug with esophageal mucosa which results in esophagitis, erosions and ulcers. Calcium, iron, antacids, mineral water, tea, coffee, fruit juice interfere with BPN absorption, because metal salts and other

food constituents form nonabsorbable complex with BPNs. NSAIDs accentuate gastric irritation caused by BPNs.

Etidronate This is the first BPN to be used clinically. It has been employed in hypercalcaemia, Paget's disease and heterotopic ossification (deposition of bone in skeletal muscles and other soft tissues). However, it also interferes with bone mineralization: continuous therapy produces osteomalacia. Therefore, it has been largely replaced by second or third generation BPNs.

Dose: 5–7.5 mg/kg/day.

DRONATE-OS 200 mg tab, 300 mg inj.

Pamidronate A second generation potent BPN which is administered only by i.v. infusion in a dose of 60–90 mg over 2–4 hours weekly or monthly depending on the condition. It is used in Paget's disease, hypercalcaemia of malignancy and in bony metastasis. Adverse effects are thrombophlebitis of injected vein, bone pain, fever and leukopenia. A flu-like reaction may occur initially due to cytokine release.

AREDIA 15, 30, 60 mg inj; AREDRONET 30, 90 mg inj. BONAPAM 30, 60, 90 mg inj.

Alendronate This potent orally effective second generation amino-BPN is used primarily for prevention and treatment of osteoporosis both in women and in men, as well as for Paget's disease. Adverse effects are esophagitis, gastric erosion, retrosternal pain, flatulence, headache, bodyache and initial fall in serum Ca^{2+} level.

Dose: 5–10 mg OD; or 35–70 mg weekly; weekly treatment is equally effective, more convenient and better tolerated.

OSTEOPHOS, DENFOS 5, 10, 35, 70 mg tab. RESTOFOS, DRONAL 10, 70 mg tab.

Oral bioavailability of alendronate is ~1%. Up to 50% of the drug entering the body is sequestrated in bone while the rest is excreted unchanged mainly by the kidney. Dose reduction is needed in patients with renal impairment. The terminal elimination t½ of alendronate has been measured as 10.5 years.

Ibandronate This is another amino-BPN, similar in properties to alendronate. Though its efficacy has not been directly compared with other BPNs in clinical trials, it has been reported to reduce the risk of vertebral fractures, but not nonvertebral fractures among osteoporotic patients. It has also been used in Paget's disease and by i.v. infusion (2–4 mg over 1–2 hours) for hypercalcaemia of malignancy.

Dose: 2.5 mg daily or 150 mg once a month

BONIVA, BONRONIC 150 mg tab.

Risedronate It is an oral 3rd generation BPN, more potent than alendronate, but equally efficacious. Oral bioavailability of 1% and other features are similar to alendronate. It is indicated in the treatment of osteoporosis and Paget's disease.

Dose: 5 mg daily or 35 mg/week or 150 mg once a month oral in the morning with a full glass of water.

RISOFOS 5, 35, 75, 150 mg tabs. GEMFOS, ACTONEL 35 mg tab.

Zoledronate This parenteral highly potent 3rd generation BPN is indicated for hypercalcaemia, bony metastasis, osteolytic lesions, and Paget's disease. Osteoclastic activity is markedly suppressed and an additional antitumour effect may be exerted by interference with mevalonate pathway. Proliferation of bony metastasis of prostate/breast cancer and multiple myeloma cells may be arrested. For hypercalcaemia, it is more effective, faster acting than pamidronate and therefore the drug of choice now. Another advantage is that it can be infused over 15 min (because of less venous irritation), whereas pamidronate needs 2–4 hours. Flu-like symptoms due to cytokine release attend the i.v. infusion. Nausea, vomiting, bodyache and dizziness are also common. Renal toxicity has been encountered. Osteonecrosis of the jaw is a rare complication of i.v. high dose BPN therapy.

Zoledronate 4 mg infused i.v. once every 12 months for a maximum of 5 years has been used for osteoporosis in postmenopausal women who do not tolerate oral alendronate/risedronate.

Dose: 4 mg diluted in 100 ml saline/glucose solution and infused i.v. over 15 min; may be repeated after 7 days and then at 3–4 week intervals.

ZOBONE, ZOLDRIA, ZOLTERO 4 mg/vial inj.

Other drugs for osteoporosis

1. Denosumab: It is a fully human monoclonal antibody against RANKL. By binding to and neutralizing RANKL, denosumab prevents RANK activation thereby inhibiting proliferation and differentiation of osteoclast precursors as well as

osteoclast function. As a result, bone resorption is inhibited to an extent equal to or greater than potent BPNs. It is now being used as a treatment option for osteoporosis in both women and men, as well as to limit bony metastasis in breast and prostate cancers. The bone loss caused by gonadal suppressant therapy of these tumours is also counteracted.

In osteoporotic patients with high fracture risk, denosumab has been found to lower vertebral as well as hip fracture risk by 40–68%. It can be given to patients with severe renal disease, in whom BPNs are contraindicated. Adverse effects of denosumab are flu-like symptoms, initial fall in serum Ca^{2+} level, dermatitis, susceptibility to infections (because RANKL is a signal molecule for many immune cells as well), rarely osteonecrosis of the jaw.

Dose: 60 mg s.c. once every 6 months (max. 3–5 years).

2. Strontium ranelate: This organic compound of strontium inhibits bone resorption by preventing osteoclast differentiation and promoting their apoptosis. In addition, it stimulates bone formation. In clinical trials it has been found to increase bone mineral density and to decrease the risk of vertebral as well as hip fracture. However, it can increase the risk of serious cardiovascular disease like MI, stroke and thromboembolism. Therefore, it is indicated only as a reserve drug for severe osteoporosis in elderly women and in men at high risk of fracture in whom BPNs and other drugs are contraindicated or not tolerated. Other adverse effects are headache, g.i. upset, rashes and serious skin reactions.

Dose: 2 g/day; avoid food for 2 hours before and after the dose.

STRONAT 2 g oral granules sachet.

Other drugs for hypercalcaemia

1. Gallium nitrate: It is a potent inhibitor of bone resorption; acts by depressing ATP-dependent proton pump at the ruffled membrane of osteoclasts. Indicated in resistant cases of malignancy associated hypercalcaemia, it is given by continuous i.v. infusion daily for 5 days. It is nephrotoxic and only a reserve drug.

2. *Glucocorticoids:* High doses of prednisolone (and other glucocorticoids) enhance calcium excretion, decrease calcium absorption and lower plasma Ca^{2+} level, but act slowly. They have adjuvant role in hypercalcaemia due to lymphoma, myeloma, leukaemia, carcinoma breast, etc. Administered over several days, glucocorticoids play more important role in normalizing plasma Ca^{2+} level in hypercalcaemia due to hypervitaminosis D and sarcoidosis.

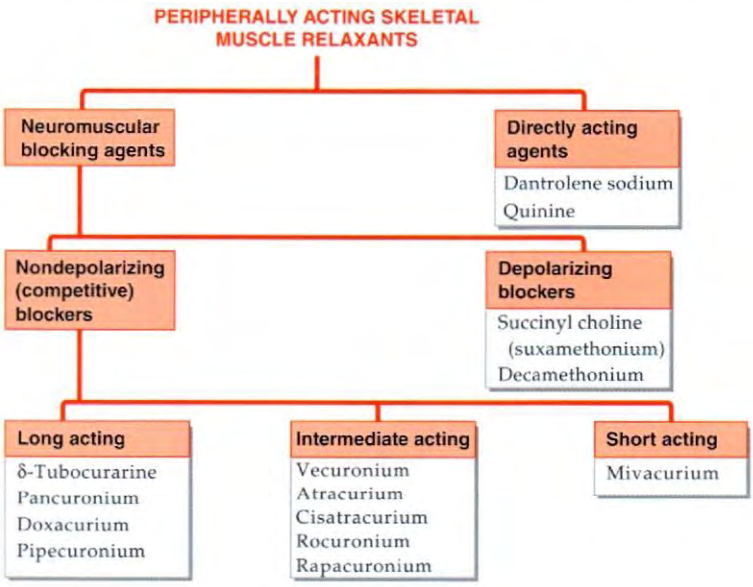
SECTION 6

DRUGS ACTING ON PERIPHERAL (SOMATIC) NERVOUS SYSTEM

Chapter 25 Skeletal Muscle Relaxants

Skeletal muscle relaxants are drugs that act peripherally at neuromuscular junction/muscle fibre itself or centrally in the cerebrospinal axis to cause paralysis or reduce muscle tone. The neuromuscular blocking agents are used primarily in conjunction with general anaesthetics to provide muscle relaxation for surgery, while centrally acting muscle relaxants are used mainly for painful muscle spasms and spastic neurological conditions.

PERIPHERALLY ACTING MUSCLE RELAXANTS



Note: 1. Tubocurarine and Decamethonium are not used clinically.
2. Aminoglycoside, tetracycline, polypeptide antibiotics (at high doses) interfere with neuromuscular transmission, but are not employed as muscle relaxants.

NEUROMUSCULAR BLOCKING AGENTS

Curare It is the generic name for certain plant extracts which were used by south American tribals as arrow poison for game hunting. The animals got paralysed even if not killed by the arrow. Natural sources of curare are *Strychnos toxifera, Chondrodendron tomentosum* and related plants. The muscle paralysing active principles of these are tubocurarine, toxiferins, etc.

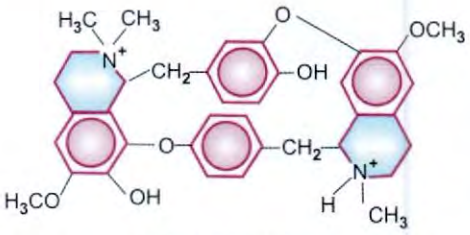
Tubocurarine was first clinically used in 1930s; many synthetic compounds including *Succinylcholine* were introduced subsequently. Search has continued for neuromuscular blockers to provide greater cardiovascular stability during surgery, and for drugs with differing onset and duration of action to suit specific requirements.

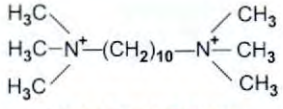
MECHANISM OF ACTION

The site of action of both competitive and depolarizing blockers is the end plate of skeletal muscle fibres.

Competitive block (Nondepolarizing block) This is produced by curare and related drugs. Claude Bernard (1856) precisely localized the site of action of curare to be the neuromuscular junction. He stimulated the sciatic nerve of pithed frog and recorded the contractions of gastrocnemius muscle. Injection of curare in the ventral lymph sac caused inhibition of muscle twitches but there was no effect if the blood supply of the hind limb was occluded. This showed that curare acted peripherally and not centrally. Soaking a portion of the sciatic nerve in curare solution did not affect the twitches and a curarized muscle still responded to direct stimulation—thus, nervous conduction and muscle contraction were intact. The only possible site of action could be the neuromuscular junction. This has now been confirmed by close iontophoretic application of d-TC to the muscle end plate and by other modern techniques.

The competitive blockers have affinity for the nicotinic (N_M) cholinergic receptors at the muscle end plate, but have no intrinsic activity. The N_M receptor has been isolated and studied in detail. It is a protein with 5 subunits ($\alpha 2\ \beta\ \varepsilon$ or γ and δ) which are arranged like a rosette surrounding the Na^+ channel (*see* Fig. 4.4). The two α subunits carry two ACh binding sites; these have negatively charged groups which combine with the cationic head of ACh. This triggers opening of Na^+ channels. Most of the competitive blockers have two or more quaternary N^+ atoms (Fig. 25.1) which provide the necessary attraction to the same site, but the bulky nature of the antagonist molecule does not allow conformational changes in the subunits needed for opening the channel. Competitive blockers generally have thick bulky molecules and were termed *Pachycurare* by Bovet (1951). Some of the ACh molecules released from motor nerve endings are not able to combine with the receptors, and magnitude of the end plate potential (EPP) falls. When the magnitude of EPP falls below a critical level, it is unable to trigger propagated muscle action potential (MAP) and muscle fails to contract in response to the nerve impulse. The antagonism is surmountable by increasing the concentration of ACh *in vitro* and by anticholinesterases *in vivo*. At very high concentrations, curare like





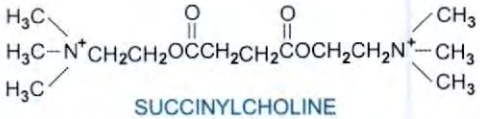


Fig. 25.1: Chemical structure of three neuromuscular blockers. Note the thick, bulky molecule of competitive blocker d-tubocurarine and slender, flexible molecules of depolarizing blockers decamethonium and succinylcholine

drugs enter the Na^+ channels and directly block them to produce more intense noncompetitive neuromuscular block that is only partly reversed by neostigmine.

The competitive blockers also block prejunctional nicotinic receptors located on motor nerve endings. Since activation of these receptors by ACh normally facilitates mobilization of additional quanta of ACh from the axon to the motor nerve endings, their blockade contributes to depression of neuromuscular transmission. Accordingly, the competitive blockers exhibit the 'fade' phenomenon (Fig. 25.3), i.e. twitch responses during partial block are progressively depressed on repetitive stimulation.

Tetanic stimulation during partial nondepolarizing block increases the response to a subsequent single stimulation (twitch). This is called *'post-tetanic potentiation'*, and is probably due to a transient increase in prejunctional ACh mobilization following tetanic stimulation.

Depolarizing block Decamethonium and SCh have affinity as well as submaximal intrinsic activity at the N_M cholinoceptors. They depolarize muscle end plates by opening Na^+ channels (just as ACh does) and initially produce twitching and fasciculations. Because in the focally innervated mammalian muscle, stimulation is transient; longer lasting depolarization of muscle end plate produces repetitive excitation of the fibre. In the multiplely innervated contracture muscle (rectus abdominis of frog) stimulation is prolonged resulting in sustained contraction. These drugs do not dissociate rapidly from the receptor and are not hydrolysed by AChE. They induce prolonged partial depolarization of the region around muscle end plate resulting in inactivation of Na^+ channels (because transmembrane potential drops to about –50 mV). In this state ACh released from motor nerve endings is unable to generate a propagated MAP causing flaccid paralysis in mammals. In other words, a zone of inexcitability, is created around the end plate preventing activation of the muscle fibre. In birds, the area of depolarization is more extensive and spastic paralysis occurs.

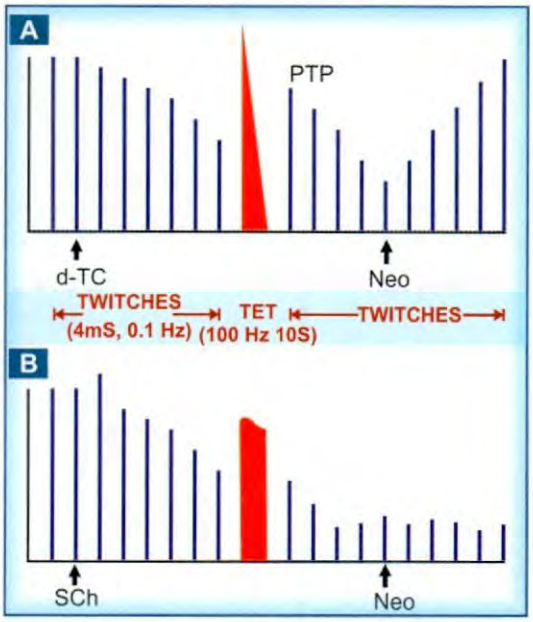


Fig. 25.2: Illustration of characteristics of competitive (A) and depolarizing (B) neuromuscular blockade in sciatic nerve-gastrocnemius muscle of cat

A. Tubocurarine (d-TC) produces progressive decrease in twitch tension; tetanic stimulation (TET) produces poorly sustained contracture, which is followed by post-tetanic potentiation (PTP); Neostigmine (Neo) restores the twitch contractions.

B. Succinylcholine (SCh) produces initial augmentation of twitches followed by progressive block; tetanus is well sustained, but there is no PTP; block is not reversed (rather worsened) by neostigmine.

Depolarizing blockers also have 2 quaternary N^+ atoms, but the molecule is long, slender and flexible—termed *Leptocurare* by Bovet. The features of classical depolarizing block differ markedly from that of nondepolarizing block (*see* Fig. 25.2 and Table 25.1).

However, in many species, e.g. dog, rabbit, rat, monkey, in slow contracting soleus muscle of cat, and under certain conditions in man the depolarizing agents injected in high doses or infused continuously produce dual mechanism neuromuscular blockade which can be divided into two phases:

Phase I block It is rapid in onset, results from persistent depolarization of muscle end plate and has features of classical depolarization

Table 25.1: Features of competitive and typical depolarizing block

	Competitive block (d-TC)	*Depolarizing (phase I) block (SCh)*
1. Paralysis in man	Flaccid	Fasciculations → flaccid
2. Paralysis in chick	Flaccid	Spastic
3. Effect on isolated frog's rectus muscle	No contraction, antagonism of ACh	Contraction
4. Species sensitivity	Rat > rabbit > cat	Cat > rabbit > rat
5. Human neonates	More sensitive	Relatively resistant
6. Tetanic stimulation during partial block	Poorly sustained contraction	Well sustained contraction
7. Neostigmine	Antagonises block	No effect
8. Post tetanic potentiation	Present	Absent
9. Ether anaesthesia	Synergistic	No effect
10. Order of paralysis	Fingers, eyes → limbs → neck, face → trunk → respiratory	Neck, limbs → face, jaw, eyes, pharynx → trunk → respiratory
11. Effect of lowering temperature	Reduces block	Intensifies block
12. Effect of cathodal current to end plate	Lessens block	Enhances block

blockade. This depolarization declines shortly afterwards and repolarization occurs gradually despite continued presence of the drug at the receptor, but neuromuscular transmission is not restored and phase II block supervenes.

Phase II block It is slow in onset and results from desensitization of the receptor to ACh. It, therefore, superficially resembles block produced by d-TC. The muscle membrane is nearly repolarized, recovery is slow, contraction is not sustained during tetanic stimulation ('fade' occurs) and the block is partially reversed by anticholinesterases.

In man and fast contracting muscle (tibialis anterior) of cat, normally only phase I block occurs. Phase II block may be seen in man when SCh is injected in high dose or infused continuously, particularly, if fluorinated anaesthetics have been used. SCh readily produces phase II block in patients with atypical or deficient pseudocholinesterase.

ACTIONS

1. Skeletal muscles Intravenous injection of nondepolarizing blockers rapidly produces muscle weakness followed by flaccid paralysis. Small fast response muscles (fingers, extraocular) are affected first; paralysis spreads to hands, feet—arm, leg, neck, face—trunk—intercostal muscles—finally diaphragm: respiration stops. The rate of attainment of peak effect and the duration for which it is maintained depends on the drug (Table 25.2), its dose, anaesthetic used, haemodynamic, renal and hepatic status of the patient and several other factors. Recovery occurs in the reverse sequence; diaphragmatic contractions resume first. In general, the more potent nondepolarizing blockers have a longer onset of action.

Depolarizing blockers typically produce fasciculations lasting a few seconds before inducing flaccid paralysis, but fasciculations are not prominent in well-anaesthetized patients. Though the sequence in which muscles are involved is somewhat different from the competitive blockers (Table 25.1), the action of SCh develops with such rapidity that this is difficult to perceive. Apnoea generally occurs within 45–90 sec, but lasts only 2–5 min; recovery is rapid.

Clinical monitoring of neuromuscular block

In anaesthetic practice neuromuscular block (especially during recovery) is monitored by recording contractile responses of thumb muscles to transcutaneous ulnar nerve

stimulation. Since single twitch responses have to be interpreted in comparison to twitches before the blocker, and are not reliable, several other protocols are used. One such method is 'train-of-four' (TOF) protocol. Four supramaximal electrical stimuli are applied in 2S (2Hz) and contractions of thumb muscle are recorded (Fig. 25.3A). The TOF-ratio is obtained by dividing the strength of 4th contraction by that of the 1st. In the untreated subject all the 4 contractions remain equal and TOF-ratio is 1.0.

During partial competitive block (as occurs during onset and recovery or reversal) the degree of block corresponds to the decrease in TOF-ratio, because competitive blockers exhibit 'fade' phenomenon. As the muscles recover, the TOF-ratio improves and becomes 1.0 at complete recovery. Spontaneous breathing may be resumed when TOF-ratio recovers to > 0.7.

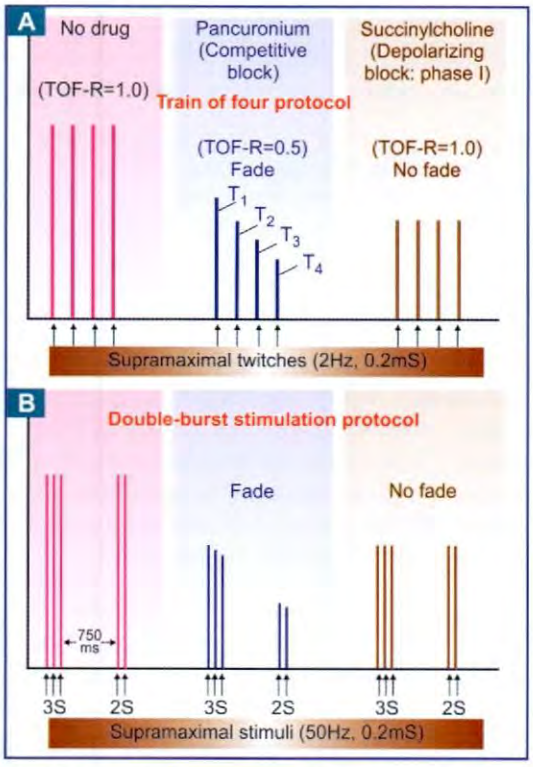


Fig. 25.3: Clinical assessment of neuromuscular block. (A) *Train-of-four (TOF) protocol:* Contractile responses of adductor pollicis muscle to transcutaneous ulnar nerve stimulation with train-of-four protocol of impulses during recovery of neuromuscular block. TOF-R—Train of four ratio (strength of 4th contraction divided by that of the 1st). (B) *Double-burst stimulation ($DBS_{3,2}$):* Evoked responses to burst of three 0.2 ms pulses at 50 Hz followed 750 ms later by a second burst of two similar pulses. Note 'fade' in the second burst after nondepolarizing block.

On the other hand, classical or phase-I depolarizing block does not exhibit fade; the TOF-ratio remains 1.0, though all the 4 twitches are depressed equally depending on the degree of block. Fade is again seen when phase II or desensitization block occurs with prolonged use of a depolarizing agent and TOF-ratio is depressed as in the case of competitive block. However, SCh generally requires no monitoring.

Rather than measuring each contraction and calculating TOF ratio, in practice, it is easier to simply observe the disappearance (during onset) or reappearance (during recovery) of the successive twitches. Reappearance of 2nd twitch (T_2) corresponds to ~10% recovery (~90% residual block) and that of 4th twitch (T_4) to ~25% recovery.

Because fade is more prominent during sustained stimulation, an alternate method is 'tetanic stimulation' protocol, in which 0.2 ms pulses are applied at 50–100 Hz for 4–5 seconds and presence or absence of fade is noted (*see* fade in Fig. 25.2A).

Many anaesthesiologists prefer to use the less painful variant of tetanic stimulation, *viz* 'double-burst stimulation' (DBS). A burst of three 0.2 ms pulses at 50 Hz is followed after a gap of 750 ms by a second burst of 2 or 3 similar pulses (Fig. 25.3B). The strength of response during the 2nd burst relative to the first is a measure of the recovery from block.

Measurement of 'post-tetanic count (PTC)' is another clinically used method.

2. Autonomic ganglia Because the cholinergic receptors in autonomic ganglia are nicotinic (though of a different subclass N_N), competitive neuromuscular blockers produce some degree of ganglionic blockade; d-TC has the maximum propensity in this regard, while the newer drugs (vecuronium, etc.) are practically devoid of it. SCh may cause ganglionic stimulation by its agonistic action on ganglionic nicotinic receptors.

3. Histamine release d-TC releases histamine from mast cells. This does not involve immune system and is due to the bulky cationic nature of the molecule. Histamine release contributes to the hypotension produced by d-TC. Flushing, bronchospasm and increased respiratory secretions are the other effects. Intradermal injection of d-TC produces a wheal similar to that produced by injecting histamine. Atracurium and mivacurium have significant histamine releasing potential. Histamine releasing potential of neuromuscular blockers is graded in Table 25.2.

Heparin may also be simultaneously released from mast cells.

Table 25.2: Comparative properties of neuromuscular blocking drugs

Drug	Dose£ (mg/kg)	Onset* (min)	Duration@ (min)	Hist. release	Gang. block	Vagal block
LONG ACTING						
1. d–Tubocurarine	0.2–0.4	4–6	40–60	+++	++	±
2. Pancuronium	0.04–0.1	4–6	60–120	±	±	+
3. Doxacurium	0.03–0.08	4–8	60–120	+	–	–
4. Pipecuronium	0.05–0.08	2–4	50–100	±	–	–
INTERMEDIATE ACTING						
5. Vecuronium	0.08–0.1	2–4	30–50	±	–	±
6. Atracurium	0.3–0.6	2–4	20–40	+	–	–
7. Cisatracurium	0.15–0.2	3–6	25–50	–	–	–
8. Rocuronium	0.6–0.9	1–2	25–40	–	–	±
SHORT ACTING						
9. Mivacurium	0.15–0.2	2–4	15–30	+	–	–
10. Succinylcholine	0.5–0.8	1–1.5	5–8	++	St.	St.

£ Initial paralysing dose for opioid/nitrous oxide + oxygen anaesthesia. In patients anaesthetised with ether/halothane/isoflurane, the dose may be $^1/_3$–$^1/_2$ of the figure given.

* Time to maximal block after i.v. injection.

@ Duration of surgical grade relaxation after usual clinical doses; time to 95% recovery of muscle twitch is nearly double of the figure given (especially for long-acting drugs). Duration is dose dependent as well.

St.—Stimulation

4. C.V.S.

d-Tubocurarine produces significant fall in BP. This is due to—

(a) ganglionic blockade
(b) histamine release and
(c) reduced venous return—a result of paralysis of limb and respiratory muscles.

Heart rate may increase due to vagal ganglionic blockade. Pancuronium tends to cause tachycardia and rise in BP, while atracurium may cause hypotension. All newer nondepolarizing drugs *viz.* vecuronium, rocurorinium and cisatracurium have negligible effects on BP and HR.

Cardiovascular effects of SCh are variable. Generally bradycardia occurs initially due to activation of vagal ganglia followed by tachycardia and rise in BP due to stimulation of sympathetic ganglia. BP occasionally falls on account of its muscarinic action causing vasodilatation. Prolonged administration of SCh has caused cardiac arrhythmias and even arrest in patients with burns, soft tissue injury and tetanus. Efflux of intracellular K^+ occurs in these conditions which is augmented by prolonged depolarization of skeletal muscles.

5. G.I.T. The ganglion blocking activity of competitive blockers may enhance postoperative paralytic ileus after abdominal operations.

6. C.N.S. All neuromuscular blockers are quaternary compounds—do not cross blood-brain barrier. Thus, on i.v. administration no central effects follow. However, d-TC applied to brain cortex or injected in the cerebral ventricles produces strychnine like effects.

PHARMACOKINETICS

All neuromuscular blockers are polar quaternary compounds; therefore not absorbed orally, do not cross cell membranes, have low volumes of distribution and do not penetrate placental or blood-brain barrier. They are practically always given i.v., though i.m. administration is possible. Muscles with higher blood flow receive more drug and are affected earlier. Redistribution to non-muscular tissues plays a significant role in the termination of surgical grade muscle relaxation, but residual block may persist for a longer time depending on the elimination t½. The duration of action of competitive blockers is

directly dependent on the elimination t½. Drugs that are primarily metabolized in the plasma/liver, e.g. vecuronium, atracurium, cisatracurium, rocuronium, and especially mivacurium have relatively shorter t½ and duration of action (20–40 min), while those largely excreted by the kidney, e.g. pancuronium, d-Tc, doxacurium and pipecuronium have longer t½ and duration of action (>60 min). With repeated administration, redistribution sites are filled up and duration of action is prolonged. The unchanged drug is excreted in urine as well as in bile.

SCh is rapidly hydrolysed by plasma pseudocholinesterase to succinylmonocholine and then succinic acid + choline (action lasts 5–8 min). Some patients have genetically determined abnormality (low affinity for SCh) or deficiency of pseudocholinesterase. In subjects who are homozygous for the abnormal enzyme (1 in > 3000 population), SCh causes prolonged phase II blockade resulting in muscle paralysis and apnoea lasting 4–6 hours, because SCh is a poor substrate for the more specific AChE found at the motor end plate. However, duration of paralysis is increased only by 2–3 times in subjects who are heterozygous for the abnormal enzyme (1 in ~ 50), or have only relative deficiency. The prolonged apnoea can be tided over only by mechanical ventilation.

NOTES ON INDIVIDUAL COMPOUNDS

1. d-Tubocurarine Because of its prominent histamine releasing, ganglion blocking and cardiovascular actions as well as long duration of paralysis needing pharmacological reversal, d-TC is not used now.

2. Succinylcholine Despite its propensity to cause muscle fasciculations and soreness, changes in BP and HR, arrhythmias, histamine release and K^+ efflux from muscles causing hyperkalaemia and its complications, SCh is the most commonly used muscle relaxant for passing tracheal tube. It induces rapid, complete and predictable paralysis with spontaneous recovery in ~5 min. Excellent intubating condition *viz.* relaxed jaw, vocal cords apart and immobile with no diaphragmatic movements, is obtained within 1–1.5 min. Occasionally SCh is used by continuous i.v. infusion for producing controlled muscle relaxation of longer duration. It should be avoided in younger children unless absolutely necessary, because risk of hyperkalaemia and cardiac arrhythmia is higher. Risk of regurgitation and aspiration of gastric contents is increased by SCh in GERD patients and in the obese, especially if stomach is full.

MIDARINE, SCOLINE, MYORELEX, ENTUBATE 50 mg/ml inj, 2 ml amp.

3. Pancuronium A synthetic steroidal compound, ~5 times more potent and longer acting than d-TC, which provides good cardiovascular stability (little ganglionic blockade), seldom induces flushing, bronchospasm or cardiac arrhythmias because of lower histamine releasing potential. Rapid i.v. injection of pancuronium often causes rise in BP and tachycardia due to vagal blockade and NA release. It is primarily eliminated by renal excretion. Because of longer duration of action, needing reversal, its use is now restricted to prolonged operations, especially neurosurgery.

PAVULON, PANURON, NEOCURON 2 mg/ml in 2 ml amp.

4. Doxacurium A bisquaternary muscle relaxant having the least rapid onset and the longest action. It is suitable for long duration surgeries. It is primarily eliminated by kidney, though hepatic metabolism also occurs. Cardiovascular changes are less marked.

5. Pipecuronium Another steroidal muscle relaxant with a slow onset and long duration of action; which is recommended for prolonged surgeries. It exerts little cardiovascular action, though transient hypotension and bradycardia can occur. Elimination occurs through both kidney and liver.

ARDUAN 4 mg/2 ml inj.

6. Vecuronium A close congener of pancuronium with a shorter duration of action due to rapid distribution and considerable hepatic metabolism. It is excreted mainly in bile, recovery is generally spontaneous, but may need neostigmine reversal. Cardiovascular stability is still better due to mild histamine releasing and ganglionic action; tachycardia sometimes occurs. Currently, it is one of the most

commonly used muscle relaxant for routine surgery and in intensive care units.
NORCURON 4 mg amp, dissolve in 1 ml solvent supplied. NEOVEC 4 mg amp, 10 mg vial.

7. Atracurium A bisquaternary competitive blocker, 4 times less potent than pancuronium and shorter acting, so that reversal is mostly not required. The unique feature of atracurium is inactivation in plasma by spontaneous non-enzymatic degradation (Hofmann elimination) in addition to that by cholinesterases. Consequently its duration of action is not altered in patients with hepatic/renal insufficiency or hypodynamic circulation. Atracurium causes dose dependent histamine release; hypotension can occur. When used for long periods (e.g. to facilitate positive pressure ventilation in I.C.Us), one of its metabolites may accumulate and cause CNS toxicity. Availability of less toxic cisatracurium has sent racemic atracurium in the background.
TRACRIUM 10 mg/ml inj in 2 ml vial.

8. Cisatracurium This *R-Cis, R-Cis* enantiomer of atracurium is nearly 4 times more potent, slower in onset, but similar in duration of action. Like atracurium it undergoes Hofmann elimination, but in contrast to the racemate, it is not hydrolysed by plasma cholinesterase and hepatic metabolism is limited, so that less of the toxic metabolite is formed. Most importantly, it does not provoke histamine release and side effects are fewer. Currently, cisatracurium is one of the preferred muscle relaxants, especially for liver/kidney disease patients and for the elderly.
NIMBEX 2 mg/ml inj.

9. Rocuronium A newer nondepolarizing blocker with the most rapid onset and intermediate duration of action which can be used as alternative to SCh for tracheal intubation without the disadvantages of depolarizing block and cardiovascular changes. The same drug also serves as maintenance muscle relaxant, seldom needing reversal. The onset of action is dose-dependent; intubating conditions are attained in 90 sec with 0.6 mg/kg, but within 60 sec at 1.0 mg/kg. Within limits, the duration of paralysis is also dose-dependent. This neuromuscular blocker is gaining popularity for its versatility and more precisely timed onset and duration of action. Infused i.v. (0.3–0.6 mg/kg/hour), it is also being used to facilitate mechanical ventilation in intensive care units. Though little metabolized, it is eliminated mainly in bile. Mild vagolytic action increases HR somewhat.
ROCUNIUM, CUROMID 50 mg/5 ml, 100 mg/10 ml vials.

10. Mivacurium It is the shortest acting competitive blocker; does not need reversal. Dose and speed of injection related transient cutaneous flushing can occur due to histamine release. Fall in BP is possible, but change in HR is minimal. It is metabolized rapidly by plasma cholinesterases. Prolonged paralysis can occur in pseudocholinesterase deficiency, but this can be reversed by neostigmine (unlike paralysis due to SCh which cannot be reversed).

INTERACTIONS

1. *Thiopentone sod* and SCh solutions should not be mixed in the same syringe—react chemically.

2. *General anaesthetics* potentiate competitive blockers; ether in particular, followed by fluorinated hydrocarbons of which isoflurane is most potentiating and halothane the least. Desflurane and sevoflurane are intermediate. Nitrous oxide potentiates the least. Ketamine also intensifies nondepolarizing block. Fluorinated anaesthetics predispose to phase II blockade by SCh. Malignant hyperthermia produced by halothane and isoflurane in rare (genetically predisposed) individuals is more common in patients receiving SCh as well.

3. *Anticholinesterases* reverse the action of competitive blockers. Neostigmine 0.5–2 mg (30–50 µg/kg) i.v. is almost routinely used after pancuronium and other long/intermediate acting blockers to hasten recovery at the end of operation. It is important to reverse the residual block, because residual weakness can cause hypoventilation and hypoxia in the recovery room. Though neostigmine also reverses ganglionic blockade to some extent, hypotension and bronchospasm can occur due to muscarinic action of neostigmine; this can be prevented by prior atropinization (atropine or glycopyrrolate 5–10 µg/kg i.v.). Pretreatment with H_1 antihistamines reduces hypotension due to histamine releasing neuromuscular blockers.

4. *Antibiotics* Aminoglycoside antibiotics reduce ACh release from prejunctional nerve endings by competing with Ca^{2+}. They interfere with mobilization of ACh containing vesicles from a central location to near the terminal membrane, and have a weak stabilizing action on the postjunctional membrane. In clinically used doses, they do not by themselves produce muscle relaxation, but potentiate competitive blockers. The dose of competitive blocker should be reduced in patients receiving high doses of these antibiotics. Application of streptomycin powder locally at the end of bowel surgery has caused prolonged apnoea if a competitive blocker had been used during the operation. Tetracyclines (by chelating Ca^{2+}), polypeptide antibiotics, clindamycin and lincomycin also synergise with competitive blockers.
5. *Calcium channel blockers* Verapamil and others potentiate both competitive and depolarizing neuromuscular blockers.
6. *Diuretics* may produce hypokalemia which enhances competitive block.
7. *Diazepam*, *propranolol* and *quinidine* intensify competitive block, while high dose of corticosteroids reduces it.

Sugamadex This is a novel reversing agent developed for terminating the action of nondepolarizing muscle relaxants rocuronium and vecuronium. Sugamadex is a modified γ-cyclodextrin with high affinity for rocuronium and vecuronium. It encapsulates one molecule of the blocker within its molecule forming an inactive chelate which is excreted in urine with a t½ of ~ 2 hours. As the plasma concentration of free rocuronium falls, it rapidly dissociates from the Nm receptor and neuromuscular transmission is restored. Thus, the mechanism of reversal by sugamadex is entirely different from that of the currently used reversing agents neostigmine and edrophonium. Sugamadex 2–4 mg/kg i.v. reverses rocuronium block within 3 min. in majority of patients. Its side effects are mild precordial pain, nausea, alteration of taste and rarely allergy. No cardiovascular effects have been noted.

TOXICITY

1. Respiratory paralysis and prolonged apnoea is the most important complication of neuromuscular blockers.
2. Flushing (due to histamine release) is common with d-TC, can occur with atracurium and mivacurium, rare with others.
3. Fall in BP and cardiovascular collapse can occur, especially in hypovolemic patients. This is less likely with the newer drugs. Muscle relaxants should be used with great caution in patients with severe hepatic and renal disease.
4. Cardiac arrhythmias and even arrest have occurred, especially with SCh, particularly in digitalized patients, because SCh releases K^+ from muscles. Intubating dose generally raises serum K^+ by 0.5 mEq/L, but dangerous hyperkalemia can occur, especially in patients with extensive burns, nerve damage and soft tissue injuries.
5. Precipitation of asthma by histamine releasing neuromuscular blockers.
6. Postoperative muscle soreness and myalgia may be complained after SCh, particularly when larger dose is used.
7. Malignant hyperthermia can be triggered by SCh in patients anaesthetized with fluorinated anaesthetics.

USES

1. The most important use of neuromuscular blockers is as adjuvants to general anaesthesia. By the use of these drugs, adequate muscle relaxation can be achieved at lighter planes. Many surgical procedures are performed more safely and rapidly by employing muscle relaxants. They also reduce reflex muscle contraction in the region undergoing surgery, and facilitate maintenance of controlled ventilation during anaesthesia. They are particularly helpful in abdominal and thoracic surgery, intubation and endoscopies, orthopedic manipulations, etc.

Choice of the neuromuscular blocker depends on the nature and duration of the procedure, pharmacokinetics of the blocker and cardiovascular stability that it provides. Vecuronium, cisatracurium and rocuronium are the most frequently selected nondepolarizing blockers.

SCh is employed for brief procedures, e.g. endotracheal intubation, laryngoscopy, bronchoscopy, esophagoscopy, reduction of fractures,

dislocations, and to treat laryngospasm. For ocular surgery competitive blockers are preferred, because they paralyse extraocular muscles at doses which have little effect on larger muscles. Other factors which should be considered in selecting the relaxant are—onset of action, duration of blockade required, cardiovascular effects of the drug as well as patient's hepatic, renal and haemodynamic status.

Advantages of newer neuromuscular blockers over the older ones

- No or minimal ganglionic, cardiac or vascular effects.
- No or minimal histamine release.
- Many are short acting: easy reversal.
- Some are rapid acting: provide alternative to SCh without the attendant complications.

2. Assisted ventilation: Critically ill patients in intensive care units often need ventilatory support. This can be facilitated by continuous infusion of subparalysing doses of a competitive neuromuscular blocker which reduces the chest wall resistance to inflation. Vecuronium is most commonly used, but after prolonged infusion it can cause blockade lasting 1–3 days due to accumulation of an active metabolite and/or development of neuropathy.
3. Convulsions and trauma from electroconvulsive therapy can be avoided by the use of muscle relaxants without decreasing the therapeutic benefit. SCh is most commonly used for this purpose. The short acting competitive blocker mivacurium is an alternative.
4. Severe cases of tetanus and status epilepticus, who are not controlled by diazepam or other drugs, may be paralysed by a neuromuscular blocker (repeated doses of a competitive blocker) and maintained on intermittent positive pressure respiration till the disease subsides.

DIRECTLY ACTING MUSCLE RELAXANTS

Dantrolene This muscle relaxant is chemically and pharmacologically entirely different from neuromuscular blockers. Its effects superficially resemble those of centrally acting muscle relaxants. Neuromuscular transmission or MAP are not affected, but muscle contraction is uncoupled from depolarization of the membrane. Dantrolene acts on the RyR1 (Ryanodine Receptor) calcium channels in the sarcoplasmic reticulum of skeletal muscles and prevents Ca^{2+} induced Ca^{2+} release through these channels. Intracellular release of Ca^{2+} needed for excitation-contraction coupling is interfered with. Fast contracting 'twitch' muscles are affected more than slow contracting 'antigravity' muscles. Since Ca^{2+} channels in the sarcoplasmic reticulum of cardiac and smooth muscles are of a different subtype (RyR2), these muscles are affected little by dantrolene.

Dantrolene is slowly and incompletely absorbed from the g.i.t. It penetrates brain and produces some sedation, but has no selective effect on polysynaptic reflexes responsible for spasticity. It is metabolized in the liver and excreted by kidney with a t½ of 8–12 hours.

Used orally dantrolene (25–100 mg QID) reduces spasticity in upper motor neurone disorders, hemiplegia, paraplegia, cerebral palsy and multiple sclerosis. However, it also reduces voluntary power; the resulting weakness considerably neutralizes the benefit and limits use to bedridden patients.

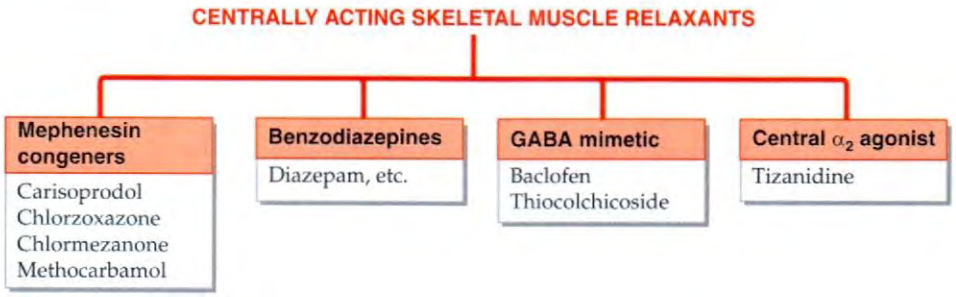
Used i.v. (1 mg/kg repeated as required) it is the drug of choice for malignant hyperthermia which is due to persistent release of Ca^{2+} from sarcoplasmic reticulum (induced by fluorinated anaesthetics and SCh in genetically susceptible individuals with abnormal RyR1, *see* p. 406). Reversal has also been obtained in neuroleptic malignant syndrome, though this reaction has a different pathogenesis.

Adverse effects Muscular weakness is the dose limiting side effect. Sedation, malaise, light headedness and other central effects occur, but are less pronounced than with centrally acting muscle relaxants. Troublesome diarrhoea is another problem. Long term use causes dose dependent serious liver toxicity in 0.1–0.5% patients. Use in chronic disorders is therefore restricted.

Quinine (*see* Ch. 61) It increases refractory period and decreases excitability of motor end plates. Thus, responses to repetitive nerve stimulation are reduced. It decreases muscle tone in myotonia congenita. Taken at bed time (200–300 mg) it may abolish nocturnal leg cramps in some patients.

CENTRALLY ACTING MUSCLE RELAXANTS

These are drugs which reduce skeletal muscle tone and lessen muscle spasm by a selective action in the cerebrospinal axis, without altering consciousness. They selectively depress spinal and supraspinal polysynaptic reflexes involved in the regulation of muscle tone without significantly affecting monosynaptically mediated stretch reflex. Polysynaptic pathways in the ascending reticular formation which are involved in the maintenance of wakefullness are also depressed, though to a



lesser extent. Thus, all centrally acting muscle relaxants do have some sedative property. They have no effect on neuromuscular transmission and on muscle fibres, but reduce decerebrate rigidity, upper motor neurone spasticity and hyperreflexia.

The prominent differences between neuromuscular blockers and centrally acting muscle relaxants are listed in Table 25.3.

1. Mephenesin It was the first drug found to cause muscle relaxation in animals without producing unconsciousness and was called *internuncial neurone blocking agent* because its primary site of action is the spinal internuncial neurone which modulates reflexes maintaining muscle tone. It is not used clinically because orally it causes marked gastric irritation, and injected i.v., it causes thrombophlebitis, haemolysis and fall in BP. It has been included in counterirritant ointments *(MEDICREME, RELAXYL)* where its irritant rather than muscle relaxant property could be affording relief.

2. Carisoprodol It has a favourable muscle relaxant: sedative activity ratio with weak analgesic, antipyretic and anticholinergic properties. It is used in tissue injury, muscle sprains and disorders associated with local muscle spasm.

CARISOMA 350 mg tab; one tab. TDS-QID, SOMAFLAM 175 mg + ibuprofen 400 mg tab.

3. Chlorzoxazone It is pharmacologically similar to mephenesin, but has a longer duration of action and better oral tolerance.

FLEXON-MR 250 mg + ibuprofen 400 mg + paracetamol 325 mg tab; ULTRAZOX 250 mg + diclofenac 50 mg + paracetamol 325 mg tab; MOBIZOX 500 mg + diclofenac 50 mg + paracetamol 500 mg tab; PARAFON: 250 mg + paracetamol 300 mg tab, 1–2 tab TDS.

4. Chlormezanone It has antianxiety and hypnotic actions as well, and has been used for tension states associated with increased muscle tone.

DOLOBAK 100 mg + paracetamol 450 mg tab, 1–2 tab TDS.

5. Methocarbamol It is less sedative and longer acting than mephenesin. Orally it has been used in reflex muscle spasms and chronic neurological diseases. It can be injected i.v. without producing thrombophlebitis and haemolysis, and has been utilized for orthopedic procedures and tetanus.

ROBINAX 0.5 g tab, 1 TDS: 100 mg/ml inj. for i.v. or i.m. use. ROBIFLAM 750 mg + ibuprofen 200 mg tab; NEUROMOL-MR 400 mg + paracetamol 500 mg tab.

Clinical efficacy of none of the above drugs as muscle relaxant is well established. Gastric irritation and sedation are the most important side effects.

6. Diazepam (*see* Ch. 29) It is the prototype of benzodiazepines (BZDs) which act in the brain on specific BZD receptors enhancing GABAergic transmission. Muscle tone is

Table 25.3: Comparative features of centrally and peripherally acting muscle relaxants

Centrally acting	*Neuromuscular blockers*
1. Decrease muscle tone without reducing voluntary power	Cause muscle paralysis, voluntary movements lost
2. Selectively inhibit polysynaptic reflexes in CNS	Block neuromuscular transmission
3. Cause some CNS depression	No effect on CNS
4. Given orally, sometimes parenterally	Practically always given i.v.
5. Used in chronic spastic conditions, acute muscle spasms, tetanus	Used for short-term purposes (surgical operations)

reduced by supraspinal rather than spinal action, but muscle relaxant: sedative activity ratio is low. No gastric irritation occurs and it is very well tolerated, though sedation limits the dose which can be used for reducing muscle tone. It is particularly valuable in spinal injuries and tetanus. Combined with analgesics, it is popular for rheumatic disorders associated with muscle spasm.

Dose: 5 mg TDS orally, 10–40 mg i.v. (in tetanus).

7. Baclofen This analogue of the inhibitory transmitter GABA acts as a selective $GABA_B$ receptor agonist. The GABA receptors have been divided into:

$GABA_A$ receptor It is an intrinsic ion channel receptor which increases Cl^- conductance, and is blocked by bicuculline; facilitated by BZDs.

$GABA_B$ receptor It is a G-protein coupled receptor, which hyperpolarizes neurones by increasing K^+ conductance and altering Ca^{2+} flux. It is bicuculline insensitive, but blocked by saclofen.

Baclofen does not affect Cl^- conductance and its actions are not antagonized by bicuculline.

The primary site of action of baclofen is considered to be in the spinal cord where it decreases excitatory transmitter release and depresses both polysynaptic and monosynaptic reflexes. As such, it does produce muscle weakness, but is less sedative than diazepam. Spasticity in many neurological disorders like multiple sclerosis, amyotropic lateral sclerosis (ALS), spinal injuries and flexor spasms is reduced. Baclofen is the preferred drug for symptomatic relief in these conditions. However, it is relatively ineffective in stroke, cerebral palsy, rheumatic and traumatic muscle spasms and parkinsonism.

Baclofen is well absorbed orally and is primarily excreted unchanged in urine with a t½ of 3–4 hours.

Side effects are drowsiness, mental confusion, weakness and ataxia; serum transaminases may rise. Sudden withdrawal after chronic use may cause hallucinations, tachycardia and seizures.

Dose: 10 mg BD to 25 mg TDS.

LIORESAL, LIOFEN 10 mg, 25 mg tab.

8. Thiocolchicoside Chemically related to colchicine, this muscle relaxant is believed to act as a GABA mimetic and glycinergic drug with additional analgesic action. Combined with NSAIDs, it is being used for painful muscle spasms, such as torticolis, sprains, backache, etc. Side effects are gastric upset and photosensitivity reactions

Dose: 4 mg TDS-QID;

NUCOXIA-MR: Thiocolchicoside 4 mg + etoricoxib 60 mg tabs.

9. Tizanidine This clonidine congener has minimal cardiovascular effects, but is a central α_2 adrenergic agonist which inhibits release of excitatory amino acids in the spinal interneurones. It may facilitate the inhibitory transmitter glycine as well. Polysynaptic reflexes are inhibited resulting in decreased muscle tone and frequency of muscle spasms without reducing muscle strength. Efficacy similar to baclofen or diazepam has been noted in multiple sclerosis, spinal injury and stroke, with fewer side effects.

Tizanidine is absorbed orally, undergoes first pass metabolism and is excreted by the kidney; t½ 2–3 hours. It is indicated in spasticity due to neurological disorders and in painful muscle spasms of spinal origin. Side effects are dry-mouth, drowsiness, night-time insomnia and hallucinations. Dose-dependent elevation of liver enzymes occurs. Though no consistent effect on BP has been observed, it should be avoided in patients receiving antihypertensives, especially clonidine.

Dose: 2 mg TDS; max 24 mg/day.

SIRDALUD 2, 4, 6 mg tab, TIZAN 2, 4 mg tab; BRUFEN-MR, TIZAFEN 2 mg+ ibuprofen 400 mg tab; TIZANAC 2 mg + diclofenac 50 mg tab, PROXIVON-MR 2 mg + nimesulide 100 mg cap.

Uses of centrally acting muscle relaxants

1. *Acute muscle spasms* Overstretching of a muscle, sprain, tearing of ligaments and tendons, dislocation, fibrositis, bursitis, rheumatic disorders, etc. cause painful spasm of muscles. The mephenesin-like and BZD muscle relaxants, combined with analgesics, are commonly used, but efficacy is not impressive.

2. *Torticollis, lumbago, backache, neuralgias* These are other conditions in which painful spasm of certain muscles is a prominent feature. They respond to centrally acting muscle relaxants in the same way as acute muscle spasms.

3. *Anxiety and tension* Increased tone of muscles often attends these states. Diazepam group of drugs and chlormezanone benefit by their antianxiety as well as muscle relaxant actions.

4. *Spastic neurological diseases* Impairment of descending pathways in the cerebrospinal axis and withdrawal of inhibitory influence over the stretch reflex causes chronic increase in muscle tone or spasticity. Hemiplegia, paraplegia, spinal injuries, multiple sclerosis, ALS and cerebral palsy fall in this category. These conditions are benefited by baclofen, diazepam, tizanidine and dantrolene but not by mephenesin group of drugs. However, therapy of these disorders is far from satisfactory.

5. *Tetanus* Most commonly diazepam is infused i.v. and the dose is titrated by the response. Methocarbamol is an alternative.

6. *Electroconvulsive therapy* Diazepam decreases the intensity of convulsions resulting from ECT, without diminishing its therapeutic effect. Often SCh is used in addition for total suppression of the muscular component of ECT.

7. *Orthopedic manipulations* These procedures may be performed under the influence of diazepam or methocarbamol given i.v.

☞ PROBLEM DIRECTED STUDY

25.1 A 30-year lady brought to the hospital emergency with 40% burn injury has to be operated under general anaesthesia.

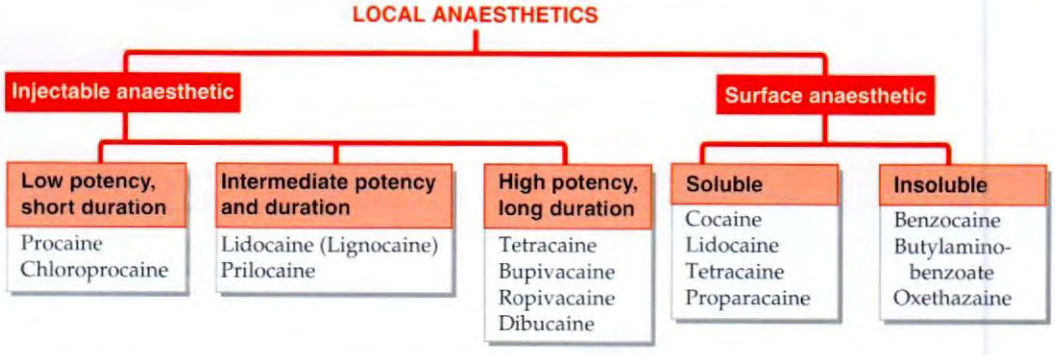
(a) Which muscle relaxant should be preferred for tracheal intubation and a brief surgical procedure in this patient? Give reasons.

(see Appendix-1 for solution)

Chapter 26 Local Anaesthetics

Local anaesthetics (LAs) are drugs which upon topical application or local injection cause reversible loss of sensory perception, especially of pain, in a restricted area of the body. They block generation and conduction of nerve impulse at any part of the neurone with which they come in contact, without causing any structural damage. Thus, not only sensory but also motor impulses are interrupted when a LA is applied to a mixed nerve, resulting in muscular paralysis and loss of autonomic control as well.

Important differences between general and local anaesthesia are tabulated in Table 26.1.



Mepivacaine, Etidocaine, Articaine, Dyclonine, are other local anaesthetics, occasionally used in some countries.

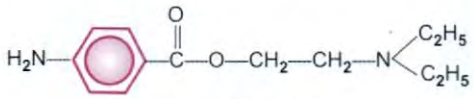
Some other drugs, e.g. propranolol, chlorpromazine, H_1 antihistaminics, quinine have significant LA activity, but are not used for this purpose because of local irritancy or other prominent systemic activity. Local anaesthesia can be produced by cooling as well, e.g. application of ice, CO_2 snow, ethylchloride spray.

Table 26.1: Comparative features of general and local anaesthesia

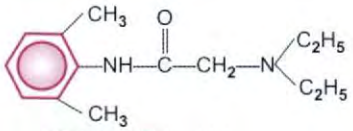
	General anaesthesia	*Local anaesthesia*
1. Site of action	CNS	Peripheral nerves
2. Area of body involved	Whole body	Restricted area
3. Consciousness	Lost	Unaltered
4. Care of vital functions	Essential	Usually not needed
5. Physiological trespass	High	Low
6. Poor health patient	Risky	Safer
7. Use in non-cooperative patient	Possible	Not possible
8. Major surgery	Preferred	Cannot be used
9. Minor surgery	Not preferred	Preferred

CHEMISTRY

The clinically useful LAs are weak bases with amphiphilic property. A hydrophilic secondary or tertiary amine on one side and a lipophilic aromatic residue on the other are joined by an alkyl chain through an *ester* or *amide* linkage.



PROCAINE (ester)



LIDOCAINE (amide)

Ester-linked LAs Cocaine, procaine, chloroprocaine, tetracaine, benzocaine.

Amide-linked LAs Lidocaine, bupivacaine, dibucaine, prilocaine, ropivacaine.

Features of amide LAs (compared to ester LAs)

- Produce more intense and longer lasting anaesthesia
- Bind to α_1 acid glycoprotein in plasma
- Not hydrolysed by plasma esterases
- Rarely cause hypersensitivity reactions; no cross sensitivity with ester LAs

Because of their short duration, less intense analgesia and higher risk of hypersensitivity, the ester-linked LAs are rarely used for infiltration or nerve block, but are still used topically on mucous membranes.

MECHANISM OF ACTION

The LAs block nerve conduction by decreasing the entry of Na^+ ions during upstroke of action potential (AP). As the concentration of the LA is increased, the rate of rise of AP and maximum depolarization decreases (Fig. 26.1) causing slowing of conduction. Finally, local depolarization fails to reach the threshold potential and conduction block ensues.

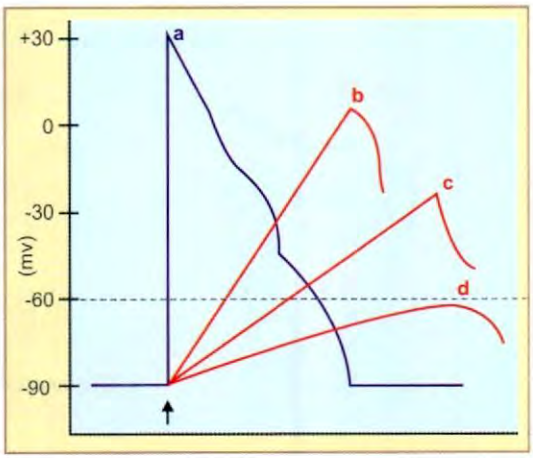


Fig. 26.1: Effect of progressively increasing concentrations (b,c,d) of a local anaesthetic on the generation of an action potential in a nerve fibre, (a) Untreated nerve fibre

The LAs interact with a receptor situated within the voltage sensitive Na^+ channel and raise the threshold of channel opening: Na^+ permeability fails to increase in response to an impulse or stimulus. Impulse conduction is interrupted when the Na^+ channels over a critical length of the fibre (2–3 nodes of Ranvier in case of myelinated fibres) are blocked. The details are explained in Fig. 26.2. At physiological pH, the LA molecule is partly ionized. The equilibrium between the unionized base form (B) and the ionized cationic form (BH^+) depends on the pKa of the LA.

Potency of a LA generally corresponds to the lipid solubility of its base form (B), because it is this form which penetrates the axon. However, the predominant active species is the cationic form of the LA which is able to approach its receptor easily when the channel is open at the inner face, and it binds more avidly to the activated and inactivated states of the channel, than to the resting state. Binding of the LA prolongs the inactivated state, so that the channel takes longer to recover. Consequently refractory period of the fibre is increased. A resting nerve is rather resistant to blockade. Blockade develops rapidly

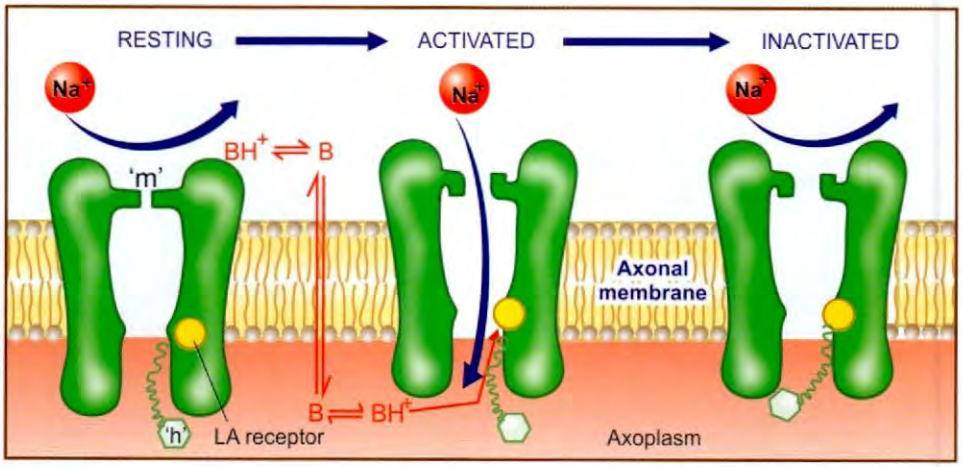


Fig. 26.2: A model of the axonal Na^+channel depicting the site and mechanism of action of local anaesthetics. The Na^+ channel has an activation gate (make or 'm' gate) near its extracellular mouth and an inactivation gate (halt or 'h' gate) at the intracellular mouth. In the resting state the activation gate is closed. Threshold depolarization of the membrane opens the activation gate allowing Na^+ ions to flow in along the concentration gradient depolarizing the membrane. This depolarization inactivates the Na^+ channels within a few msec by closing the inactivation gate; K^+ channels open quickly—outward flow of K^+ repolarizes the membrane allowing Na^+ channels to recover to the resting state in a time-dependent manner.

The local anaesthetic (LA) receptor is located within the channel in its intracellular half. The LA traverses the membrane in its unionized lipophilic form (B), reionizes in the axoplasm and approaches the LA receptor through the intracellular mouth of the channel. It is the cationic form (BH^+) of the LA which primarily binds to the receptor. The receptor has higher affinity, or is more accessible to the LA in the activated as well as inactivated states compared to the resting state. Binding of LA to its receptor stabilizes the channel in the inactivated state and thus reduces the probability of channel opening.

The neuronal Na^+ channel is a 300 KD glycoprotein composed of a large (α) and two small (β_1, β_2) subunits. The α subunit encloses the Na^+ selective pore within its 4 homologous domains (I to IV), each domain has 6 membrane spanning helical segments (S1 to S6) connected alternately by intracellular and extracellular loops. The wall of the pore is formed by all four S5-S6 segments, while the short nonhelical loops connecting S5-S6 on the extracellular surface fold into the pore and serve as the activation gate. Voltage sensors located in the S4 segments move vertically on depolarization and open the activation gate by allosteric conformational change. A few msec later, the short intracellular loop connecting domains III and IV folds into the inner mouth of the pore inactivating the channel. The LA receptor is located in the S6 segment of domain IV. Channel activation either transforms the LA receptor to a higher affinity conformation or exposes it on the wall of the pore, and this persists during the subsequent inactivation phase.

when the nerve is stimulated repeatedly. The degree of blockade is frequency dependent, i.e. greater blockade occurs at higher frequency of stimulation. Moreover, exposure of the fibre to higher concentration of Ca^{2+} reduces inactivation of Na^+ channels and lessens the degree of block. Blockade of conduction by LA is not due to hyperpolarization; in fact, resting membrane potential is unaltered, because K^+ channels are blocked only at higher concentrations of the LA.

The onset time of blockade is related primarily to the pKa of the LA. Those with lower pKa (7.6–7.8), e.g. lidocaine, mepivacaine are fast acting, because 30–40% LA is in the undissociated base form at pH 7.4 and it is this form which penetrates the axon. Procaine, tetracaine, bupivacaine have higher pKa (8.1–8.9), only 15% or less is unionized at pH 7.4; these LAs are slow acting. Chloroprocaine is an exception, having rapid onset despite high pKa (9.1).

LOCAL ACTIONS

The clinically used LAs have no/minimal local irritant action and block sensory nerve endings, nerve trunks, neuromuscular junction, ganglionic synapse and receptors (non-selectively), i.e. those structures which function through increased

Na^+ permeability. They also reduce release of acetylcholine from motor nerve endings. Injected around a mixed nerve they cause anaesthesia of skin and paralysis of the voluntary muscle supplied by that nerve.

Sensory and motor fibres are inherently equally sensitive, but some LAs do exhibit unequal ability to block them, e.g. epidural bupivacaine produces sensory block at much lower concentration than that needed for motor block. The differential sensory blockade is greatly advantageous for pain relief in normal labour by enabling the mother to actively push the foetus down during uterine contractions. Similarly, in continuous epidural analgesia for postoperative pain relief (e.g. after knee replacement) absence of motor block is helpful in early ambulation and performance of exercises.

The sensitivity to LA is determined by diameter of the fibres as well as by fibre type. Diameter remaining the same, myelinated nerves are blocked earlier than nonmyelinated. In general, smaller fibres are more sensitive than larger fibres; but this is not always true. Fibres differ in the critical length of the axon that must be exposed to the LA for effective blockade. In myelinated fibres the critical length usually covers 2–3 nodes of Ranvier. Smaller fibres tend to have shorter critical lengths, because in them voltage changes propagate passively for shorter distances. Further, more slender axons have shorter internodal distances, and LAs easily enter the axon at the nodes of Ranvier. The density of Na^+ channels is much higher at these nodes. Moreover, frequency dependence of blockade makes smaller sensory fibres more vulnerable since they generate high frequency longer lasting action potentials than the motor fibres. Thus, fibre diameter itself may not govern sensitivity to LA.

Autonomic fibres are generally more susceptible than somatic fibres. Among the somatic afferents order of blockade is: pain—temperature sense—touch—deep pressure sense. Since pain is generally carried by smaller diameter fibres than those carrying other sensations or motor impulses, pain in the first modality to be affected. Applied to the tongue, bitter taste is lost first followed by sweet and sour, and salty taste last of all.

In general, fibres that are more susceptible to LA are the first to be blocked and the last to recover. Also, location of the fibre within a nerve trunk determines the latency, duration and often the depth of local anaesthesia. Nerve sheaths restrict diffusion of the LA into the nerve trunk so that fibres in the outer layers are blocked earlier than the inner or core fibres. As a result, the more proximal areas supplied by a nerve are affected earlier because axons supplying them are located more peripherally in the nerve than those supplying distal areas. The differential arrangement of various types of sensory and motor fibres in a mixed nerve may partly account for the differential blockade. Motor fibres are usually present circumferentially. As such, they may be blocked earlier than the sensory fibres in the core of the nerve.

The LA often fails to afford adequate pain control in inflamed tissues (like infected tooth). The likely reasons are:

a. Inflammation lowers pH of the tissue—greater fraction of the LA is in the ionized form hindering diffusion into the axolemma.
b. Blood flow to the inflamed area is increased—the LA is removed more rapidly from the site.
c. Effectiveness of Adr injected with the LA is reduced at the inflamed site.
d. Inflammatory products may oppose LA action.

Addition of a vasoconstrictor, e.g. adrenaline (1:50,000 to 1:200,000):

- Prolongs duration of action of LAs by decreasing their rate of removal from the local site into the circulation: contact time of the LA with the nerve fibre is prolonged.
- Enhances the intensity of nerve block.
- Reduces systemic toxicity of LAs: rate of absorption is reduced and metabolism keeps the plasma concentration lower.
- Provides a more bloodless field for surgery.
- Increases the chances of subsequent local tissue edema and necrosis as well as delays

wound healing by reducing oxygen supply and enhancing oxygen consumption in the affected area.
- May raise BP and promote arrhythmia in susceptible individuals.

SYSTEMIC ACTIONS

Any LA injected or applied locally is ultimately absorbed and can produce systemic effects depending on the concentration attained in the plasma and tissues.

C.N.S.

All LAs are capable of producing a sequence of stimulation followed by depression. *Cocaine* is a powerful CNS stimulant causing in sequence euphoria—excitement—mental confusion—restlessness—tremor and twitching of muscles—convulsions—unconsciousness—respiratory depression—death, in a dose-dependent manner.

The synthetic LAs are much less potent in this regard. At safe clinical doses, they produce little apparent CNS effects. Higher dose or accidental i.v. injection produces CNS stimulation followed by depression.

The early neurological symptoms of overdose with *lidocaine* and other clinically used LAs are—circumoral numbness, abnormal sensation in the tongue, dizziness, blurred vision, tinnitus followed by drowsiness, dysphoria and lethargy. Still higher doses produce excitation, restlessness, agitation, muscle twitching, seizures and finally unconsciousness.

The basic action of all LAs is neuronal inhibition; the apparent stimulation seen initially is due to inhibition of inhibitory neurones. At high doses, all neurones are inhibited and flattening of waves in the EEG is seen.

C.V.S.

Heart LAs are cardiac depressants, but no significant effects are observed at conventional doses. At high doses (2–3 times the doses producing CNS effects) or on inadvertent i.v. injection, they decrease automaticity, excitability, contractility, conductivity and prolong effective refractory period (ERP). They have a quinidine-like antiarrhythmic action. While *procaine* is not used clinically as antiarrhythmic because of short duration of action and propensity to produce CNS effects, its amide derivative *procainamide* is a class IA antiarrhythmic (*see* Ch. 39). Electrophysiological properties of heart may be markedly altered at high plasma concentrations of LAs: QTc interval is prolonged and LAs can themselves induce cardiac arrhythmias. *Bupivacaine* is relatively more cardiotoxic and has produced ventricular tachycardia, fibrillation and arrest. *Lidocaine* has little effect on contractility and conductivity; it abbreviates ERP and has minimal proarrhythmic potential. It is used as an antiarrhythmic (*see* Ch. 39).

Blood vessels LAs tend to produce fall in BP. This is primarily due to sympathetic blockade, but high concentrations, as obtained locally at the site of injection, do cause direct relaxation of arteriolar smooth muscle. Bupivacaine is more vasodilatory than lidocaine, while prilocaine is the least vasodilatory. Toxic doses of LAs produce cardiovascular collapse. *Cocaine* has sympathomimetic property; increases sympathetic tone, causes local vasoconstriction, marked rise in BP and tachycardia.

Procaine and related drugs have weak anticholinergic, antihistaminic, ganglion blocking, neuromuscular blocking and smooth muscle relaxant properties, but these are clinically insignificant.

PHARMACOKINETICS

Because LAs act near their site of administration, pharmacokinetic characteristics are not important determinants of their efficacy, but markedly influence their systemic effects and toxicity.

Soluble surface anaesthetics (lidocaine, tetracaine) are rapidly absorbed from mucous membranes and abraded areas, but absorption from intact skin is minimal. Procaine does not significantly penetrate mucous membranes. Rate of absorption depends on the blood flow to the area of application or injection, e.g. absorption and blood levels are higher after intercostal block than after sciatic block. The absorbed LA being lipophilic, is widely distributed; rapidly

enters highly perfused brain, heart, liver, and kidney, followed by muscle and other viscera.

Procaine is negligibly bound to plasma proteins, but amide LAs are bound to plasma α_1 acid glycoprotein. LAs are rapidly but temporarily bound to tissues, especially nerves, at the site of injection. Ester-linked LAs (procaine, etc.) are rapidly hydrolysed by plasma pseudocholinesterase and the remaining by esterases in the liver. Amide-linked LAs (lidocaine, etc.) are degraded only in the liver microsomes by dealkylation and hydrolysis. Metabolism of lidocaine is hepatic blood-flow dependent. The maximal safe dose of LAs is lower in patients with hepatic disease and in the elderly who have decreased liver function.

After oral ingestion both procaine and lidocaine have high first pass metabolism in the liver. Thus, they are not active orally for antiarrhythmic purposes.

ADVERSE EFFECTS

Systemic toxicity on rapid i.v. injection is related to the intrinsic anaesthetic potency of the LA. However, toxicity after topical application or regional injection is influenced by the relative rates of absorption and metabolism. Those rapidly absorbed but slowly metabolized are more toxic.

- CNS effects are light-headedness, dizziness, auditory and visual disturbances, mental confusion, disorientation, shivering, twitchings, involuntary movements, finally convulsions and respiratory arrest. This can be prevented and treated by diazepam/midazolam.
- Cardiovascular toxicity of LAs is manifested as bradycardia, hypotension, cardiac arrhythmias, asystole and vascular collapse.
- Injection of LAs may be painful, but local tissue toxicity of LAs is low. However, wound healing may be sometimes delayed. Addition of vasoconstrictors enhances the local tissue damage; rarely necrosis results. Vasoconstrictors should not be added for ring block of hands, feet, fingers, toes, penis and in pinna. Bupivacaine has the highest local tissue irritancy.
- Hypersensitivity reactions like rashes, angioedema, dermatitis, contact sensitization, asthma and rarely anaphylaxis occur. Allergic reactions are more common with ester-linked LAs, but rare with lidocaine or its congeners. Cross reactivity is frequent among ester compounds, but not with amide-linked LAs.

Often methylparaben added as preservative in certain LA solutions is responsible for the allergic reaction.

Precautions and interactions

1. Before injecting the LA, aspirate lightly to avoid intravascular injection.
2. Inject the LA slowly and take care not to exceed the maximum safe dose, especially in children.
3. Propranolol (probably other β blockers also) may reduce metabolism of lidocaine and other amide LAs by reducing hepatic blood flow.
4. Vasoconstrictor (adrenaline) containing LA should be avoided for patients with ischaemic heart disease, cardiac arrhythmia, thyrotoxicosis, uncontrolled hypertension, and those receiving β blockers (rise in BP can occur due to unopposed α action) or tricyclic antidepressants (uptake blockade and potentiation of Adr).

INDIVIDUAL COMPOUNDS

Important properties of local anaesthetics are compared in Table 26.2.

Cocaine It is a natural alkaloid from leaves of *Erythroxylon coca*, a south American plant growing on the foothills of the Andes. The natives of Peru and Bolivia habitually chew these leaves. Cocaine is a good surface anaesthetic and is rapidly absorbed from buccal mucous membrane. It was first used for ocular anaesthesia in 1884. Cocaine should never be injected; it is a protoplasmic poison and causes tissue necrosis. Cocaine produces prominent CNS stimulation with marked effect on mood and behaviour. It induces a sense of wellbeing, delays fatigue and increases power of endurance. In susceptible individuals it produces a state referred to as 'high' leadting to strong psychological but little physical dependence. Cocaine is unique among drugs of abuse in not producing significant tolerance on repeated use; sometimes reverse tolerance is seen (behavioural effects are experienced at lower doses).

Cocaine also stimulates vagal centre→bradycardia; vasomotor centre→rise in BP; vomiting centre→nausea

Table 26.2: Comparative features of commonly used local anaesthetics

Drug	Surface anaesthesia	Nerve block					Cardio-toxicity
		Relative potency	Conc. used (%)	Max. dose	Onset	Duration (Min)	
Lidocaine	+	1	0.5–2.0	300 mg	Fast	60–120	+
Bupivacaine	–	4–5	0.25–0.5	150 mg	Interm.	120–360	+++
Ropivacaine	–	3–4	0.25–0.75	200 mg	Slow	120–300	++

and vomiting; temperature regulating centre→pyrexia (also due to increased heat production as a result of enhanced muscular activity).

In the periphery, it blocks uptake of NA and Adr into adrenergic nerve endings, (*see* Fig. 9.4) resulting in higher concentration of the transmitter around the receptors→ sympathomimetic effect, potentiation of directly acting sympathomimetics and suppression of indirectly acting sympathomimetics. Local vasoconstriction, tachycardia, rise in BP and mydriasis are the manifestations of its sympathomimetic action.

The only indication for cocaine is in ocular anaesthesia. However, it causes constriction of conjunctival vessels, clouding and rarely sloughing of cornea (due to drying and local tissue toxicity). Its use, therefore, is not warranted.

Procaine It is the first synthetic local anaesthetic introduced in 1905. Its popularity declined after the introduction of lidocaine, and it is not used now. It is not a surface anaesthetic.

Procaine forms poorly soluble salt with benzyl penicillin; *procaine penicillin* injected i.m. acts for 24 hours due to slow absorption from the site of injection.

Lidocaine (Lignocaine) Introduced in 1948, it is currently the most widely used LA. It is a versatile LA, good both for surface application as well as injection and is available in a variety of forms. Injected around a nerve it blocks conduction within 3 min, whereas procaine may take 15 min; also anaesthesia is more intense and longer lasting. Vasodilatation occurs in the injected area. It is used for surface application, infiltration, nerve block, epidural, spinal and intravenous regional block anaesthesia. Lidocaine 2% with or without adrenaline is the most popular dental anaesthetic. Cross-sensitivity with ester LAs is not seen. The early central effects of lidocaine are depressant, i.e. drowsiness, mental clouding, dysphoria, altered taste and tinnitus. Overdose causes muscle twitching, convulsions, cardiac arrhythmias, fall in BP, coma and respiratory arrest like other LAs. Lidocaine is a popular antiarrhythmic (*see* Ch. 39).

XYLOCAINE, GESICAIN 4% topical solution, 2% jelly, 2% viscous, 5% ointment, 1% and 2% injection (with or without adrenaline), 5% heavy (for spinal anaesthesia); 100 mg/ml spray (10 mg per actuation).

XYLOCAINE 2% with adrenaline 1:80,000 in 1.5 ml cartridge for dental anaesthesia.

A transdermal patch of lidocaine has been produced for application over the affected skin for relief of burning pain due to postherpetic neuralgia.

Prilocaine It is similar to lidocaine but does not cause vasodilatation at the site of infiltration and has lower CNS toxicity due to larger volume of distribution and faster clearance. One of its metabolites has the potential to cause methaemoglobinaemia. Prilocaine has been used for infiltration, nerve block, spinal and intravenous regional anaesthesia.

Eutectic lidocaine/prilocaine Also called eutectic mixture of local anaesthetics (EMLA), this is a unique preparation which can anaesthetise intact skin after surface application. *Eutectic mixture* refers to lowering of melting point of two solids when they are mixed. This happens when lidocaine and prilocaine are mixed in equal proportion at 25°C. The resulting oil is emulsified into water to form a cream that is applied under occlusive dressing for 1 hr before i.v. cannulation, split skin graft harvesting and other superficial procedures. Numbness up to a depth of 5 mm lasts for 1–2 hr after removal. It can be used as an alternative to lidocaine infiltration.

PRILOX 5% cream.

Bupivacaine It is a more lipophilic and more potent long-acting amide-linked LA, which is used for infiltration, nerve block, epidural and spinal anaesthesia of long duration. Because of slow onset of action, it is not preferred for peripheral nerve block. A 0.25% solution injected epidurally produces adequate

analgesia without significant motor blockade. As a result, it has become very popular in obstetrics (mother can actively cooperate by 'bearing down' during vaginal delivery) and for postoperative pain relief by continuous epidural infusion. Due to high lipid-solubility it distributes more in tissues than in blood after spinal/epidural injection. Therefore, it is less likely to reach the foetus (when used during labour) to produce neonatal depression.

Bupivacaine is more prone to prolong QTc interval and induce ventricular tachycardia or cause cardiac depression. Epidural anaesthesia with 0.75% bupivacaine during labour has caused few fatalities due to cardiac arrest. As such, use of this concentration is contraindicated.

Cardiac toxicity is a major concern which limits the total dose of bapivacaine. Recently, i.v. infusion of lipid emulsion has been found to reverse bupivacaine cardiotoxicity, probably by extracting lipophilic bupivacaine from plasma and cardiac tissues.

The strength of bupivacaine solution for different types of blocks is:
Peripheral nerve block: 0.25–0.5%
Spinal anaesthesia: 0.5% (hyperbaric)
Epidural anaesthesia: 0.25–0.5%
Continuous epidural analgesia: 0.125%.
MARCAIN 0.5%, inj. for nerve block, o.5% hyperbaric for spinal anaesthesia. SENSORCAINE 0.25%, 0.5% inj, 0.5% heavy inj.

Levobupivacaine The S(–) enantiomer of bupivacaine is equally potent but less cardiotoxic and less prone to cause seizures (after inadvertent intravascular injection) than racemic bupivacaine. It is being used in some countries as a single enantiomer preparation.

Ropivacaine A newer bupivacaine congener, nearly as long acting but less cardiotoxic. It blocks Aδ and C fibres (involved in pain transmission) more completely than Aβ fibres which control motor function. Lower lipid solubility of ropivacaine makes it less likely to penetrate large myelinated motor fibres than the sensory fibres. The same may account for its lower CNS and cardiac toxicity. Used as the S(–) enantiomer, equieffective concentrations of ropivacaine are higher than those of bupivacaine, but a greater degree of separation between sensory and motor block has been obtained with epidural ropivacaine. Continuous epidural ropivacaine has become popular for relief of postoperative and labour pain. It can also be employed for nerve blocks.
ROPIN 0.2% inj.

Tetracaine (Amethocaine) A highly lipid-soluble PABA ester, more potent and more toxic due to slow hydrolysis by plasma pseudocholinesterase. It is both surface and conduction block anaesthetic, but its use is restricted to topical application to the eye, nose and throat. Though it is slow acting, absorption from tracheobronchial spray is very fast and blood concentrations approach those attained after i.v. injection. Therefore, its use for bronchoscopy is contraindicated.
ANETHANE powder for solution, 1% ointment

Proparacaine (proxymetacaine) This newer surface anaesthetic is the most commonly used ophthalmic anaesthetic now. It is a meta-amino benzoic acid derivative which is equally effective but faster acting than tetracaine. Tonometry can be performed 30 sec. after instilling one drop 0.5% proparacaine in the eye. Corneal anaesthesia lasts for 10–20 min. Deeper anaesthesia needed for cataract extraction can be obtained by applying 1–2 drops every 5–10 min. for a maximum of 5 applications, while for foreign body/suture removal 2–3 applications may be enough. Proparacaine causes minimal ocular irritation. Allergic reactions are infrequent compared to tetracaine. However, severe immediate corneal reaction may occur rarely.
PARACAINE, PROPCAINE 0.5% eye drops, 5 ml bottle.

Dibucaine (Cinchocaine) It is the most potent, most toxic and longest acting LA. It is used as a surface anaesthetic on less delicate mucous membranes (anal canal). Use for spinal anaesthesia of long duration has been abandoned.
NUPERCAINAL 1% ointment, in OTOGESIC 1% ear drops.

Benzocaine and Butylaminobenzoate (Butamben) Because of very low aqueous solubility, these LAs are not significantly absorbed from mucous membranes or abraded skin. They produce long-lasting numbness without systemic toxicity. When absorbed, benzocaine can cause methaemoglobinemia. These LAs are used as lozenges for stomatitis, sore throat; as dusting powder/ointment on wounds/ulcerated surfaces and as suppository for anorectal lesions. Both are PABA derivative, therefore can antagonize sulfonamides locally.
PROCTOSEDYL-M: Butylaminobenzoate 1% oint with framycetin and hydrocortisone acetate: for piles.
PROCTOQUINOL 5% ointment of benzocaine. ZOKEN 20% gel.

Oxethazaine A potent topical anaesthetic, unique in ionizing to a very small extent even at low pH values. It is, therefore, able to anaesthetise gastric mucosa despite acidity of the medium. Swallowed along with antacids it affords symptomatic relief in gastritis, drug induced gastric irritation, gastroesophageal reflux and heartburn of pregnancy. Doses exceeding 100 mg/day may produce dizziness and drowsiness.
MUCAINE Oxethazaine 0.2% in alumina gel + magnesium hydroxide suspension; 5–10 ml orally.
TRICAINE-MPS: Oxethazaine 10 mg with methyl polysiloxane 125 mg, alum. hydroxide gel 300 mg, mag. hydroxide 150 mg per 5 ml gel.

USES AND TECHNIQUES OF LOCAL ANAESTHESIA

1. Surface anaesthesia This is produced by topical application of a surface anaesthetic to mucous membranes or abraded skin. Only the superficial layer is anaesthetised and there is no loss of motor function. Onset and duration depends on the site, the drug, its concentration and form, e.g. lidocaine (10%) sprayed in the throat acts in 2–5 min and produces anaesthesia for 30–45 min. Addition of Adr does not affect duration of topical anaesthesia, but phenylephrine can cause mucosal vasoconstriction and prolong topical anaesthesia. Absorption of soluble LAs from mucous membranes is rapid; blood concentrations of tetracaine sprayed in throat/tracheobronchial tree approach those attained on i.v. injection—toxicity can occur. Except for eutectic lidocaine/prilocaine, no other LA is capable of anaesthetizing intact skin. The sites and purposes for which surface anaesthesia is used are given in Table 26.3.

2. Infiltration anaesthesia Dilute solution of LA is infiltrated under the skin in the area of operation so that sensory nerve endings are blocked. Onset of action is almost immediate and duration is shorter than that after nerve block, e.g. lidocaine 30–60 min, bupivacaine 90–180 min. Infiltration is used for minor operations, e.g. incisions, excisions, hydrocele, herniorrhaphy, etc. when the area to be anaesthetised is small. Relatively larger amount of LA is required compared to the area anaesthetised, but motor function is not affected.

3. Conduction block The LA is injected around nerve trunks so that the area distal to injection is anaesthetised and paralysed. Choice of

Table 26.3: Sites and uses of surface anaesthesia

Site	*Drugs*		*Form*	*Purpose*
1. Eye	Proparacaine Tetracaine	0.5% 1–2%	drops ointment, drops	tonometry, cataract and other ocular surgery
2. Nose, ear	Lidocaine Tetracaine	2–4% 1–2%	drops	painful lesions, polyps
3. Mouth, throat	Benzocaine Lidocaine	 2%	lozenges rinse solution	stomatitis, sore throat painful ulcers
4. Pharynx, larynx, trachea, bronchi	Lidocaine	4–10% 2%	spray jelly	tonsillectomy, endotracheal intubation, endoscopies
5. Esophagus, stomach	Oxethazaine	0.2%	suspension	gastritis, esophagitis, heartburn
6. Abraded skin	Tetracaine Benzocaine Butamben	1% 1–2% 1–2%	cream, ointment, dusting powder	ulcers, burns, itching dermatoses
7. Intact skin	Eutectic lidocaine/ prilocaine	5%	cream under occlusion	i.v. cannulation, skin surgery
8. Urethra	Lidocaine	2%	jelly	for dilatation, catheterisation
9. Anal canal, rectum	Lidocaine Dibucaine Benzocaine	2–4% 1% 5%	ointment, cream, suppository	fissure, painful piles, surgery, proctoscopy

the LA and its concentration is mainly dictated by the required duration of action; lidocaine (1–2%) with shorter duration of action is most commonly used, but for longer lasting anaesthesia bupivacaine may be selected.

(a) *Field block* It is produced by injecting the LA subcutaneously in a manner that all nerves coming to a particular field are blocked—as is done for herniorrhaphy, appendicectomy, dental procedures, scalp stitching, operations on forearms and legs, etc. Larger area beginning 2–3 cm distal to the line of injection can be anaesthetised with lesser drug compared to infiltration. The same concentration of LA as for infiltration is used for field block.

(b) *Nerve block* It is produced by injecting the LA around the appropriate nerve trunks or plexuses. The area of resulting anaesthesia is larger compared to the amount of drug used. Muscles supplied by the injected nerve/plexus are paralysed. The latency of anaesthesia depends on the drug and the area to be covered by diffusion, e.g. lidocaine anaesthetises intercostal nerves within 3 min, but brachial plexus block may take 15 min. For plexus block a 'flooding' technique is used and larger volumes are needed. Nerve block lasts longer than field block or infiltration anaesthesia. Frequently performed nerve blocks are—lingual, intercostal, ulnar, sciatic, femoral, brachial plexus, trigeminal, facial, phrenic, etc.—used for tooth extraction, operations on eye, limbs, abdominal wall, fracture setting, trauma to ribs, neuralgias, persistent hiccup, etc. The primary purpose of nerve block anaesthesia is to abolish pain and other sensations. The accompanying motor paralysis may be advantageous by providing muscle relaxation during surgery, as well as disadvantageous if it interferes with breathing, ability to walk after the operation, or participation of the patient in labour or produces postural hypotension.

4. Spinal anaesthesia The LA is injected in the subarachnoid space between L2–3 or L3–4, i.e. below the lower end of spinal cord. The primary site of action is the nerve roots in the cauda equina rather than the spinal cord. Lower abdomen and hind limbs are anaesthetised and paralysed. The level of anaesthesia depends on the volume and speed of injection, specific gravity of drug solution and posture of the patient. The drug solution could be hyperbaric (in 10% glucose) or isobaric with CSF.

The nerve roots rapidly take up and retain the LA, therefore, its concentration in CSF falls quickly after injection. The level of anaesthesia does not change with change of posture (becomes fixed) after 10 min. Also, higher segments are exposed to progressively lower concentrations of the LA. Since autonomic preganglionic fibres are more sensitive and somatic motor fibres less sensitive than somatic sensory fibres, the level of sympathetic block is about 2 segments higher and the level of motor paralysis about 2 segments lower than the level of cutaneous analgesia.

The duration of spinal anaesthesia depends on the drug used and its concentration (Table 26.4). Addition of 0.2–0.4 mg of adrenaline to the LA prolongs spinal anaesthesia by about 1/3rd when measured by the time taken for the level of sensory block to recede to L1. Adr may be enhancing spinal anaesthesia by reducing spinal cord blood flow or by its own analgesic effect exerted through spinal α_2 adrenoceptors (intrathecal clonidine, an α_2 agonist, produces spinal analgesia by itself).

Women during late pregnancy require less drug for spinal anaesthesia, because inferior vena cava compression by the enlarged uterus leads to engorgement of the vertebral system and a decrease in the capacity of subarachnoid space.

Spinal anaesthesia is used for operations on the lower limbs, pelvis, lower abdomen, e.g. prostatectomy, fracture setting, obstetric procedures, caesarean section, etc. Choice of the LA for spinal anaesthesia primarily depends on the nature and duration of the operative procedure. The LAs employed with their doses and duration of anaesthesia are given in Table 26.4.

Advantages of spinal anaesthesia over general anaesthesia are:

- It is safer.
- Produces good analgesia and muscle relaxation without loss of consciousness.
- Cardiac, pulmonary, renal disease and diabetes pose less problem.

Table 26.4: Local anaesthetics used for spinal and epidural anaesthesia and continuous epidural analgesia

Drug	Spinal			Epidural (lumbar)		Cont. epidural
	Concn.	Total dose	Duration	Concn.	Total dose	Concn. (max. dose)
Lidocaine	1.5–5% (Heavy)	25–75 mg	60–90 min	1–2%	200–300 mg	–
Bupivacaine	0.5% (Heavy)	10–20 mg	90–150 min	0.25–0.5%	75–150 mg	0.125% (400 mg/day)
Ropivacaine	0.75%	25 mg	90–120 min	0.75%	100–200 mg	0.2% (12–24 mg/hour)

Complications of spinal anaesthesia

1. *Respiratory paralysis* With proper care, this is rare. Even when intercostal muscles are paralysed, the diaphragm (supplied by phrenic nerve) maintains breathing. Hypotension and ischaemia of respiratory centre is more frequently the cause of respiratory failure than diffusion of the anaesthetic to higher centres. Due to paralysis of external abdominal and intercostal muscles, coughing and expectoration becomes less effective. This may lead to pulmonary complications.

2. *Hypotension* It is due to blockade of sympathetic vasoconstrictor outflow to the blood vessels; venous pooling and decreased return to the heart contributes more to the fall in BP than arteriolar dilatation. Paralysis of skeletal muscles of lower limb is another factor reducing venous return. Decreased sympathetic flow to heart and low venous return produce bradycardia. Raising the foot end overcomes the hypotension by promoting venous drainage. Sympathomimetics, especially those with prominent constrictor effect on veins (ephedrine, mephentermine) effectively prevent and counteract the hypotension.

3. *Neurological symptoms* Pain and/or paraesthesias in the back and lower limbs lasting short periods are felt by some patients after recovery from spinal anaesthesia, especially when lidocaine is used. This is infrequent with bupivacaine. However, no neurological deficit attends the symptoms.

4. *Headache* It may occur due to seepage of CSF, which can be minimised by using smaller bore needle.

5. *Cauda equina syndrome* It is a very rare neurological complication resulting in prolonged loss of control over bladder and bowel sphincters. The cause is uncertain, but may be due to traumatic damage to nerve roots or chronic arachnoiditis caused by inadvertent introduction of the antiseptic in the subarachnoid space. Neurotoxicity of the LA has also been blamed, especially when high/repeated doses are given.

6. *Nausea and vomiting* This is more common after abdominal operations, and is due to reflexes triggered by traction on abdominal viscera. Premedication with ondansetron or metoclopramide prevents it.

5. Epidural anaesthesia

The spinal dural space is filled with semiliquid fat through which nerve roots travel. The LA injected in this space—acts primarily on the nerve roots (in the epidural as well as subarachnoid spaces to which it diffuses) and small amount permeates through intervertebral foramina to produce multiple paravertebral blocks. Epidural anaesthesia can be divided into 3 categories depending on the site of injection.

(i) *Thoracic* The LA is injected in the midthoracic region. The epidural space in this region is relatively narrow; therefore smaller volume of the drug is needed and a wide segmental band of analgesia involving the middle and lower thoracic dermatomes is produced. It is used generally for pain relief following thoracic/upper abdominal surgery. Specially designed catheters are available which can be placed for repeated injections or continuous infusion of the LA to achieve epidural analgesia lasting few days.

Contraindications to spinal anaesthesia

- Hypotension and hypovolemia.
- Uncooperative or mentally ill patients.
- Infants and children—control of level is difficult.
- Bleeding diathesis.
- Raised intracranial pressure.
- Vertebral abnormalities e.g. kyphosis, lordosis, etc.
- Sepsis at injection site.

(ii) *Lumbar* Relatively large volume of drug is needed because epidural space is wide. It produces anaesthesia of lower abdomen, pelvis and hind limbs. Use of lumbar epidural anaesthesia is similar to that of spinal anaesthesia.

(iii) *Caudal* Injection is given in the sacral canal through the sacral hiatus. This produces anaesthesia of pelvic and perineal region. It is used mostly for vaginal delivery, anorectal and genitourinary operations.

Lidocaine (1–2%) and bupivacaine (0.25–0.5%) are popular drugs for epidural anaesthesia. Onset is slower and duration of anaesthesia is longer with bupivacaine and action of both the drugs is prolonged by addition of adrenaline. Technically epidural anaesthesia is more difficult than spinal anaesthesia and relatively larger volumes of drug are needed. Consequently, blood concentrations of the LA are higher. Cardiovascular complications are similar to those after spinal anaesthesia, but headache and neurological complications are less likely, because intrathecal space is not entered and the LA is not restricted to a small area for long periods. Spread of the LA in the epidural space is governed by the volume injected: larger volume anaesthetizes more extensive area. Zone of differential sympathetic blockade is not evident after epidural injection but motor paralysis is 4–5 segments caudal, especially with lower concentrations of the LA. Greatest separation between sensory and motor block is obtained by use of 0.25% bupivacaine and ropivacaine. This is especially valuable for obstetric purposes (mother can participate in labour without feeling pain) and for postoperative pain relief.

6. Intravenous regional anaesthesia (Intravascular infiltration anaesthesia, or Bier's block) It consists of injection of the LA solution in a large vein of a tourniquet occluded limb such that the drug diffuses retrograde from the peripheral vascular bed to nonvascular tissues including nerve endings. The limb is first elevated to ensure venous drainage by gravity and then tightly wrapped in an elastic bandage for maximal exsanguination. Tourniquet is then applied proximally and inflated to above arterial BP. Elastic bandage is now removed and 20–40 ml of 0.5% lidocaine is injected i.v. under pressure distal to the tourniquet. Regional analgesia is produced within 2–5 min and lasts till 5–10 min after deflating the tourniquet which is kept inflated for not more than 15–60 min to avoid ischaemic injury. Deflation in < 15 min may allow toxic amounts of the LA to enter systemic circulation. The safety of the procedure depends on the rapid uptake of LA by peripheral tissues; only 1/4 of the injected drug enters systemic circulation when the tourniquet is released. Bradycardia can occur.

It is mainly used for the upper limb and for orthopaedic procedures. Obstructing the blood supply of lower limb is more difficult and larger volume of the anaesthetic is needed. Therefore, it is rarely used for lower limb, except the foot. Bupivacaine should not be employed because of its higher cardiotoxicity.

☞ PROBLEM DIRECTED STUDY

26.1 A healthy full-term primigravida aged 26 years who has gone into labour presents for delivery. There is no cephalopelvic disproportion or any other contraindication to normal vaginal delivery. However, she demands relief of pain associated with labour and delivery.
(a) Can some form of regional anaesthesia be used to relieve her pain? If so, which type of regional anaesthesia with which drug would be most suitable for her?
(see Appendix-1 for solution)

DRUGS ACTING ON CENTRAL NERVOUS SYSTEM

Chapter 27 General Anaesthetics

General anaesthetics (GAs) are drugs which produce reversible loss of all sensation and consciousness. The cardinal features of general anaesthesia are:

- Loss of all sensation, especially pain
- Sleep (unconsciousness) and amnesia
- Immobility and muscle relaxation
- Abolition of somatic and autonomic reflexes.

In the modern practice of balanced anaesthesia, these modalities are achieved by using combination of inhaled and i.v. drugs, each drug for a specific purpose. Anaesthesia has developed as a highly specialized science in itself.

History Before the middle of 19th century a number of agents like alcohol, opium, cannabis, or even concussion and asphyxia were used to obtund surgical pain, but operations were horrible ordeals. Horace Wells, a dentist, picked up the idea of using *nitrous oxide* (N_2O) from a demonstration of laughing gas in 1844. However, he often failed to relieve dental pain completely and the use of N_2O had to wait till other advances were made. Morton, a dentist and medical student at Boston, after experimenting on animals, gave a demonstration of *ether* anaesthesia in 1846, and it soon became very popular. *Chloroform* was used by Simpson in Britain for obstetrical purpose in 1847, and despite its toxic potential, it became a very popular surgical anaesthetic. *Cyclopropane* was introduced in 1929, but the new generation of anaesthetics was heralded by *halothane* in 1956. The first i.v. anaesthetic *thiopentone* was introduced in 1935.

MECHANISM OF GENERAL ANAESTHESIA

The mechanism of action of GAs is not precisely known. A wide variety of chemical agents produce general anaesthesia. Therefore, GA action had been related to some common physicochemical property of the drugs. Mayer and Overton (1901) pointed out a direct parallelism between lipid/water partition coefficient of the GAs and their anaesthetic potency.

Minimal alveolar concentration (MAC) It is the lowest concentration of the anaesthetic in the pulmonary alveoli needed to produce immobility in response to a painful stimulus (surgical incision) in 50% individuals. It is accepted as a valid measure of potency of inhalational GAs, because it remains fairly constant for most young adults. The MAC of all inhalational anaesthetics declines progressively as age advances beyond 50 years.

The MAC of a number of GAs shows excellent correlation with their oil/gas partition coefficient. However, this only reflects capacity of the anaesthetic to enter into CNS and attain sufficient concentration in the neuronal membrane, but not the mechanism by which

anaesthesia is produced. The *'unitary hypothesis'* that some single common molecular mechanism (like membrane expansion or membrane perturbation or membrane fluidization) is responsible for the action of all inhalational anaesthetics has now been replaced by the *'agent specific theory'* according to which different GAs produce anaesthesia by different mechanisms.

Recent evidence favours a direct interaction of the GA molecules with the hydrophobic domains of membrane proteins or the lipid-protein interface.

Not only different anaesthetics appear to act by different molecular mechanisms, they also may exhibit stereospecific effects, and that various components of the anaesthetic state may involve action at discrete loci in the cerebrospinal axis. The principal locus of causation of unconsciousness appears to be in the thalamus or reticular activating system, amnesia may result from action in cerebral cortex and hippocampus, while spinal cord is the likely seat of immobility on surgical stimulation.

Recent findings show that ligand gated ion channels (but not voltage sensitive ion channels) are the major targets of anaesthetic action. The $GABA_A$ receptor gated Cl^- channel is the most important of these. Many inhalational anaesthetics, barbiturates, benzodiazepines and propofol potentiate the action of inhibitory transmitter GABA to open Cl^- channels. Each of the above anaesthetics appears to interact with its own specific binding site on the $GABA_A$ receptor-Cl^- channel complex, but none binds to the GABA binding site as such; though some inhaled anaesthetics and barbiturates (but not benzodiazepines) can directly activate Cl^- channels. Action of glycine (another inhibitory transmitter which also activates Cl^- channels) in the spinal cord and medulla is augmented by barbiturates, propofol and many inhalational anaesthetics. This action may block responsiveness to painful stimuli resulting in immobility of the anaesthetic state. Certain fluorinated anaesthetics and barbiturates, in addition, inhibit the neuronal cation channel gated by nicotinic cholinergic receptor which may mediate analgesia and amnesia.

On the other hand, N_2O and ketamine do not affect GABA or glycine gated Cl^- channels. Rather they selectively inhibit the excitatory NMDA type of glutamate receptor. This receptor gates mainly Ca^{2+} selective cation channels in the neurones, inhibition of which appears to be the primary mechanism of anaesthetic action of ketamine as well as N_2O. The volatile anaesthetics have little action on this receptor.

Neuronal hyperpolarization caused by GAs has been ascribed to activation of a specific type of K^+ channels called 'two-pore domain' channels. This may cause inhibition of presynaptic transmitter release as well as postsynaptic activation. Inhibition of transmitter release from presynaptic neurones has also been related to interaction with certain critical synaptic proteins. Thus, different facets of anaesthetic action may have distinct neuronal basis, as opposed to the earlier belief of a global neuronal depression.

Unlike local anaesthetics which act primarily by blocking axonal conduction, the GAs appear to act by depressing synaptic transmission.

STAGES OF ANAESTHESIA

GAs cause an irregularly descending depression of the CNS, i.e. the higher functions are lost first and progressively lower areas of the brain are involved, but in the spinal cord lower segments are affected somewhat earlier than the higher segments. The vital centres located in the medulla are paralysed the last as the depth of anaesthesia increases.

Guedel (1920) described four stages with *ether* anaesthesia, dividing the III stage into 4 planes. These clear-cut stages are not seen now-a-days with the use of faster acting GAs, premedication and employment of many drugs together. The precise sequence of events differs somewhat with anaesthetics other than ether. However, description of these stages still serves to define the effects of light and deep anaesthesia. Important features of different stages are depicted in Fig. 27.1.

I. Stage of analgesia Starts from beginning of anaesthetic inhalation and lasts upto the loss of consciousness. Pain is progressively abolished. Patient remains conscious, can hear and see, and feels a dream like state; amnesia develops by the end of this stage. Reflexes and respiration remain normal.

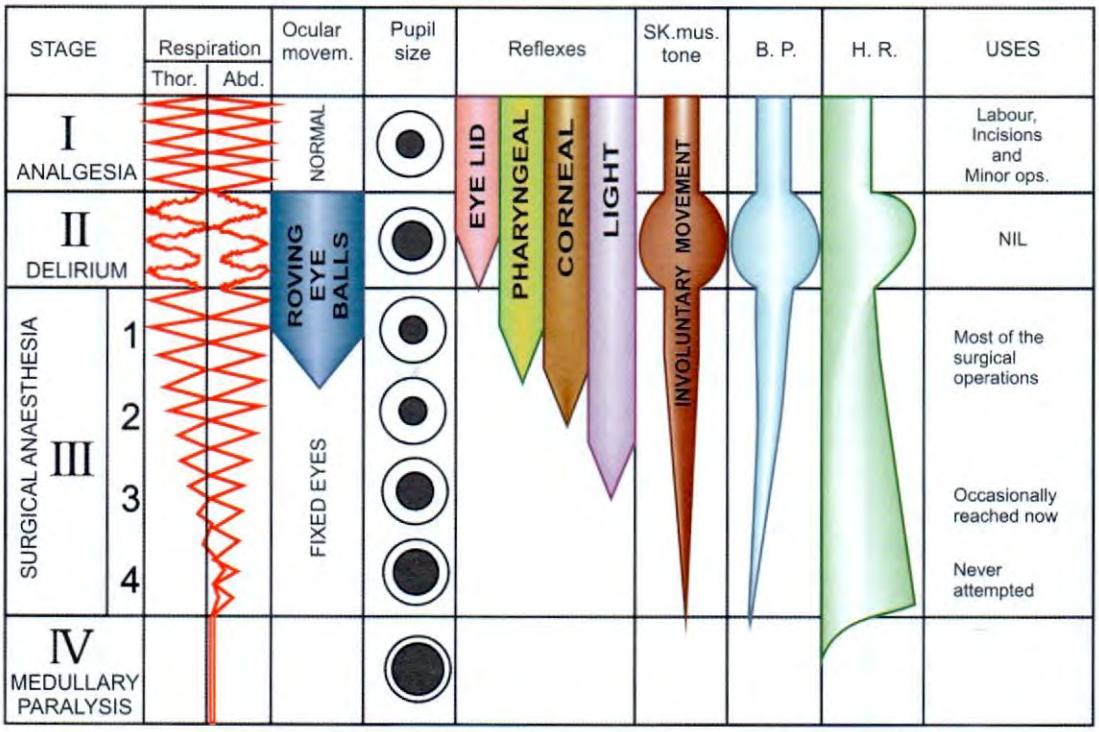


Fig. 27.1: Physiological changes during stages of general anaesthesia (with ether)

Though some minor operations can be carried out during this stage, it is rather difficult to maintain—use is limited to short procedures.

II. Stage of delirium From loss of consciousness to beginning of regular respiration. Apparent excitement is seen—patient may shout, struggle and hold his breath; muscle tone increases, jaws are tightly closed, breathing is jerky. Heart rate and BP may rise and pupils dilate due to sympathetic stimulation.

No stimulus should be applied or operative procedure carried out during this stage. This stage is inconspicuous in modern anaesthesia.

III. Surgical anaesthesia Extends from onset of regular breathing to cessation of spontaneous breathing. This has been divided into 4 planes which may be distinguished as:

Plane 1 Roving eyeballs. This plane ends when eyes become fixed.
Plane 2 Loss of corneal and laryngeal reflexes.
Plane 3 Pupil starts dilating and light reflex is lost.
Plane 4 Intercostal paralysis, shallow abdominal respiration, dilated pupil.

As anaesthesia passes to deeper planes, progressively—muscle tone decreases, BP falls, HR increases with weak pulse, respiration decreases in depth and later in frequency as well. Thoracic respiration lags behind abdominal respiration.

IV. Medullary paralysis Cessation of breathing to failure of circulation and death. Pupil is widely dilated, muscles are totally flabby, pulse is thready or imperceptible and BP is very low.

Many of the above indices of anaesthesia have been obscured by the use of fast acting anaesthetics, premedication and muscle relaxants. The modern anaesthetist has to depend on several other observations to gauge the depth of anaesthesia.

- If eyelash reflex is present and patient is making swallowing movements—stage II has not been reached.
- Loss of response to painful stimulus (e.g. pressure on the upper nasal border of orbit) — stage III has been reached.
- Incision of the skin causes reflex increase in respiration, BP rise or other effects; insertion of endotracheal tube is resisted and induces coughing, vomiting, laryngospasm; tears

appear in eye; passive inflation of lungs is resisted—anaesthesia is light.
- Fall in BP, cardiac and respiratory depression are signs of deep anaesthesia.

In the present day practice, anaesthesia is generally kept light; adequate analgesia, amnesia and muscle relaxation are produced by the use of intravenous drugs. Premedication with CNS depressants and opioids or their concurrent use lowers MAC of the inhaled anaesthetic. When a combination of two inhalational anaesthetics (e.g. N_2O + isoflurane) is used, their MACs are additive: lower concentration of each is required, e.g. 0.5 MAC of N_2O (53%) and 0.5 MAC of isoflurane (0.6%) produce CNS depression equivalent to 1 MAC of isoflurane alone. The dose-response relationship of inhaled anaesthetics is very steep; just 30% higher concentration (1.3 MAC) immobilizes 95% subjects. Concentrations of inhalational anaesthetics exceeding 1.5 MAC are rarely used, and 2–3 MAC is often lethal. Anaesthetized subjects generally wake up when anaesthetic concentration falls to 0.4 MAC.

Some effects common to most inhalational anaesthetics are:
- The EEG initially shows activation, but increasing concentrations of potent GAs cause progressive EEG suppression culminating in electrical silence at > 2 MAC.
- Decrease in cerebral metabolic rate which indirectly reduces cerebral blood flow (CBF). However, at higher concentrations, their direct vasodilatory action predominates and CBF may actually increase. These higher concentrations should be avoided in patients with raised intracranial pressure.
- All fluorinated anaesthetics depress cardiac contractility and lower BP.
- Respiratory depression, bronchodilatation and reduced airway mucociliary function occurs; so that prolonged anaesthesia predisposes to respiratory complications.
- Limited and reversible lowering of GFR and urine flow.
- Reduced gastrointestinal motility.

PHARMACOKINETICS OF INHALATIONAL ANAESTHETICS

Inhalational anaesthetics are gases or vapours that diffuse rapidly across pulmonary alveoli and tissue barriers. The depth of anaesthesia depends on the potency of the agent (MAC is an index of potency) and its partial pressure (PP) in the brain, while induction and recovery depend on the rate of change of PP in the brain. Transfer of the anaesthetic between lung and brain depends on a series of tension gradients which may be summarized as—

Alveoli ⟷ Blood ⟷ Brain

Factors affecting the PP of anaesthetic attained in the brain are—

1. *PP of anaesthetic in the inspired gas* This is proportional to its concentration in the inspired gas mixture. Higher the inspired tension more anaesthetic will be transferred to the blood. Thus, induction can be hastened by administering the GA at high concentration in the beginning.

2. *Pulmonary ventilation* It governs delivery of the GA to the alveoli. Hyperventilation will bring in more anaesthetic per minute and respiratory depression will have the opposite effect. Influence of minute volume on the rate of induction is greatest in the case of agents which have high blood solubility because their PP in blood takes a long time to approach the PP in alveoli. However, it does not affect the terminal depth of anaesthesia attained at any given concentration of a GA.

3. *Alveolar exchange* The GAs diffuse freely across alveoli, but if alveolar ventilation and perfusion are mismatched (as occurs in emphysema and other lung diseases) the attainment of equilibrium between alveoli and blood is delayed: well perfused alveoli may not be well ventilated—blood draining these alveoli carries less anaesthetic and dilutes the blood coming from well ventilated alveoli. Induction and recovery both are slowed.

4. *Solubility of anaesthetic in blood* This is the most important property determining induction and recovery. Large amount of an anaesthetic that is highly soluble in blood (ether) must dissolve before its PP is raised. The rise as well as fall of PP in blood and consequently induction as well as recovery are slow. Drugs with low blood solubility, e.g. N_2O, sevoflurane, desflurane induce quickly.

Blood: gas partition coefficient (λ) given by the ratio of the concentration of the anaesthetic in blood to that in the gas phase at equilibrium is the index of solubility of the GA in blood.

5. *Solubility of anaesthetic in tissues* Relative solubility of the anaesthetic in blood and a tissue determines its concentration in that tissue at equilibrium. Most of the GAs are equally soluble in lean tissues as in blood, but more soluble in fatty tissue. Anaesthetics with higher lipid solubility (halothane) continue to enter adipose tissue for hours and also leave it slowly. The concentration of these agents is much higher in white matter than in grey matter.

6. *Cerebral blood flow* Brain is a highly perfused organ; as such GAs are quickly delivered to it. This can be hastened by CO_2 inhalation which causes cerebral vasodilatation—induction and recovery are accelerated. Carbon dioxide stimulates respiration and this also speeds up the transport.

Elimination When inhalation of the anaesthetic is discontinued, gradients are reversed and the channel of absorption (pulmonary epithelium) becomes the channel of elimination. All inhaled anaesthetics are eliminated mainly through lungs. The same factors which govern induction also govern recovery. Anaesthetics, in general, continue to enter and persist for long periods in adipose tissue because of their high lipid solubility and low blood flow to fatty tissues. Muscles occupy an intermediate position between brain and adipose tissue. Most GAs are eliminated unchanged. Metabolism is significant only for halothane which is >20% metabolized in liver. Others are practically not metabolized. Recovery may be delayed after prolonged anaesthesia, especially in case of more lipid-soluble anaesthetics (halothane, isoflurane), because large quantities of the anaesthetic have entered the muscle and fat, from which it is released slowly into blood.

Second gas effect and diffusion hypoxia In the initial part of induction, diffusion gradient from alveoli to blood is high and larger quantity of anaesthetic is entering blood. If the inhaled concentration of anaesthetic is high, substantial loss of alveolar gas volume will occur and the gas mixture will be sucked in, independent of ventilatory exchange—gas flow will be higher than tidal volume. This is significant only with N_2O, since it is given at 70–80% concentration. Though it has low solubility in blood, about 1 litre/min of N_2O enters blood in the first few minutes. As such, gas flow is 1 litre/min higher than minute volume. If another potent anaesthetic, e.g. halothane (1–2%) is being given at the same time, it will also be delivered to blood at a rate 1 litre/min higher than minute volume and induction will be faster. This is called *'second gas effect'*.

The reverse occurs when N_2O is discontinued after prolonged anaesthesia; N_2O having low blood solubility rapidly diffuses into alveoli and dilutes the alveolar air, and PP of oxygen in alveoli is reduced. The resulting hypoxia, called *diffusion hypoxia*, is not of much consequence if cardiopulmonary reserve is normal, but may be dangerous if it is low. Diffusion hypoxia can be prevented by continuing 100% O_2 inhalation for a few minutes after discontinuing N_2O, instead of straight away switching over to air. Diffusion hypoxia is not significant with other anaesthetics, because they are administered at low concentrations (0.2–4%) and cannot dilute alveolar air by more than 1–2% in any case.

TECHNIQUES OF INHALATION OF ANAESTHETICS

Different techniques are used according to facility available, agent used, condition of the patient, type and duration of operation.

1. Open drop method Liquid anaesthetic is poured over a mask with gauze and its vapour is inhaled with air. A lot of anaesthetic vapour escapes in the surroundings and the

concentration of anaesthetic breathed by the patient cannot be determined. It is wasteful—can be used only for a cheap anaesthetic. However, it is simple and requires no special apparatus. Use now is limited to peripheral areas. Ether is the only agent administered by this method, especially in children.

2. Through anaesthetic machines Use is made of gas cylinders, specialized graduated vaporizers, flow meters, unidirectional valves, corrugated rubber tubing and reservoir bag.

The gases are delivered to the patient through a tightly fitting face mask or endotracheal tube. Administration of the anaesthetic can be more precisely controlled and in many situations its concentration estimated. Respiration can be controlled and assisted by the anaesthetist.

(a) *Open system* The exhaled gases are allowed to escape through a valve and fresh anaesthetic mixture is drawn in each time. No rebreathing is allowed—flow rates are high—more drug is consumed. However, predetermined O_2 and anaesthetic concentration can be accurately delivered.

(b) *Closed system* The patient rebreaths the exhaled gas mixture after it has circulated through sodalime which absorbs CO_2. Only as much O_2 and anaesthetic as have been taken up by the patient are added to the circuit. Flow rates are low. This is especially useful for expensive and explosive agents (little anaesthetic escapes in the surrounding air). Halothane, isoflurane, desflurane can be used through closed system. However, control of inhaled anaesthetic concentration is imprecise.

(c) *Semiclosed system* Partial rebreathing is allowed through a partially closed valve. Conditions are intermediate with moderate flow rates.

Properties of an ideal anaesthetic

A. *For the patient* It should be pleasant, non-irritating, should not cause nausea or vomiting.

Induction and recovery should be fast with no after effects.

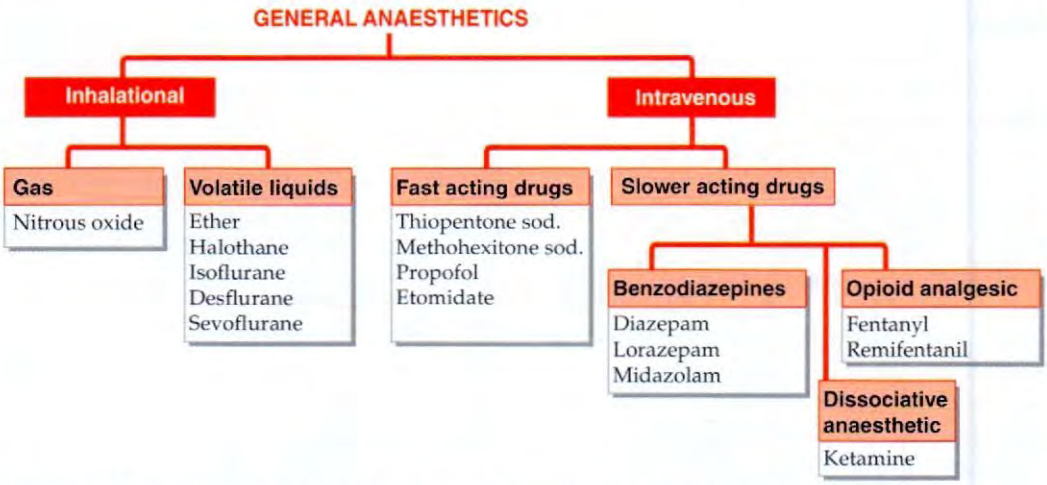
B. *For the surgeon* It should provide adequate analgesia, immobility and muscle relaxation.

It should be noninflammable and nonexplosive so that cautery may be used.

C. *For the anaesthetist* Its administration should be easy, controllable and versatile.

- Margin of safety should be wide—no fall in BP.
- Heart, liver and other organs should not be affected.
- It should be potent so that low concentrations are needed and oxygenation of the patient does not suffer.
- Rapid adjustments in depth of anaesthesia should be possible.
- It should be cheap, stable and easily stored.
- It should not react with rubber tubing or soda lime.

The important physical and anaesthetic properties of inhalational anaesthetics are presented in Table 27.1.



Cyclopropane, trichloroethylene, methoxyflurane and enflurane are no longer used.

Table 27.1 : Physical and anaesthetic properties of inhalational anaesthetics

Anaesthetic	*Boiling point (°C)*	*Inflammability*	*Irritancy (odour)*	*Oil: Gas partition coefficient**	*Blood: Gas partition coefficient**	*MAC (%)*	*Induction*	*Muscle relaxation*
1. Ether	35	Infl. + Explo.	+++ (Pungent)	65	12.1	1.9	Slow	V. good
2. Halothane	50	Noninfl.	– (Pleasant)	224	2.3	0.75	Interm.	Fair
3. Isoflurane	48	Noninfl.	± (Unpleasant)	99	1.4	1.2	Interm.	Good
4. Desflurane	24	Noninfl.	+ (Unpleasant)	19	0.42	6.0	Fast	Good
5. Sevoflurane	59	Noninfl.	– (Pleasant)	50	0.68	2.0	Fast	Good
6. Nitrous oxide	Gas	Noninfl.	–	1.4	0.47	105	Fast	Poor

*At 37°C; Oil: gas and blood: gas partition coefficients are measures of solubility of the anaesthetic in lipid and blood respectively.
MAC—Minimal alveolar concentration; Infl.—Inflammable; Explo.—Explosive; Interm.—Intermediate

INHALATIONAL ANAESTHETICS

1. Nitrous oxide (N_2O) It is a colourless, odourless, heavier than air, noninflammable gas supplied under pressure in steel cylinders. It is nonirritating, but low potency anaesthetic; unconsciousness cannot be produced in all individuals without concomitant hypoxia; MAC is 105% implying that even pure N_2O cannot produce adequate anaesthesia at 1 atmosphere pressure. Patients maintained on 70% N_2O + 30% O_2 along with muscle relaxants often recall the events during anaesthesia, but some lose awareness completely.

Nitrous oxide is a good analgesic; even 20% produces analgesia equivalent to that produced by conventional doses of morphine. Muscle relaxation is minimal. Neuromuscular blockers are mostly required. Onset of N_2O action is quick and smooth (but thiopentone is often used for induction), and recovery is rapid, because of its low blood solubility. Second gas effect and diffusion hypoxia occur with N_2O only. Post-anaesthetic nausea is not marked. It tends to increase sympathetic tone which increases cerebral blood flow and counteracts the weak direct depressant action on heart and circulation.

Nitrous oxide is generally used as a carrier and adjuvant to other anaesthetics. A mixture of 70% N_2O + 25–30% O_2 + 0.2–2% another potent anaesthetic is employed for most surgical procedures. In this way concentration of the other anaesthetic can be reduced to 1/3 for the same level of anaesthesia. Because N_2O has little effect on respiration, heart and BP: breathing and circulation are better maintained with the mixture than with the potent anaesthetic given alone in full doses. However, N_2O can expand pneumothorax and other abnormal air pockets in the body. It increases cerebral blood flow and tends to elevate intracranial pressure. Thus, N_2O alone is not suitable for patients with raised intracranial pressure.

As the sole agent, N_2O (50%) has been used with O_2 for dental and obstetric analgesia. It is nontoxic to liver, kidney and brain. However, prolonged N_2O anaesthesia has the potential to depress bone marrow and cause peripheral neuropathy, probably by depressing methionine synthase activity. Metabolism of N_2O does not occur; it is quickly removed from the body by lungs. It is cheap and commonly used.

2. Ether (Diethyl ether) It is a highly volatile liquid, produces irritating vapours which are inflammable and explosive.

$$(C_2H_5 — O — C_2H_5)$$

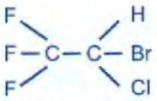
Ether is a potent anaesthetic, produces good analgesia and marked muscle relaxation by reducing ACh output from motor nerve endings. The dose of competitive neuromuscular blockers should be reduced to about 1/3.

It is highly soluble in blood. Induction is prolonged and unpleasant with struggling, breath-holding, salivation and marked respiratory secretions (atropine must be given as premedication to prevent the patient from drowning in his own secretions). Recovery is slow; post-anaesthetic nausea, vomiting and retching are marked.

Respiration and BP are generally well maintained because of reflex stimulation and high sympathetic tone. It does not sensitize the heart to Adr, and is not hepatotoxic.

Ether is not used now, except in peripheral and resource-poor areas, because of its unpleasant and inflammable properties. However, it is cheap, can be given by open drop method (though congestion of eye, soreness of trachea and ether burns on face can occur) without the need for any equipment, and is relatively safe even in inexperienced hands.

3. Halothane (FLUOTHANE) It is a volatile liquid with sweet odour, nonirritant and noninflammable. Solubility in blood is moderate—induction is reasonably quick and pleasant.



HALOTHANE

Halothane is a potent anaesthetic; therefore precise control of administered concentration is essential. For induction 2–4% and for maintenance 0.5–1% is delivered by the use of a special vapourizer. It is not a good analgesic or muscle relaxant, but it potentiates competitive neuromuscular blockers.

Halothane causes direct depression of myocardial contractility by reducing intracellular Ca^{2+} concentration. Moreover, sympathetic activity fails to increase reflexly. Cardiac output is reduced with deepening anaesthesia. BP starts falling early and parallels the depth. A 20–30 mm Hg drop in BP is common. Many vascular beds dilate but total peripheral resistance is not significantly reduced. Heart rate is reduced by vagal stimulation, direct depression of SA nodal automaticity and absence of baroreceptor activation even when BP falls. It tends to sensitize the heart to the arrhythmogenic action of Adr. The electrophysiological effects are conducive to reentry—tachyarrhythmias occur occasionally, particularly if sympathetic stimulation occurs due to inadequate anaesthesia.

Halothane causes relatively greater depression of respiration; breathing is shallow and rapid—PP of CO_2 in blood rises if respiration is not assisted. Cerebral blood flow increases. Ventilatory support with added oxygen is frequently required. It tends to accentuate perfusion-ventilation mismatch in the lungs by causing vasodilatation in hypoxic alveoli.

Pharyngeal and laryngeal reflexes are abolished early and coughing is suppressed while bronchi dilate. As such, halothane is the preferred anaesthetic for asthmatics. It inhibits intestinal and uterine contractions. This property is utilized for facilitating external or internal version during late pregnancy. However, its use during labour can prolong delivery and increase postpartal blood loss.

Urine formation is decreased during halothane anaesthesia—primarily due to low g.f.r. as a result of fall in BP.

Hepatitis occurs in rare susceptible individuals (1 in 35000 to 1 in 10,000) especially after repeated use and in those with familial predisposition. A metabolite of halothane is probably involved which is believed to cause chemical or immunological injury. Halothane toxicity is less frequent in children.

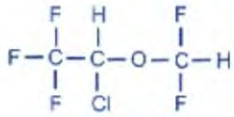
A genetically determined reaction *malignant hyperthermia* occurs rarely. Many susceptible subjects have an abnormal RyR1 (Ryanodine receptor) calcium channel at the sarcoplasmic reticulum of skeletal muscles. This channel is triggered by halothane to release massive amounts of Ca^{2+} intracellularly causing persistent muscle contraction and increased heat production. Succinylcholine accentuates the condition (*see* Ch. 25). Rapid external cooling, bicarbonate infusion, 100% O_2 inhalation and i.v. dantrolene (*see* p. 382) are used to treat malignant hyperthermia.

About 20% of halothane that enters blood is metabolized in the liver, the rest is exhaled out. Elimination may continue for 24–48 hours after prolonged administration due to accumulation in fatty and other tissues. Recovery from halothane anaesthesia is smooth and reasonably quick; shivering may occur but nausea and vomiting are rare. Psychomotor performance and mental

ability remain depressed for several hours after regaining consciousness.

Halothane is a frequently used anaesthetic in developing countries, because it is relatively cheap and nonirritant, noninflammable, pleasant with relatively rapid action. It is particularly suitable for use in children, both for induction as well as maintenance. In adults, it is mainly used as a maintenance anaesthetic after i.v. induction. However, in affluent countries it has been largely replaced by the newer agents which are costlier. Its deficiencies in terms of poor analgesia and muscle relaxation are compensated by concomitant use of N_2O or opioids and neuromuscular blockers.

4. Isoflurane (SOFANE, FORANE, ISORANE) This fluorinated anaesthetic introduced in 1981 is currently the routinely used anaesthetic. It has totally replaced its earlier introduced isomer enflurane. Isoflurane is somewhat less potent and less soluble in blood as well as in fat than halothane, but equally volatile. Compared to halothane, it produces relatively rapid induction and recovery, and is administered through a special vapourizer; 1.5–3% induces anaesthesia in 7–10 min, and 1–2% is used for maintenance.



ISOFLURANE

Magnitude of fall in BP is similar to that with halothane, but unlike halothane, this is primarily due to vasodilatation, while cardiac output is well maintained. As such, isoflurane is a suitable anaesthetic for patients with latent or overt myocardial insufficiency. Heart rate is increased. These cardiovascular effects probably result from stimulation of β adrenergic receptors, but isoflurane does not sensitize the heart to adrenergic arrhythmias. It dilates coronaries. Though not encountered clinically, possibility of 'coronary steal' has been apprehended in coronary artery disease patients on theoretical grounds. Respiratory depression is prominent and assistance is usually needed to avoid hypercarbia. Secretions are slightly increased.

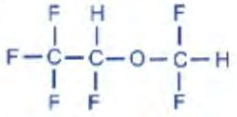
Uterine and skeletal muscle relaxation is similar to that with halothane, but potentiation of neuromuscular blockers is greater.

Pupils do not dilate and light reflex is not lost even at deeper levels.

Metabolism of isoflurane is negligible. Renal and hepatic toxicity has not been encountered. Postanaesthetic nausea and vomiting is mild.

Though mildly pungent, isoflurane has many advantages, i.e. better adjustment of depth of anaesthesia and low toxicity. It is a good maintenance anaesthetic, but not preferred for induction because of ether-like odour which is not liked by conscious patients, especially children. In contrast to enflurane, it does not provoke seizures and is particularly suitable for neurosurgery.

5. Desflurane It is a newer all fluorinated congener of isoflurane which has gained popularity as an anaesthetic for out patient surgery. Though it is highly volatile, a thermostatically heated special vapourizer is used to deliver a precise concentration of pure desflurane vapour in the carrier gas ($N_2O + O_2$) mixture. Its distinctive properties are lower lipid solubility as well as very low solubility in blood and tissues, because of which induction and recovery are very fast. Depth of anaesthesia changes rapidly with change in inhaled concentration giving the anaesthetist better control. Postanaesthetic cognitive and motor impairment is shortlived, so that patient can be discharged a few hours after surgery.

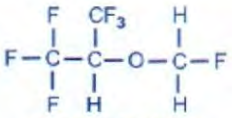


DESFLURANE

Desflurane is 5 times less potent than isoflurane; higher concentration has to be used for induction, which irritates the air passage and may induce coughing, breath-holding and laryngospasm. A somewhat pungent odour also makes it unsuitable for induction. Rapid induction sometimes causes brief sympathetic stimulation and tachycardia which may be risky in those with

cardiovascular disease. The degree of respiratory depression, muscle relaxation, vasodilatation and fall in BP are similar to that with isoflurane. Cardiac contractility and coronary blood flow are maintained. Lack of seizure provoking potential arrhythmogenicity and absence of liver as well as kidney toxicity are also similar to isoflurane. Desflurane is rapidly exhaled unchanged. As such, it can serve as a good alternative to isoflurane for routine surgery as well, especially prolonged operations. If closed circuit is used, the soda lime should be fresh and well hydrated to prevent formation of carbon monoxide.

6. Sevoflurane (SEVORANE) This new polyfluorinated anaesthetic has properties intermediate between isoflurane and desflurane. Solubility in blood and tissues as well as potency are less than isoflurane but more than desflurane.



SEVOFLURANE

Induction and emergence from anaesthesia are fast so that rapid changes in depth can be achieved. Absence of pungency makes it pleasant and administrable through a face mask. Unlike desflurane, it poses no problem in induction and is frequently selected for this purpose. Acceptability is good even by pediatric patients. Recovery is smooth; orientation, cognitive and motor functions are regained almost as quickly as with desflurane. Sevoflurane is suitable both for outpatient as well as inpatient surgery, induction as well as maintenance, but its high cost and need for high-flow open or semiclosed system makes it very expensive to use. In India, only high-end hospitals are using it.

Sevoflurane does not cause sympathetic stimulation and airway irritation even during rapid induction; can be used in patients prone to bronchospasm. Fall in BP is due to vasodilatation as well as modest cardiac depression. Respiratory depression, and absence of seizure or arrhythmia precipitating propensity are similar to isoflurane. However, occasional epileptiform patterns have been seen in the EEG during sevoflurane anaesthesia. About 3% of absorbed sevoflurane is metabolized, but the amount of fluoride liberated is safe for the kidney and liver. However, it reacts with sodalime, and is not recommended for use in fully closed circuit.

INTRAVENOUS ANAESTHETICS

FAST ACTING DRUGS

These are drugs which on i.v. injection produce loss of consciousness in one arm-brain circulation time (~11 sec). They are generally used for induction because of rapidity of onset of action. Except in children, they have largely replaced inhalational anaesthetics for induction. Anaesthesia is then usually maintained by an inhalational agent. They also serve to reduce the amount of maintenance anaesthetic. Supplemented with analgesics and muscle relaxants, they can also be used as the sole anaesthetic.

1. Thiopentone sod. It is an ultrashort acting thiobarbiturate, highly soluble in water yielding a very alkaline solution, which must be prepared freshly before injection. Extravasation of the solution or inadvertent intraarterial injection produces intense pain; necrosis and gangrene can occur.

Injected i.v. (3–5 mg/kg) as a 2.5% solution, thiopentone sod. produces unconsciousness in 15–20 sec. Its undissociated form has high lipid solubility; therefore it enters brain almost instantaneously. Initial distribution depends on organ blood flow—brain gets large amounts. However, as other less vascular tissues (muscle, fat) gradually take up the drug, blood concentration falls and it back diffuses from the brain: consciousness is regained in 6–10 min ($t_{1/2}$ of distribution phase is 3 min).

On repeated injection, the extracerebral sites are gradually filled up, so that lower doses produce anaesthesia which lasts longer. Its ultimate disposal occurs mainly by hepatic metabolism (elimination $t_{1/2}$ is 8–12 hr), but this is irrelevant for termination of action of a single dose. Residual CNS depression may

persist for > 12 hr. The patient should not be allowed to leave the hospital without an attendant before this time.

Thiopentone is a poor analgesic. Painful procedures should not be carried out under its influence unless an opioid or N_2O has been given; otherwise, the patient may struggle, shout and show reflex changes in BP and respiration.

It is a weak muscle relaxant; does not irritate air passages. Respiratory depression with inducing doses of thiopentone is generally marked; transient apnoea can occur. The BP falls immediately after injection, mainly due to vasodilatation, but recovers rapidly. However, cardiovascular collapse may occur if hypovolemia, shock or sepsis are present. Cardiac contractility is reduced, but reflex tachycardia occurs. However, thiopentone does not sensitize the heart to Adr, arrhythmias are rare.

Cerebral blood flow is reduced, both due to fall in BP as well as constriction of cerebral vessels. However, cerebral oxygenation does not suffer, because there is greater decrease in cerebral metabolic rate and O_2 consumption, while cerebral perfusion is maintained. A comparative summary of effects of i.v. anaesthetics is presented in Table 27.2.

Thiopentone was a commonly used inducing agent, but has now been largely replaced by propofol.

Adverse effects Laryngospasm occurs generally when respiratory secretions or other irritants are present in the airways, or when intubation is attempted while anaesthesia is light. This can be prevented by atropine premedication and administration of succinylcholine immediately after thiopentone. Succinylcholine and thiopentone react chemically—should not be mixed in the same syringe.

Shivering and delirium may occur during recovery. Pain in the postoperative period is likely to induce restlessness; adequate analgesia should be provided. Postanaesthetic nausea and vomiting are uncommon.

Thiopentone can precipitate acute intermittent porphyria in susceptible individuals, and is contraindicated in such subjects.

Other uses Thiopentone is occasionally used for rapid control of convulsions.

Gradual i.v. infusion of subanaesthetic doses can be used to facilitate verbal communication with psychiatric patients and for 'narcoanalysis' of criminals. It acts by knocking off guarding.

PENTOTHAL, INTRAVAL SODIUM 0.5, 1 g powder for making fresh injectable solution.

2. Methohexitone sod. It is similar to thiopentone, 3 times more potent, has a quicker and briefer (5–8 min) action. Excitement during induction and recovery is more common. It is more rapidly metabolized (t½ 4 hr) than thiopentone: patient may be roadworthy more quickly.

3. Propofol Currently, propofol has superseded thiopentone as an i.v. anaesthetic, both for induction as well as maintenance. It is an oily liquid employed as a 1% emulsion. Sensitive patients may develop allergic reaction to the emulsifier. Unconsciousness after propofol injection occurs in 15–45 sec and lasts 5–10

Table 27.2 : Effects of intravenous anaesthetics on vital functions

Anaesthetic drug	*HR*	*BP*	*Resp.*	*CBF*
1. Thiopentone	↑↑	↓↓	↓↓	↓↓↓
2. Propofol	–, ↓	↓↓↓	↓↓↓	↓↓↓
3. Etomidate	–	↓	↓	↓↓↓
4. Diazepan	–, ↑	↓	↓↓	↓↓
5. Ketamine	↑↑	↑↑	↓, –	↑↑↑
6. Fentanyl	↓	↓	↓↓↓	↓

HR—Heart rate; BP—Systemic arterial blood pressure; Resp.—Respiratory drive; CBF—Cerebral blood flow. (Changes in intracranial pressure parallel CBF).

min. Propofol distributes rapidly (distribution t½ 2–4 min). Elimination t½ (100 min) is much shorter than that of thiopentone due to rapid metabolism.

Propofol is believed to cause CNS depression by enhancing $GABA_A$ receptor mediated neuronal inhibition. Intermittent injection or continuous infusion of propofol is also used for total i.v. anaesthesia when supplemented by fentanyl. It lacks airway irritancy and is not likely to induce bronchospasm, therefore preferred in asthmatics. It is particularly suited for outpatient surgery, because residual impairment is less marked and shorter-lasting. Incidence of postoperative nausea and vomiting is low; patient acceptability is very good. Excitatory effects and involuntary movements are noted in few patients. Induction apnoea lasting ~1 min is common. Fall in BP is more profound than that with thiopentone. This is due primarily to vasodilatation with less marked cardiac depression. However, hypotension is short lasting. Baroreflex is suppressed; heart rate remains unchanged or may decrease. Maintenance anaesthesia with propofol produces dose-dependent respiratory depression which is more marked than with thiopentone. Effect on cerebral blood flow and O_2 consumption is similar to that of thiopentone. Pain during injection is frequent; but can be minimized by combining with lidocaine.

Dose: 2 mg/kg bolus i.v. for induction; 100–200 μg/kg/min for maintenance.

PROPOVAN 10 mg/ml and 20 mg/ml in 10, 20 ml vials.

In subanaesthetic doses (25–50 μg/kg/min) it is the drug of choice for sedating intubated patients in intensive care units. However, it is not approved for such use in children. Prolonged sedation with higher doses has caused severe metabolic acidosis, lipaemia and heart failure even in adults.

4. Etomidate It is another induction anaesthetic (0.2–0.5 mg/kg) which has a briefer duration of action (4–8 min) than thiopentone; produces little cardiovascular and respiratory depression, but motor restlessness and rigidity is more prominent as are pain on injection or nausea and vomiting on recovery. It is a poor analgesic and has not found much favour except for patients with compromized cardiovascular status.

SLOWER ACTING DRUGS

1. Benzodiazepines (BZDs) In addition to preanaesthetic medication, BZDs are now frequently used for inducing, maintaining and supplementing anaesthesia as well as for 'conscious sedation'. Relatively large doses (diazepam 0.2–0.3 mg/kg or equivalent) injected i.v. produce sedation, amnesia and then unconsciousness in 5–10 min. If no other anaesthetic or opioid is given, the patient becomes responsive in 1 hr or so due to redistribution of the drug (distribution t½ of diazepam is 15 min), but amnesia persists for 2–3 hr and sedation for 6 hr or more. Recovery is further delayed if larger doses are given. BZDs are poor analgesics: an opioid or N_2O is usually added if the procedure is painful.

By themselves, BZDs donot markedly depress respiration, cardiac contractility or BP, but when opioids are also given these functions are considerably compromised. BZDs decrease muscle tone by central action, but require neuromuscular blocking drugs for muscle relaxation of surgical grade. They do not provoke postoperative nausea or vomiting. Involuntary movements are not stimulated.

BZDs are now the preferred drugs for endoscopies, cardiac catheterization, angiographies, conscious sedation during local/regional anaesthesia, fracture setting, ECT, etc. They are a frequent component of balanced anaesthesia employing several drugs. Another advantage of BZDs is that their anaesthetic action can be rapidly reversed by flumazenil 0.5–2 mg i.v.

Diazepam 0.2–0.5 mg/kg by slow undiluted injection in a running i.v. drip: this technique reduces the burning sensation in the vein and incidence of thrombophlebitis. Because of the irritant property of i.v. diazepam formulation (an organic solvent is included due to its poor water solubility) it has become less popular in anaesthetic practice.

VALIUM, CALMPOSE 10 mg/2 ml inj.

Lorazepam Three times more potent, slower acting and less irritating than diazepam. It

distributes more gradually—awakening may be delayed. Amnesia is more profound.
Dose: 2–4 mg (0.04 mg/kg) i.v. CALMESE 4 mg/2 ml inj.

Midazolam This BZD is water soluble, non-irritating to veins, faster and shorter acting (t½ 2 hours) and 3 times more potent than diazepam. Fall in BP is somewhat greater than with diazepam. It is being preferred over diazepam for anaesthetic use: 1–2.5 mg i.v. followed by 1/4th supplemental doses. Because of its short duration of action, midazolam is the only BZD suitable for sedation of intubated and mechanically ventilated patients. It is being commonly used in critical care anaesthesia as 0.02–0.1 mg/kg/hr continuous i.v. infusion.
FULSED, MEZOLAM, SHORTAL 1 mg/ml, 5 mg/ml inj.

2. Ketamine This unique anaesthetic is pharmacologically related to the hallucinogen phencyclidine. It induces the so called '*dissociative anaesthesia*' characterized by profound analgesia, immobility, amnesia with only light sleep. The patient appears to be conscious, i.e. opens his eyes, makes swallowing movements and his muscles are rigid, but he is unable to process sensory stimuli and does not react to them. Thus, the patient appears to be dissociated from his body and surroundings. The primary site of action of ketamine is in the cortex and subcortical areas, but not in the reticular activating system, which is the site of action of barbiturates. Ketamine acts mainly by inhibiting the NMDA type of excitatory amino acid receptors in the brain, and not by interacting with $GABA_A$ receptor.

Respiration is not depressed, bronchi dilate, airway reflexes are maintained, muscle tone increases. Non-purposive limb movements occur. Heart rate, cardiac output and BP are elevated due to sympathetic stimulation. Ketamine is highly lipid soluble and acts rapidly. A dose of 1–2 (average 1.5) mg/kg i.v. or 3–5 mg/kg i.m. produces the above effects within a minute, and recovery starts after 10–15 min, but the patient remains amnesic for 1–2 hr. Emergence delirium, hallucinations, fear reactions and involuntary movements occur in upto 50% patients during recovery. However, Ketamine injection is not painful. Children tolerate the drug better and emergence reactions are milder. Ketamine is rapidly metabolized in the liver and has an elimination t½ of 2–4 hr.

Ketamine has been used for operations on the head and neck, in patients who have bled, in asthmatics (relieves bronchospasm), in those who do not want to lose consciousness and for short operations. It is good for repeated use; particularly suitable for burn dressing. Combined with diazepam/midazolam it has found use in angiographies, cardiac catheterization and trauma surgery. However, Ketamine can be dangerous for hypertensives, in ischaemic heart disease (increases cardiac work), in congestive heart failure and in those with raised intracranial pressure (ketamine increases cerebral blood flow and O_2 consumption), but is good for hypovolemic patients.
KETMIN, KETAMAX, ANEKET 50 mg/ml in 2 ml amp, 10 ml vial.

Clandestinely mixed in drinks, ketamine has been misused as rape drug.

3. Fentanyl This highly lipophilic, short acting (30–50 min) potent opioid analgesic related to pethidine (*see* Ch. 34) is generally given i.v. at the beginning of painful surgical procedures. Reflex effects of painful stimuli are abolished. It is frequently used to supplement anaesthetics in balanced anaesthesia. This permits use of lower anaesthetic concentrations with better haemodynamic stability. Combined with BZDs, it can obviate the need for inhaled anaesthetics for diagnostic, endoscopic, angiographic and other minor procedures in poor risk patients, as well as for burn dressing. Anaesthetic awareness with dreadful recall is a risk.

After i.v. fentanyl (2–4 μg/kg) the patient remains drowsy but conscious and his cooperation can be commanded. Respiratory depression is marked, but predictable; the patient may be encouraged to breathe and ventilatory assistance may be provided. Tone of chest muscles and masseters may increase with rapid fentanyl injection: a muscle relaxant is then required

to facilitate mechanical ventilation. Heart rate decreases, because fentanyl stimulates vagus. Fall in BP is slight and heart is not sensitized to Adr. Cerebral blood flow and O_2 consumption are slightly decreased. Supplemental doses of fentanyl are needed every 30 min or so, but recovery is prolonged after repeated doses.

Nausea, vomiting and itching often occurs during recovery. The opioid antagonist naloxone can be used to counteract persisting respiratory depression and mental clouding. Fentanyl is also employed as adjunct to spinal and nerve block anaesthesia, and to relieve postoperative pain.

TROFENTYL, FENDOP, FENT 50 µg/ml in 2 ml amp, 10 ml vial.

Alfentanil and *Sufentanil* are other shorter acting analogues which can be used in place of fentanyl.

Remifentanil It is a faster acting congener of fentanyl with a shorter and more predictable duration of action. It is similar to fentanyl in analgesic potency, respiratory depressant action and other properties, including potential to cause spasm of chest muscles. After i.v. injection it produces analgesia within 1–2 min which fades in 10–15 min. The duration of action is not changed even after prolonged i.v. infusion. The very brief action is due to rapid metabolism by plasma and tissue esterases to yield a plasma t½ of 10–15 min. The dose and duration of action are not altered by liver or kidney disease, because remifentanil elimination is not dependent on these organs. Administered by bolus i.v. injection followed by continuous infusion remifentanil is mainly used to provide strong analgesia to cover short and painful procedures. It is particularly suitable when titratable action and quick recovery are desired.

Dose: 0.5 mg/kg/min i.v. infusion, followed by 0.25-0.5 mg/kg/min.

ULTIVA 1 mg/3 ml, 2 mg/5 ml and 5 mg/10 ml inj.

4. Dexmedetomidine Activation of central α_2 adrenergic receptors has been known to cause sedation and analgesia. Clonidine (a selective α_2 agonist antihypertensive) given before surgery reduces anaesthetic requirement. Dexmedetomidine, the active S-enantiomer of medetomidine, is a centrally acting selective α_{2A} agonist that has been introduced for sedating critically ill/ventilated patients in intensive care units. It is also being used to sedate patients during endoscopies, spinal/epidural/regional anaesthesia and as adjunct to GA by lowering the dose of the inhalational anaesthetic. On i.v. infusion of 0.5–1 µg/kg/hour, it produces sedation and analgesia with little respiratory depression, amnesia or anaesthesia. Sympathetic response to stress and noxious stimulus is blunted. Dexmedetomidine is metabolized rapidly by the liver with a t½ of 2–3 hours and excreted in urine as well as in bile. Side effects are similar to those with clonidine, *viz.* hypotension, bradycardia and dry mouth.

DEXDINE, DEXEM, XAMDEX 100 µg/ml inj, 1 ml and 2 ml amp.

CONSCIOUS SEDATION

'Conscious sedation' is a monitored state of altered consciousness that can be employed (supplemented with local/regional anaesthesia), to carryout diagnostic/short therapeutic/dental procedures in apprehensive subjects or medically compromised patients, in place of general anaesthesia. It allows the operative procedure to be performed with minimal physiologic and psychologic stress. In conscious sedation, drugs are used to produce a state of CNS depression (but not unconsciousness), sufficient to withstand the trespass of the procedure, while maintaining communication with the patient, who at the same time responds to commands and is able to maintain a patent airway. The difference between conscious sedation and anaesthesia is one of degree. The protective airway and other reflexes are not lost, making it safer. Drugs used for conscious sedation are: diazepam, midazolam, nitrous oxide, dexmedetomidine and fentanyl.

COMPLICATIONS OF GENERA ANAESTHESIA

A. *During anaesthesia*

1. Respiratory depression and hypercarbia. This is more prominent with isoflurane; may be countered by providing ventilatory assistance by the anaesthetist.
2. Salivation, respiratory secretions and depressed mucociliary function in the airway. This is less problematic with modern anaesthetics.
3. Cardiac arrhythmias, asystole.
4. Fall in BP.
5. Aspiration of acidic gastric contents.
6. Laryngospasm and asphyxia.

7. Awareness: dreadful perception and recall of events during surgery. This may occur due to use of light anaesthesia.
8. Delirium, convulsions and other excitatory effects: generally seen with i.v. anaesthetics.

B. *After anaesthesia*

1. Nausea and vomiting.
2. Persisting sedation: impaired psychomotor function.
3. Mucus plugging of airways, atelectasis and pneumonia, especially after prolonged anaesthesia.
4. Organ toxicities: liver, kidney damage.
5. Nerve palsies—due to faulty positioning.
6. Emergence delirium.
7. Cognitive defects: prolonged excess cognitive decline has been observed in some patients, especially the elderly, who have undergone general anaesthesia, particularly of long duration.

DRUG INTERACTIONS

1. Patients on antihypertensives given general anaesthetics—BP may fall markedly.
2. Neuroleptics, opioids and clonidine potentiate anaesthetics.
3. Halothane sensitizes the heart to Adr.
4. If a patient on corticosteroids is to be anaesthetized, give 100 mg hydrocortisone intraoperatively because anaesthesia is a stressful state—can precipitate adrenal insufficiency and cardiovascular collapse.
5. Insulin need of a diabetic is increased during GA: switch over to plain insulin even if the patient is on oral hypoglycaemics.

PREANAESTHETIC MEDICATION

Preanaesthetic medication refers to the use of drugs before anaesthesia to make it safe and less unpleasant. The aims are:

1. Relief of anxiety and apprehension preoperatively and to facilitate smooth induction.
2. Amnesia for perioperative events.
3. Supplement analgesic action of the anaesthetics and potentiate it so that less anaesthetic is needed.
4. Decrease secretions and vagal stimulation that may be caused by the anaesthetic.
5. Antiemetic effect extending into the postoperative period.
6. Decrease acidity and volume of gastric juice so that it is less damaging if aspirated.

Different drugs achieve different purposes. One or more drugs may be used in a patient depending on the needs.

1. Sedative-antianxiety drugs Benzodiazepines like diazepam (5–10 mg oral) or lorazepam (2 mg oral or 0.05 mg/kg i.m. 1 hour before) have become popular drugs for preanaesthetic medication because they produce tranquility and smoothen induction. There is loss of recall of perioperative events (especially with lorazepam) with little respiratory depression or accentuation of postoperative vomiting. They counteract CNS toxicity of local anaesthetics and are being used along with fentanyl for a variety of minor surgical and endoscopic procedures.

Midazolam is a good amnesic with potent and shorter lasting action. It is also better suited for i.v. injection, due to water solubility.

Promethazine (50 mg i.m.) is an antihistaminic with sedative, antiemetic and anticholinergic properties. It causes little respiratory depression, except in young children.

2. Opioids Morphine (10 mg) or pethidine (50–100 mg), i.m. allay anxiety and apprehension of the operation, produce pre- and postoperative analgesia, smoothen induction, reduce the dose of anaesthetic required and supplement poor analgesics (thiopentone, halothane) or weak anaesthetics (N_2O). Postoperative restlessness is also reduced.

Disadvantages Opioids depress respiration, interfere with pupillary signs of anaesthesia, may cause fall in BP during anaesthesia, can precipitate asthma and tend to delay recovery. Other disadvantages are flushing, delayed gastric emptying and biliary spasm. Morphine particularly contributes to postoperative constipation, vomiting and urinary retention.

Use of opioids is now mostly restricted to patients having preoperative pain. When indicated, fentanyl is mostly injected i.v. just before induction.

3. Anticholinergics (*see* Ch. 8) Atropine or hyoscine (0.6 mg or 10–20 µg/kg i.m./i.v.) or glycopyrrolate (0.2–0.3 mg or 5–10 µg/kg

i.m./i.v.) have been used, primarily to reduce salivary and bronchial secretions. This need is infrequent now due to use of non-irritant anaesthetics. The main aim of using anticholinergics now is to prevent vagal bradycardia and hypotension (which occur reflexly due to certain surgical procedures), and prophylaxis of laryngospasm which is precipitated by respiratory secretions.

Hyoscine, in addition, produces amnesia and antiemetic effect, but tends to delay recovery. Some patients get disoriented; emergence delirium is more common. Therefore, it is infrequently used.

Glycopyrrolate is twice as potent and longer acting quaternary antimuscarinic which does not produce central effects. Antisecretory action is more marked than atropine and tachycardia is less marked. It acts rapidly when given i.v. and is the preferred antimuscarinic in anaesthetic practice.

Action	Atropine	Glycopyrrolate
1. Antisecretory	++	+++
2. Tachycardia	+++	++
3. CNS effects	+	–
4. Bronchodilatation	++	++

Antimuscarinics facilitate assisted ventilation by reducing airway resistance, but tend to increase the anatomic dead space. They dilate pupils, abolish the pupillary signs and increase chances of gastric reflux by decreasing tone of lower esophageal sphincter (LES). They should not be used in febrile patients. Dryness of mouth in the pre- and postoperative period may be distressing. As such, they are now mostly used i.v. intraoperatively when need arises.

4. Neuroleptics Chlorpromazine (25 mg), triflupromazine (10 mg) or haloperidol (2–4 mg) i.m. are occasionally used in premedication. They allay anxiety, smoothen induction and have antiemetic action. However, they accentuate respiratory depression and hypotension caused by the anaesthetics and delay recovery.

Involuntary movements and muscle dystonias can occur, especially in children.

5. H_2 blockers/proton pump inhibitors Patients undergoing prolonged operations, caesarian section and obese patients are at increased risk of gastric regurgitation and aspiration pneumonia. Ranitidine (150 mg)/famotidine (20 mg) or omeprazole (20 mg)/pantoprazole (40 mg) given night before and in the morning benefit by raising the pH of gastric juice. They may also reduce its volume, thereby decreasing the chances of regurgitation. The risk of reflux and damage to lungs on aspiration is minimal if the volume of gastric juice is <25 ml and pH is >3.5. Prevention of stress ulcers is another advantage. H_2 blockers/PPIs are now routinely used before prolonged surgery.

6. Antiemetics *Metoclopramide* 10–20 mg i.m. preoperatively is effective in reducing postoperative vomiting. By enhancing gastric emptying and tone of LES, it reduces the chances of reflux and aspiration. Extrapyramidal side effects and motor restlessness can occur. Combined use of metoclopramide and H_2 blockers is more effective.

Domperidone is nearly as effective as metoclopramide and does not produce extrapyramidal side effects.

Ondansetron (4–8 mg i.v.) the selective 5-HT_3 blocker has been found highly effective in reducing the incidence of post-anaesthetic nausea and vomiting (*see* Ch. 48). It is practically devoid of side effects and has become the antiemetic of choice in anaesthetic practice.

Chapter 28 Ethyl and Methyl Alcohols

ETHYL ALCOHOL (Ethanol)

Alcohols are hydroxy derivatives of aliphatic hydrocarbons. When unqualified, 'alcohol' refers to *ethyl alcohol* or *ethanol*. Pharmacology of alcohol is important for its presence in beverages (which have been used since recorded history), alcoholism and for alcohol intoxication, rather than as a medicinal substance.

Alcohol is manufactured by fermentation of sugars:

$$\underset{\text{Glucose}}{C_6H_{12}O_6} \xrightarrow[(\textit{in yeast})]{\textit{Zymase}} 2CO_2 + \underset{\text{Ethanol}}{2C_2H_5OH}$$

Fermentation proceeds till alcohol content reaches ~ 15%. Then the reaction is inhibited by alcohol itself. Starchy cereals, e.g. barley, when soaked produce malt:

$$\text{STARCH} \xrightarrow{\textit{Convertase}} \text{MALTOSE}$$

which can then be fermented by yeast to produce alcohol. The major source of commercial alcohol is *mollases*, the leftover byproduct of sugar industry.

ALCOHOLIC BEVERAGES

There are a large variety of alcoholic beverages.

A. Malted liquors Obtained by fermentation of germinating cereals; these are undistilled—alcohol content is low (3–6%) e.g. Beers, Stout. Now strong beers (upto 10%) are also available.

B. Wines Produced by fermentation of natural sugars as present in grapes and other fruits. These are also undistilled.

Light wines Claret, Cider; alcohol content 9–12%, cannot exceed 15%.

Fortified wines Port, Sherry (alcohol 16–22%): distilled beverages are added from outside to the wine.

Effervescent wines Champagne (12–16% alcohol): these are bottled before fermentation is complete; the CO_2 produced after botteling remains dissolved under pressure.

Wines are called 'dry' when all sugar present has been fermented and 'sweet' when some is left.

C. Spirits These are produced by distillation of the fermented broth; e.g. Rum, Gin, Whiskey, Brandy, Vodka, etc. Though the alcohol content of these beverages can vary from 40–55%, in India (and almost internationally) for all licenced brands it is standardized to 42.8% v/v or 37% w/w.

The taste, flavour and value of various alcoholic beverages depends not only on alcohol content but on the presence of higher ethers, higher alcohols, aldehydes, esters, polymers, and volatile oils; many of which are formed during 'maturation' of the beverage.

Other forms of alcohol

1. *Absolute alcohol* 99% w/w ethanol (dehydrated alcohol).
2. *Rectified spirit* 90% w/w ethyl alcohol produced from fermented mollases, by distillation.
3. *Proof spirit* It is an old term. If whiskey is poured on gun powder and ignited and it explodes, then it was labelled to be of 'proof strength'. If water is mixed to it, the gun powder will not ignite. 100% proof spirit is 49.29% w/w or 57.1% v/v alcohol.
4. *Methylated spirit (industrial)* Also called 'denatured spirit' is produced by adding 5 parts of wood naphtha (methyl alcohol) to 95 parts of rectified spirit so as to render it unfit for drinking. It is tinted blue by methylene blue dye for distinction. It can be applied on the skin for antiseptic, cleaning and astringent purposes.

PHARMACOLOGICAL ACTIONS

1. Local actions Ethanol is a mild rubefacient and counterirritant when rubbed on the skin. By evaporation it produces cooling. Applied to delicate skin (scrotum) or mucous membranes it produces irritation and burning sensation. Concentrated alcohol (spirit) should not be applied in the mouth, nose, etc. Injected s.c. it causes intense pain, inflammation and necrosis followed by fibrosis. Injected around a nerve it produces permanent nerve damage.

Applied to the surface, alcohol is an astringent—precipitates surface proteins and hardens the skin. By precipitating bacterial proteins it acts as an antiseptic. The antiseptic action increases with concentration from 20 to 70%, remains constant from 70 to 90% and decreases above that. That 100% ethanol is more dehydrating but poorer antiseptic than 90% ethanol, shows that antibacterial action is not due to dehydration of bacterial protoplasm. Alcohol does not kill bacterial spores.

2. CNS Alcohol is a neuronal depressant. Since the highest areas are most easily deranged and these are primarily inhibitory—apparent excitation and euphoria are produced at lower plasma concentrations (30–60 mg/dl). Hesitation, caution, self-criticism and restraint are lost first. Mood and feelings are altered; anxiety may be allayed. At 50–100 mg/dl some individuals may experience what is labelled as 'high'. With increasing concentration (100–150 mg/dl) mental clouding, disorganization of thought, impairment of attention, memory and other faculties, alteration of gait and perception, and drowsiness supervene. At 150–200 mg/dl the person is sloppy, ataxic and drunk, 'black-outs' occur; 200–300 mg/dl result in stupor and above this unconsciousness prevails, medullary centres are paralysed and death may occur. Though, alcohol can produce anaesthesia, margin of safety is narrow.

Any measurable concentration of alcohol produces a measurable slowing of reflexes: driving is dangerous. Performance is impaired, fine discrimination and precise movements are obliterated; errors increase, except if fear of punishment and anxiety of failure has already impaired it. Under such situation performance may be improved by allaying of anxiety and fear.

At any given blood alcohol level, central effects are more marked when the concentration is rising than when it is falling. This is considered to be a manifestation of acute tolerance.

Alcohol can induce sleep but is not a dependable hypnotic. Some individuals report poor quality of sleep and repeated or early morning awakening. Sleep architecture may be disorganized and sleep apnoea aggravated. 'Hangover' (headache, dry mouth, laziness, disturbed mood, impaired performance) may occur the next morning. Alcohol raises pain threshold and also alters reaction to it, but is not a dependable analgesic—severe pain can precipitate confusion and convulsions. During the time alcohol is acting on the brain, it exerts anticonvulsant action, but this is followed by lowering of seizure threshold: seizures may be precipitated in epileptics. Chronic alcohol abuse damages brain neurones, causes shrinkage of brain.

The cortex and the reticular activating system are the most sensitive to alcohol; other areas get depressed as concentration rises.

Mechanism of action Alcohol was believed to produce CNS depression by a generalized membrane action altering the state of membrane lipids. However, lately specific effect on multiple receptor operated and voltage gated ion channels as well as other critical proteins has been demonstrated at concentrations attained during moderate drinking. Thus, several neurohumoral systems are concurrently affected producing a complex pattern of action quite different from

Alcohol : conscious ——————→ anaesthesia ——→ death.

Ether : conscious ——————→ anaesthesia ——————→ death.

that produced by other depressants like barbiturates and benzodiazepines, which predominantly facilitate $GABA_A$ receptor mediated Cl^- channel opening. Alcohol has been shown to enhance GABA release at $GABA_A$ sites in the brain. It also inhibits NMDA type of excitatory amino acid receptors (operating through cation channels) which has been implicated in memory impairment caused by alcohol. Action of 5-HT on $5\text{-}HT_3$ inhibitory autoreceptor (having an intrinsic ion channel) is augmented. Some studies suggest that cerebral nicotinic cholinergic receptor (operating through Na^+ channel) may also be one of the targets of alcohol action. Ethanol can indirectly reduce neurotransmitter release by inhibiting voltage sensitive neuronal Ca^{2+} channels. It also activates specific type of K^+ channels in certain brain areas. Release and turnover of DA in brain is enhanced through β endorphin release in nucleus accumbens and an opioid receptor dependent mechanism. This is probably important in the pleasurable reinforcing effects of alcohol and in the genesis of alcohol dependence. Activity of membrane bound enzymes like Na^+ K^+ ATPase and adenylyl cyclase is also altered. The activity and translocation of channel/enzyme proteins in the membrane could be affected by alcohol through protein kinase C (PKC) and protein kinase A (PKA) mediated alteration in the state of their phosphorylation.

3. CVS The effects of alcohol are dependent on the dose.

Small doses: produce only cutaneous (especially on the face) and gastric vasodilatation. Skin is warm and flushed and there may be conjunctival injection; BP is not affected.

Moderate doses: cause tachycardia and a mild rise in BP due to increased muscular activity and sympathetic stimulation.

Large doses: cause direct myocardial as well as vasomotor centre depression and there is fall in BP.

Epidemiological studies have confirmed that chronic alcoholism contributes to hypertension and can lead to cardiomyopathy. Atrial fibrillation and other cardiac arrhythmias may occur due to conduction defects and Q-T prolongation.

4. Blood Regular intake of small to moderate amounts of alcohol (1–2 drinks) has been found to raise HDL-cholesterol levels and decrease LDL oxidation. This may be responsible for the 15–35% lower incidence of coronary artery disease in such individuals. Risk reduction is greatest in high risk subjects and protection is lost if $\geq$ 3 drinks are consumed daily. However, it is considered inappropriate to advise nondrinkers to start drinking on this account, since other adverse consequences may more than nullify this benefit. Mild anaemia is common in chronic alcoholics. Megaloblastic anaemia occurring in chronic alcoholism is due to interference with folate metabolism.

5. Body temperature Alcohol is reputed to combat cold. It does produce a sense of warmth due to cutaneous and gastric vasodilatation, but heat loss is actually increased in cold surroundings. Drinking before going out in the cold is inadvisable. High doses depress temperature regulating centre.

6. Respiration Brandy or whiskey are reputed as respiratory stimulants in collapse. They irritate buccal and pharyngeal mucosa which may transiently stimulate respiration reflexly. However, it is better not to depend on this, because the direct action of alcohol on respiratory centre is only a depressant one.

7. GIT Alcoholic beverages have variable effect on gastric secretion depending on the beverage itself and whether the individual likes it. However, dilute alcohol (optimum 10%) put in the stomach by Ryle's tube is a strong stimulant of gastric secretion (especially of acid). It acts directly as well as reflexly. Higher concentrations (above 20%) inhibit gastric secretion, cause vomiting, mucosal congestion and gastritis. Alcoholism is an important cause of chronic gastritis. Lower esophageal sphincter (LES) tone is reduced by alcohol. Drinking may accentuate gastric reflux. Bowel movements may be altered in either direction. Acute pancreatitis is a complication of heavy drinking.

8. Liver Neither brief alcohol intoxication nor chronic intake of small-to-moderate amounts cause significant liver damage, provided adequate nutrition is maintained. However, it does mobilize peripheral fat and increases fat synthesis in liver in a dose-dependent manner producing 'fatty liver'. This is reversible, but may progress to cirrhosis if prolonged or excessive. Proteins may also accumulate in liver because their secretion is decreased. Chronic alcoholism

exposes liver to oxidative stress and causes cellular necrosis followed by fibrosis. Acetaldehyde produced during metabolism of alcohol appears to damage the hepatocytes and induce inflammation, especially on chronic ingestion of large amounts. Increased lipid peroxidation and glutathione depletion occurs. These combined with vitamin and other nutritional deficiencies may be responsible for the so called *alcoholic cirrhosis*.

Regular alcohol intake induces microsomal enzymes.

9. Skeletal muscle Alcohol produces little direct effect. Fatigue is allayed by small doses, but muscle work is increased or decreased depending on the predominating central effect. Weakness and myopathy occurs in chronic alcoholism.

10. Kidney Diuresis is often noticed after alcohol intake. This is due to water ingested along with drinks as well as alcohol induced inhibition of ADH secretion. Alcohol does not impair renal function.

11. Sex Alcohol is reputed as an aphrodisiac. Though, loss of restraint and inhibition may provoke sexual behaviour in some individuals or on some occasions, there is no uniform effect of alcohol on sexual desire. Moreover, performance of the sexual act is often impaired. Chronic alcoholism can produce impotence, testicular atrophy, gynaecomastia and infertility in both men and women.

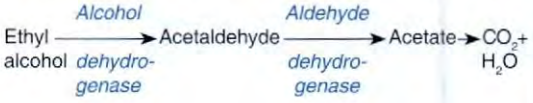
12. Endocrine effects Moderate amounts of alcohol increase Adr release which can cause hyperglycaemia and other sympathetic effects. However, acute intoxication is often associated with hypoglycaemia and depletion of hepatic glycogen, because gluconeogenesis is inhibited. Glucagon, therefore fails to reverse alcohol induced hypoglycaemia, and glucose must be given to counteract it.

13. Uterine contractions are suppressed at moderate blood levels.

PHARMACOKINETICS

Rate of alcohol absorption from the stomach is dependent on its concentration, presence of food, and other factors, but is generally quite slow. Absorption from intestines is very fast; peak levels after ingestion in the fasting state are attained after ~30 min. Thus, gastric emptying determines the rate of absorption. Limited first pass metabolism occurs in stomach and liver. Absorption of alcohol from skin of adults is minimal but may be significant in infants given alcohol sponges.

Alcohol gets distributed widely in the body (vol of distribution 0.7 L/kg, i.e. equal to volume of total body water), crosses blood-brain barrier efficiently: concentration in the brain is very near blood concentration. It also crosses placenta freely. Alcohol is oxidized in liver to the extent of 98%. Even with high doses, not more than 10% escapes metabolism. The primary pathway sequentially utilizes alcohol dehydrogenase and aldehyde dehydrogenase.



Alcohol dehydrogenase exhibits considerable genetic variability which is reflected in the rate at which individuals metabolize alcohol, and probably governs their susceptibility to alcohol.

In addition to alcohol dehydrogenase, small amounts of alcohol are oxidized by hepatic microsomal enzymes (mainly CYP2E1) as well. Metabolism of alcohol follows *zero order* kinetics, i.e. a constant amount (8–12 ml of absolute alcohol/ hour) is degraded in unit time, irrespective of blood concentration. Thus, the rate of consuming drinks governs whether a person will get drunk.

Excretion of alcohol occurs through kidney and lungs, but neither is quantitatively significant. Concentration in exhaled air is about 0.05% of blood concentration. This is utilized for medicolegal determination of drunken state. The subject blows in a portable hand-held

breath-analyser which measures the alcohol content of exhaled air and displays the result in terms of corresponding blood alcohol concentration (mg/dl).

INTERACTIONS

1. Alcohol synergises with anxiolytics, antidepressants, antihistaminics, hypnotics, opioids, so that marked CNS depression with motor impairment can occur. Chances of accidents increase.
2. Some individuals taking a sulfonylurea, cefoperazone, or metronidazole have experienced bizarre, somewhat disulfiram-like reactions when they consume alcohol. This reaction occurs only in few individuals and its basis is unclear. It passes off with time as alcohol is metabolized. Only reassurance and supportive treatment is needed.
3. Acute alcohol ingestion inhibits, while chronic intake induces CYP enzymes (especially CYP2E1). Formation of toxic metabolite of paracetamol (NABQI) is increased in chronic alcoholics (*see* p. 224). Safe dose limit of paracetamol is lower in them. Metabolism of tolbutamide, phenytoin and some other drugs is similarly affected by acute and chronic alcohol intake.
4. Hypoglycaemic action of insulin and sulfonylureas is enhanced by alcohol ingestion.
5. Aspirin and other NSAIDs cause more gastric bleeding when taken with alcohol.

Food value

Alcohol requires no digestion and is metabolized rapidly. It is an energy yielding substrate: 7 Cal/g, but these cannot be stored. However, it spares carbohydrates and fats as energy source, so that regular intake can contribute to obesity. Alcohol does not supply body building and other essential constituents of food. Those who consume substantial part of their caloric intake as alcohol, often suffer from nutritional deficiencies. Thus, alcohol is an imperfect and expensive food.

CONTRAINDICATIONS

Alcohol is seldom prescribed medically. However, it is rampently consumed. Intake of alcohol should be avoided by—

1. Patients with peptic ulcer, hyperacidity and gastroesophageal reflux disease (alcohol increases gastric secretion and relaxes LES).
2. Epileptics: seizures may be precipitated.
3. Severe liver disease patients.
4. Unstable personalities: they are likely to abuse it and become excessive drinkers.
5. Pregnant women: Even moderate drinking during pregnancy can produce *foetal alcohol syndrome* resulting in intrauterine and postnatal growth retardation, low IQ offspring, microcephaly, cranio-facial (flat face) and other abnormalities, and immunological impairment causing increased susceptibility to infections. Heavy drinking during pregnancy, in addition, increases the incidence of miscarriage, stillbirths and low birth-weight babies.

Guidelines for safe drinking Alcoholic beverages are widely consumed, and in many cultures they are served as a part of social courtesy. Moderate drinking is generally considered socially acceptable. Physicians are often asked to advise on safe ways of drinking. Various official agencies, physician organizations and alcoholism experts have putforth guidelines in this regard, but they are not uniform. The following may be concluded:

- On an average 1–2 drinks per day is usually safe.
- Not more than 3 drinks on any one occasion.
- Consumption of >3 drinks per day is associated with documented adverse health effects.
- Do not drive or engage in hazardous activities after drinking.
- Do not drink if an interacting drug has been taken.
- Subjects with any contraindication should not drink.
- Safe limits are somewhat lower for women than for men, because metabolism of alcohol

is slower and its bioavailability higher (due to less first pass metabolism in stomach) in women than in men.

[Note: 1 drink = 50 ml of spirits = 150 ml of wines = 400 ml of beer; all have roughly 16 g alcohol, which taken in empty stomach produces a peak alcohol blood level of ~ 30 mg/dl in an adult male of average built.]

TOXICITY

A. *Side effects of moderate drinking* Nausea, vomiting, flushing, hangover, traffic accidents.

B. *Acute alcoholic intoxication* Unawareness, unresponsiveness, stupor, hypotension, gastritis, hypoglycaemia, respiratory depression, collapse, coma and death.

Treatment: Gastric lavage is helpful only when the patient is brought soon after ingesting alcohol, which is rare. Since most patients are disoriented or comatose, the first priority is to maintain patent airway and prevent aspiration of vomitus. Tracheal intubation and positive pressure respiration may be needed if it is markedly depressed. Analeptics should not be given. They may precipitate convulsions. Most patients will recover with supportive treatment, maintenance of fluid and electrolyte balance and correction of hypoglycaemia by glucose infusion till alcohol is metabolized. Thiamine (100 mg in 500 ml glucose solution infused i.v.) should be added. Recovery can be hastened by haemodialysis. Insulin + fructose drip has been found to accelerate alcohol metabolism. However, its clinical impact is not remarkable.

C. *Chronic alcoholism* On chronic intake, tolerance develops to subjective and behavioural effects of alcohol, but is generally of a low degree. It is both pharmacokinetic (reduced rate of absorption due to gastritis and faster metabolism due to enzyme induction) and cellular tolerance. Mild addiction occurs in some subjects even with moderate drinking. It depends a lot on the individual's likings and attitudes. Addiction is manifested in alcohol-seeking behaviour, and the priority that the subject accords to obtaining and consuming alcohol over other needs, or the extent to which he will go for maintaining alcohol intake.

Recent studies have confirmed that a genetic basis contributes to progression from social drinking to alcoholism in about 50% individuals. Alcoholism is often a familial trait. Some differences in sensitivity of various neuronal systems to alcohol among 'predisposed' and 'not predisposed' individuals have been demonstrated.

There is no single explanation for why people drink. Diverse feelings and behaviours are provoked by alcohol in different individuals and in the same individual on different occasions. Alcohol can make people happy as well as sad, curtious as well as mean, talkative as well as silent, friendly as well as hostile. All this cannot be explained on the basis of pharmacological actions of alcohol alone. Attitudes, beliefs, peer groups, social setting and learned experiences all have a bearing. Alcohol is said to produce good mood, sense of wellbeing, self confidence, sociability, etc. But these infact are learned behaviours. In some societies, alcoholic beverages have become an acceptable form of extending courtesy and of entertainment. Drinking is often related to 'celebration' and 'high living'. There is 'wine snobbery' in high social groups.

To some individuals, excess drinking provides the excitement of risk taking. People often boast of their capacity to drink. To the young, drinking may be a symbol of rebellion against the oppressive older generation and rejection of the values of the establishment. 'Binge drinking' is a specific behavioural pattern of bouts of excessive drinking. Alcohol is often an excuse for bad behaviour. Society's view that intoxicated person is unaware of his actions (therefore not responsible) makes intoxication an attractive state, because there is increased freedom of what one can say or do after drinking. Thus, there are a variety of motivations for drinking.

Alcohol dependence occurs only on heavy and round-the-clock drinking (if alcohol is present in the body continuously). Heavy drinking is often associated with nutritional deficiencies, because food is neglected and malabsorption may occur. In addition to impaired mental and physical performance, neurological afflictions are common—polyneuritis, pellagra, tremors, seizures, loss of brain mass, Wernicke's encephalopathy, Korsakoff's psychosis and megaloblastic anaemia. Thiamine deficiency is very common in chronic alcoholism; and high dose thiamine injection partly reverses many neurological symptoms. Alcoholic cirrhosis of liver, hypertension, cardiomyopathy, CHF, arrhythmias, stroke, acute pancreatitis, impotence, gynaecomastia, infertility

and skeletal myopathy are the other complications. Incidence of oropharyngeal, esophageal and hepatic malignancy and respiratory infections is high; immune function is depressed.

Withdrawal syndrome When an alcohol dependent subject stops drinking, withdrawal syndrome appears within a day. Its severity depends on the duration and quantity of alcohol consumed by the subject. It consists of anxiety, sweating, tachycardia, tremor, impairment of sleep, confusion, hallucinations, delirium tremens, convulsions and collapse.

Treatment Psychological and medical supportive measures are needed during withdrawal. Many CNS depressants like barbiturates, phenothiazines, chloral hydrate have been used as substitution therapy in the past (to suppress withdrawal syndrome) but benzodiazepines (chordiazepoxide, diazepam) are the preferred drugs now. These drugs have a long duration of action and can be gradually withdrawn later.

Naltrexone: Several studies have demonstrated involvement of opioid system in the pleasurable reinforcing effects of alcohol through dopamine mediated reward function. Post-addict subjects treated with the long-acting opioid antagonist naltrexone (*see* Ch. 34) do not experience the same pleasurable effects on taking alcohol; reinforcement is weakened. Trials have shown that it helps prevent relapse of alcoholism. Naltrexone reduced alcohol craving, number of drinking days and chances of resumed heavy drinking. It is approved for use as adjuvant in comprehensive treatment programmes for alcohol dependent subjects and is being used in India at most deaddiction centres, after the individual has undergone withdrawal and is motivated.

Acamprosate It is a weak NMDA-receptor antagonist with modest $GABA_A$ receptor agonistic activity that is being used in USA, UK and Europe for maintenance therapy of alcohol abstinence. In conjunction with social and motivational therapy, it has been found to reduce relapse of the drinking behaviour. The efficacy of acamprosate in this regard is rated comparable to naltrexone. It should be started soon after withdrawing alcohol and then given continuously at a dose of 666 mg 2–3 times a day. Loose motion is a common side effect. Others are nausea, abdominal pain and itching.

The 5-HT_3 antagonist *ondansetron* and the antiepileptic *topiramate* have also shown some promise in treating alcoholism.

CLINICAL USES

Medicinal uses of ethanol are primarily restricted to external application and as a vehicle for liquid preparations used internally.

1. As antiseptic (*see* Ch. 67).
2. Rubefacient and counterirritant for sprains, joint pains, etc. Spirit is generally used as vehicle for other ingredients.
3. Rubbed into the skin to prevent bedsores; works by hardening the skin due to its astringent property. However, alcohol should not be applied on already formed sores. The astringent action of alcohol is also utilized in antiperspirant and aftershave lotions.
4. Alcoholic sponges have been used to reduce body temperature in fever. However, cold water/ice may be better.
5. Intractable neuralgias (trigeminal and others), severe cancer pain: Injection of alcohol round the nerve causes permanent loss of transmission.
6. To ward off cold. Alcohol in the form of whiskey or brandy may benefit by causing vasodilatation of blanched mucosae; but further exposure after taking alcohol may be deleterious because alcohol increases heat loss due to cutaneous vasodilatation.
7. As appetite stimulant and carminative: 30–50 ml of 7–10% alcohol may be taken as beverages or as tinctures (of ginger/cardemom, etc.) before meal.
8. To treat methanol poisoning (*see* below).

Aldehyde dehydrogenase inhibitor

Disulfiram It inhibits the enzyme aldehyde dehydrogenase (Fig. 28.1) probably after conversion into active metabolites. When alcohol is ingested after taking disulfiram, the concentration of acetaldehyde in tissues and blood rises and a number of highly distressing symptoms (aldehyde syndrome) are produced promptly. These are—flushing, burning sensation, throbbing headache, perspiration, uneasiness, tightness in chest, dizziness, vomiting, visual disturbances,

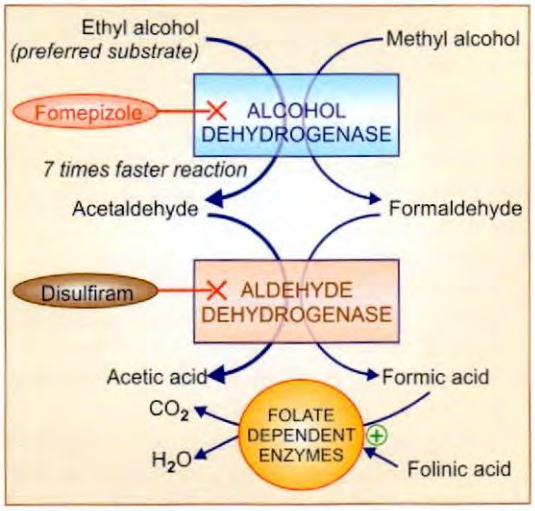


Fig. 28.1: Shared metabolic pathway of ethyl and methyl alcohols

mental confusion, postural fainting and circulatory collapse. Duration of the syndrome (1–4 hours) depends on the amount of alcohol consumed. Because of risk of severe reaction, disulfiram is to be used with great caution, only in well-motivated subjects.

Disulfiram aversion therapy is indicated in abstinent subjects who sincerely desire to leave the habit. After making sure that the subject has not taken alcohol in the past 12 hours, disufiram is given at a dose of 500 mg/day for one week followed by 250 mg daily. Sensitization to alcohol develops after 2–3 hours of first dose, reaches its peak at ~12 hours and lasts for 7–14 days after stopping it, because inhibition of aldehyde dehydrogenase with disulfiram is irreversible: synthesis of fresh enzyme is required for return of activity. The subject's resolve not to drink is reinforced by the distressing symptoms that appear if he drinks a little bit. The subject should be cautioned to avoid alcohol altogether. Disulfiram should not be given to patients who are physically dependent on alcohol.

Side effects of disulfiram (as such) are infrequent, include rashes, metallic taste, nervousness, malaise and abdominal upset. It inhibits a number of other enzymes as well including alcohol dehydrogenase, dopamine β hydroxylase and several cytochrome P450 isoenzymes. Thus, it prolongs t½ of many drugs.

ESPERAL, ANTADICT, DEADICT 250 mg tab. (internationally marketed as ANTABUSE)

METHYL ALCOHOL (Methanol, Wood alcohol)

Methyl alcohol is a commonly used industrial solvent and constituent of cleaning products. It is also added to industrial rectified spirit to render it unfit for drinking. It is only of toxicological importance. Mixing of methylated spirit with alcoholic beverages by bootlegers or its inadvertent ingestion results in methanol poisoning.

Methanol is metabolized to formaldehyde and formic acid by alcohol and aldehyde dehydrogenases respectively (Fig. 28.1), but the rate is ⅐th that of ethanol. Like ethanol, metabolism of methanol also follows *zero order* kinetics and t½ of 20–60 hours has been measured.

Methanol also is a CNS depressant, but less inebriating than ethanol. Toxic effects of methanol are largely due to formic acid, since its further metabolism is slow and folate dependent. A blood level of >50 mg/dl methanol is associated with severe poisoning. Even 15 ml of methanol has caused blindness and 30 ml has caused death; fatal dose is regarded to be 75–100 ml.

Manifestations of methanol poisoning appear after a delay of few hours when its toxic metabolites accumulate. These are vomiting, headache, epigastric pain, uneasiness, drunkenness, disorientation, tachypnoea, dyspnoea, bradycardia and hypotension. Delirium and seizures may occur and the patient may suddenly pass into coma. *Acidosis* is prominent and entirely due to production of formic acid. The specific toxicity of formic acid is *retinal damage*. Blurring of vision, congestion of optic disc followed by blindness always precedes death which is due to respiratory failure.

Treatment

1. Keep the patient in a quiet, dark room; protect the eyes from light.

2. Gastric lavage with sod. bicarbonate if the patient is brought within 2 hours of ingesting methanol. Supportive measures to maintain ventilation and BP should be instituted.
3. Combat acidosis by i.v. *Sod. bicarbonate* infusion. This is the most important measure, which prevents retinal damage and other symptoms; large quantities may be needed.
4. Pot. chloride infusion is needed only when hypokalemia occurs due to alkali therapy.
5. *Ethanol* is preferentially metabolized by alcohol dehydrogenase over methanol. At a concentration of 100 mg/dl in blood it saturates alcohol dehydrogenase and retards methanol metabolism. This helps by reducing the rate of generation of formaldehyde and formic acid. Ethanol (10% in water) is administered through a nasogastric tube; loading dose of 0.7 ml/kg is followed by 0.15 ml/kg/hour. Because pharmacokinetics of alcohol changes over time and no i.v. formulation is available, maintenance of uniform blood alcohol concentration is difficult. Alcohol blood level needs to be repeatedly measured. Moreover, the enzyme saturating concentration of ethanol itself produces intoxication and can cause hypoglycaemia. Use of ethanol for this purpose is tricky. Treatment has to be continued for several days because the sojourn of methanol in body is long.
6. Haemodialysis: clears methanol as well as its toxic metabolite–formate and hastens recovery.
7. *Fomepizole* (4-methylpyrazole) is a specific inhibitor of alcohol dehydrogenase and the drug of choice for methanol poisoning, which acts by retarding its metabolism. A loading dose of 15 mg/kg infused i.v. over 30 min is followed by 10 mg/kg every 12 hours till serum methanol falls below 20 mg/dl. This has been found effective and safe, and has several advantages over ethanol, *viz.* longer $t_{1/2}$, lack of inebriating action, and i.v. dosage form for regulated administration. Marketed elsewhere as ANTIZOL, it is not available commercially in India.

   Adverse effects of fomepizole are burning pain in infused limb, headache, nausea, taste disturbance and hypotension.
8. Folate therapy: Calcium leucovorin 50 mg injected 6 hourly has been shown to reduce blood formate levels by enhancing its oxidation. This is a promising adjuvant approach.

Ethylene glycol poisoning Ethylene glycol poisoning has occurred sporadically, especially among children. It is an industrial solvent, coolant and antifreeze. Ethylene glycol is oxidized in the body by alcohol dehydrogenase to glycoaldehyde and then to glycolic acid—glyoxylic acid—oxalic acid in steps. Ethylene glycol itself can cause intoxication similar to ethanol, but generation of metabolites results in acidosis, cardiopulmonary complications and renal tubular necrosis.

Fomepizole used in the same manner as for methanol poisoning is the drug of choice. It is approved by US-FDA for this indication and has 'orphan drug status'. Ethanol is employed as an alternative.

PROBLEM DIRECTED STUDY

28.1 A school boy aged 16 years developed tonic-clonic epilepsy and was maintained on carbamazepine 200 mg 3 times a day. He was seizure free for the last one year, but reported back one afternoon with the complaint of recurrence of two seizure episodes since morning. On questioning, he revealed that last evening he attended a party with his friends and consumed 4 drinks of whiskey, and was awake till late night. This was the first time that he had taken an alcoholic drink.

(a) Could the recurrence of seizures be related to the intake of alcohol previous night? If so, what could be the mechanism?

(b) Does his antiepileptic therapy need any change or adjustment of doses due to this recurrence of seizures. What further advise will you give to this patient?

(see Appendix-1 for solution)

Chapter 29 Sedative-Hypnotics

Sedative A drug that subdues excitement and calms the subject without inducing sleep, though drowsiness may be produced. Sedation refers to decreased responsiveness to stimulation; is associated with some decrease in alertness, ideation and motor activity.

Hypnotic A drug that induces and/or maintains sleep, similar to normal arousable sleep. This is not to be confused with 'hypnosis' meaning a trans-like state in which the subject becomes passive and highly suggestible.

The sedatives and hypnotics are CNS depressants with somewhat differing time-action and dose-action relationships. Those with quicker onset, shorter duration and steeper dose-response curves are preferred as *hypnotics* while more slowly acting drugs with flatter dose-response curves are employed as *sedatives*. However, there is considerable overlap; a hypnotic at lower dose may act as sedative. Thus, sedation—hypnosis—general anaesthesia may be regarded as increasing grades of CNS depression. Hypnotics given in high doses can produce general anaesthesia. However, benzodiazepines (BZDs) cannot be considered nonselective or global CNS depressants like barbiturates and other older hypnotics.

Treatment of insomnia is the most important use of this class of drugs.

Alcohol and opium have been the oldest hypnotics and continue to be used for this purpose as self-medication by people. Bromides introduced in 1857 became obsolete long back, as did chloral hydrate (1869) and paraldehyde (1882). Fischer and von Mering introduced barbitone in 1903 and phenobarbitone in 1912. Barbiturates reigned supreme till 1960s when benzodiazepines started eroding their position and have now totally replaced them. In the mean time, a number of other sedative-hypnotics (glutethimide, methyprylon, methaqualone) were introduced but none was significantly different from barbiturates; all are redundant now. Few non-BZD hypnotics have also become popular over the past two decades, and some novel hypnotics, *viz ramelteon* (melatonin receptor agonist) and *suvorexant* (orexin receptor antagonist) have been recently introduced.

Sleep

The duration and pattern of sleep varies considerably among individuals. Age has an important effect on quantity and depth of sleep. It has been recognized that sleep is an architectured cyclic process (Fig. 29.1). The different phases of sleep and their characteristics are—

Stage 0 (awake) From lying down to falling asleep as well as the occasional nocturnal awakenings; it constitutes 1–2% of sleep time. The EEG shows α activity when eyes are closed and β activity when eyes are open. Eye movements are irregular or slowly rolling.

Stage 1 (dozing) α activity is interspersed with θ waves. Eye movements are reduced but there may be bursts of rolling. Neck muscles relax. It occupies 3–6% of sleep time.

Stage 2 (unequivocal sleep) θ waves with interspersed spindles, K complexes can be evoked on sensory stimulation; little eye movement; subjects are easily arousable. This comprises 40–50% of sleep time.

Stage 3 (deep sleep transition) The EEG shows θ, δ and spindle activity. K complexes can be evoked with strong stimuli only. Eye movements are few; subjects are not easily arousable. It comprises 5–8% of sleep time.

The EEG waves have been divided into—
- α: high amplitude, 8–14 c.p.s. (cycles per second)
- β: low amplitude, 15–35 c.p.s.
- θ: low amplitude, 4–7 c.p.s.
- δ: high amplitude, 0.5–3 c.p.s.

K complex: deep negative wave followed by positive wave and a few spindles.

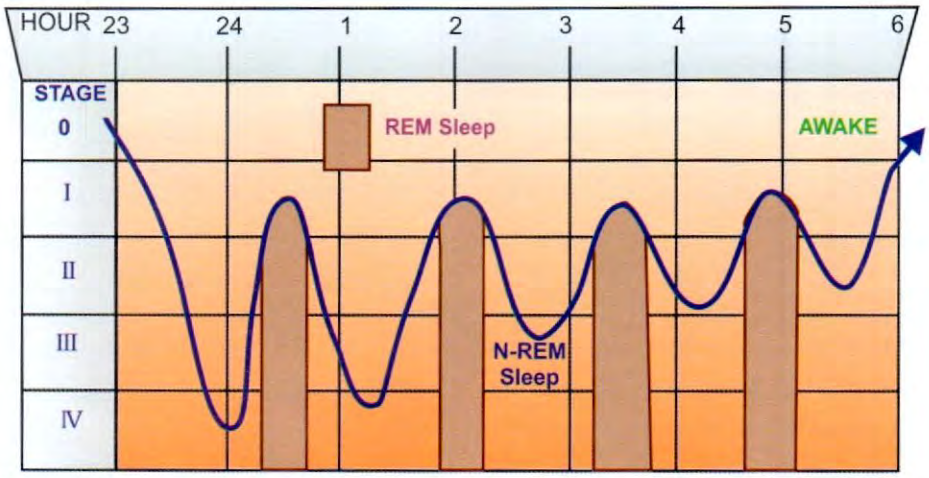
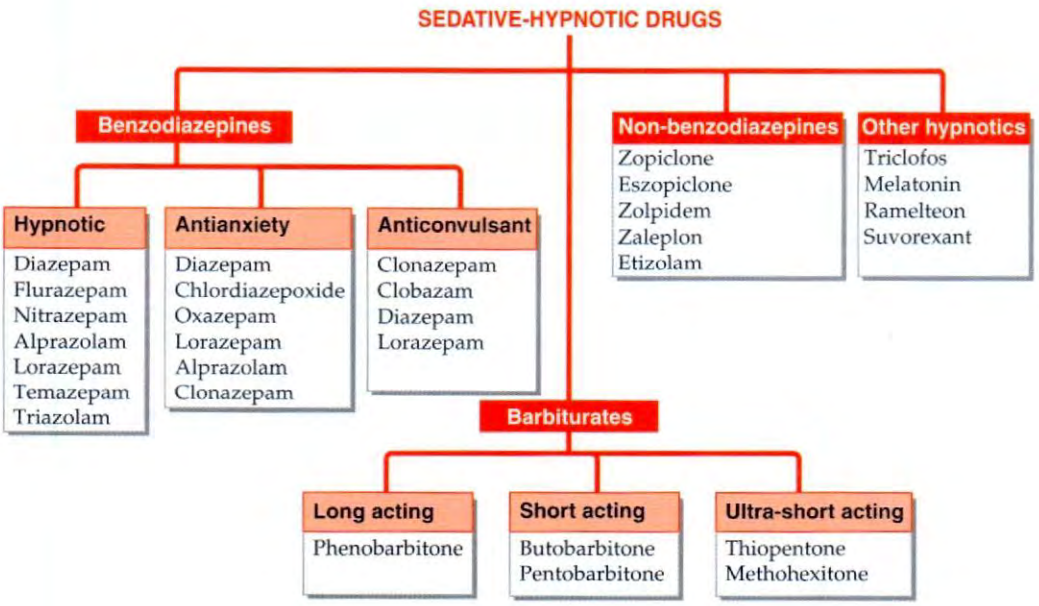


Fig. 29.1: A normal sleep cycle

Stage 4 (cerebral sleep) δ activity predominates in the EEG, K complexes cannot be evoked. Eyes are practically fixed; subjects are difficult to arouse. Night terror may occur at this time. It comprises 10–20% of sleep time.
During stage 2, 3 and 4 heart rate, BP and respiration are steady and muscles are relaxed. Stages 3 and 4 together are called slow wave sleep (SWS).
REM sleep (paradoxical sleep) The EEG has waves of all frequency, K complexes cannot be elicited. There are marked, irregular and darting eye movements; dreams and nightmares occur, which may be recalled if the subject is aroused. Heart rate and BP fluctuate; respiration is irregular. Muscles are fully relaxed, but irregular body movements occur occasionally. Erection occurs in males. About 20–30% of sleep time is spent in REM.

Normally stages 0 to 4 and REM occur in succession over a period of 80–100 min. Then stages 1–4–REM are repeated cyclically.



In addition some antihistaminics (promethazine, diphenhydramine), some neuroleptic/antidepressants (chlorpromazine, amitriptyline), some anticholinergic (hyoscine) and opioids (morphine, pethidine) have significant sedative action, but are not reliable for treatment of insomnia.

BARBITURATES

Barbiturates have been popular hypnotics and sedatives of the last century upto 1960s, but are not used now to promote sleep or to calm patients. However, they are briefly described first because they are the prototype of more or less global CNS depressants.

Barbiturates are substituted derivatives of barbituric acid (malonyl urea). Barbituric acid as such is not a hypnotic but compounds with alkyl or aryl substitution on C5 have this property (*see* phenobarbitone structure on p. 443). Replacement of O with S at C2 yields *thiobarbiturates* which are more lipid-soluble and more potent.

PHARMACOLOGICAL ACTIONS

Barbiturates are general depressants for all excitable cells, more so for the CNS.

1. CNS Barbiturates produce dose-dependent effects:

sedation → sleep → anaesthesia → coma.

Hypnotic dose shortens the time taken to fall asleep and increases sleep duration. Night awakenings are reduced. REM and stage 3, 4 sleep are decreased; REM-NREM sleep cycle is disrupted. The effects on sleep become progressively less marked if the drug is taken every night consecutively. A rebound increase in REM sleep and nightmares is often noted when the drug is discontinued after a few nights of use and it takes several nights for normal pattern to be restored (Fig. 29.2). Hangover (headache, dizziness, distortions of mood, irritability and lethargy) may occur in the morning after a nightly dose.

Sedative dose (smaller dose of a longer acting barbiturate) given at daytime can produce drowsiness, reduction in anxiety and excitability. However, barbiturates do not have selective antianxiety action. They can impair learning, short-term memory and judgement. Euphoria may be experienced by addicts.

Barbiturates have anticonvulsant property. Phenobarbitone has higher anticonvulsant : sedative activity ratio, i.e. it has specific anticonvulsant action independent of general CNS depression (*see* Ch. 30).

Mechanism of action Barbiturates appear to act primarily at the GABA:BZD receptor–Cl^- channel complex (*see* Fig. 29.3) and potentiate GABAergic inhibition by increasing the lifetime of Cl^- channel opening induced by GABA (contrast BZDs which enhance frequency of Cl^- channel opening). They do not bind to the BZD receptor, but bind to another site on the same macromolecular complex to exert the GABA-facilitatory action. The barbiturate site appears to be located on the α or β subunit. At high concentrations, barbiturates directly increase Cl^- conductance (GABA-mimetic action). This is in contrast to BZD action which have only GABA-facilitatory property. Moreover, at high doses barbiturates inhibit Ca^{2+} dependent release of neurotransmitters, depress glutamate induced neuronal depolarization through AMPA receptors (a type of excitatory amino acid receptors) and depress voltage sensitive Na^+ and K^+ channels. A dose-dependent effect on multiple neuronal targets appears to confer barbiturates the ability to produce any grade of CNS depression.

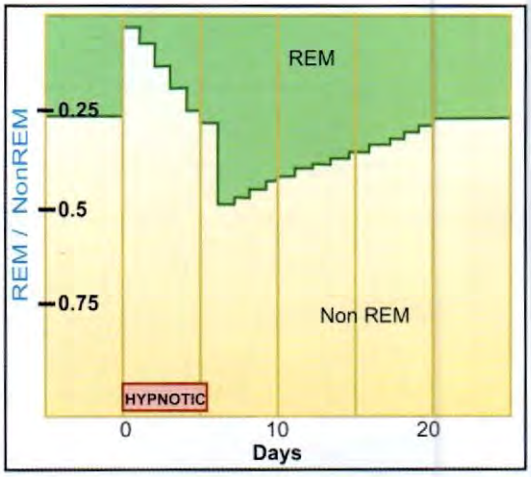


Fig. 29.2: Effect of hypnotic use for 6 consecutive nights on the ratio of REM / Non-REM sleep duration

2. Other actions

At relatively higher doses, barbiturates depress respiration, lower BP, decrease cardiac contractility and heart rate, but reflex tachycardia can occur due to fall in BP. Muscle tone, bowel motility and urine output are also reduced. Toxic does cause respiratory failure and cardiovascular collapse.

PHARMACOKINETICS

Barbiturates are well absorbed from the g.i. tract. They are widely distributed in the body. The rate of entry into CNS is dependent on lipid solubility. Highly-lipid soluble thiopentone has practically instantaneous entry, while less lipid-soluble ones (pentobarbitone) take longer; phenobarbitone enters very slowly. Barbiturates cross placenta and are secreted in milk; can produce effects on the foetus and suckling infant.

Three processes *viz.* redistribution, metabolism and excretion, are involved in termination of action of barbiturates: the relative importance of each varies with the compound. On i.v. injection, the highly lipid soluble compounds (e.g. thiopentone) enter CNS rapidly → produce anaesthesia in < 1 min, and then diffuse back quickly to redistribute to less vascular tissues (muscle, fat). Consciousness is regained in 6-10 min, but ultimate disposal occurs by metabolism (t½ 9 hours).

Intermediate lipid solubility barbiturates are primarily metabolized in the liver by oxidation, dealkylation and conjugation. Their plasma t½ ranges between 12–36 hours.

Barbiturates with low lipid-solubility, in addition to being metabolized, are significantly excreted unchanged in urine. The t½ of phenobarbitone is 80–120 hours. Alkalinization of urine increases ionization and excretion of phenobarbitone.

Barbiturates induce several hepatic microsomal enzymes (CYP3A4/5, CYP2D6, CYP2C8/9, CYP2B6, UGTs) and increase the rate of their own metabolism as well as that of many other drugs.

USES

Except for phenobarbitone in epilepsy (Ch. 30) and thiopentone/methohexitone in anaesthesia (Ch. 27) no other barbiturate is commercially available or used now. As hypnotic and anxiolytic they have been superseded by BZDs. Phenobarbitone 30–60 mg oral OD–TDS; 100–200 mg i.m./i.v. GARDENAL 30, 60 mg tab, 20 mg/5 ml syr; LUMINAL 30 mg tab; PHENOBARBITONE SOD 200 mg /ml inj.

ADVERSE EFFECTS

Hangover was common after the use of barbiturates as hypnotic. Mental confusion, impaired performance and traffic accidents may occur (also *see* Ch. 30).

Tolerance and dependence Both cellular and pharmacokinetic (due to enzyme induction) tolerance develops on repeated use. However, fatal dose is not markedly increased: addicts may present with acute barbiturate intoxication. There is partial cross tolerance with other CNS depressants.

Addiction and dependence occurs, and barbiturates have considerable abuse liability. This is one of the major disadvantages. Withdrawal symptoms are—excitement, hallucinations, delirium, convulsions; deaths have occurred.

Acute barbiturate poisoning Mostly suicidal, sometimes accidental. It is infrequently encountered now due to inavailability of barbiturates. However, the principles of treatment apply to any CNS depressant poisoning.

Manifestations are due to excessive CNS depression—patient is flabby and comatose with shallow and failing respiration, fall in BP and cardiovascular collapse, renal shut down, pulmonary complications, bullous eruptions.

Treatment

1. Gastric lavage; leave a suspension of activated charcoal in the stomach to prevent absorption of the drug from intestines.
2. Supportive measures: such as, patent airway, assisted respiration, oxygen, maintenance of blood volume by fluid infusion and use of vasopressors—dopamine may be preferred for its renal vasodilating action.
3. Alkaline diuresis: with sodium bicarbonate 1 mEq/kg i.v. with or without mannitol is helpful only in the case of long-acting barbiturates which are eliminated primarily by renal excretion.
4. Haemodialysis and haemoperfusion (through a column of activated charcoal or other adsorbants) is highly effective in removing long-acting as well as short-acting barbiturates.

There is no specific antidote for barbiturates.

INTERACTIONS

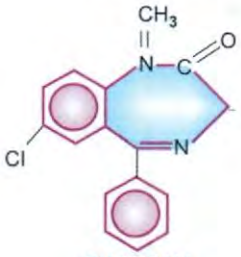
1. Barbiturates induce several CYP iso-enzymes, including glucuronyl transferase, and increase the metabolism of many drugs, thereby reducing their effectiveness—warfarin, steroids (including contraceptives), tolbutamide, griseofulvin, chloramphenicol, theophylline.
2. Additive action with other CNS depressants —alcohol, antihistamines, opioids, etc.

BENZODIAZEPINES (BZDs)

Benzodiazepines (BZDs) are selective CNS depressants which produce sedation, relieve anxiety, facilitate sleep, suppress seizure and reduce muscle tone.

Chlordiazepoxide and diazepam, the first BZDs, were introduced around 1960 as antianxiety drugs. Since then this class has proliferated and has replaced barbiturates and other similar drugs as hypnotic and sedative as well, because—

1. BZDs produce a lower ceiling CNS depression than barbiturates. They have a high therapeutic index. Ingestion of even 20 hypnotic doses does not usually endanger life; there is no loss of consciousness (though amnesia occurs) and patient can be aroused; respiration is mostly not so depressed as to need assistance.



DIAZEPAM

2. Hypnotic doses do not affect respiration or cardiovascular functions. Higher doses produce mild respiratory depression and hypotension which is problematic only in patients with respiratory insufficiency or cardiac/haemodynamic abnormality.

3. BZDs have practically no action on other body systems. Only on i.v. injection the BP falls (fall in BP may be marked in an occasional patient) and cardiac contractility decreases. Fall in BP in case of diazepam and lorazepam is due to reduction in cardiac output while that caused by midazolam is due to decrease in peripheral resistance. The coronary arteries dilate on i.v. injection of diazepam.
4. BZDs cause less distortion of sleep architecture; rebound phenomena on discontinuation after regular use are less marked.
5. BZDs do not alter disposition of other drugs by microsomal enzyme induction.
6. They have lower abuse liability than barbiturates and similar drugs; tolerance is mild, psychological and physical dependence, drug seeking and withdrawal syndrome are less marked.
7. A specific BZD antagonist *flumazenil* is available which can be used in case of poisoning.

CNS actions The overall action of all BZDs is qualitatively similar, but there are prominent differences in selectivity for different facets of action, and in their time-course of action. Different members are used for different purposes. In contrast to barbiturates, they are not general depressants, but exert relatively selective anxiolytic, hypnotic, muscle relaxant and anticonvulsant effects in different measures. Even when apparently anaesthetic dose of diazepam is administered i.v., some degree of awareness is maintained, though because of anterograde amnesia (interference with establishment of memory trace) the patient does not clearly recollect the events on recovery.

Antianxiety: Some BZDs exert relatively selective antianxiety action (*see* Ch. 33) which is probably not dependent on their sedative property. With chronic administration relief of anxiety is maintained, but drowsiness wanes off due to development of tolerance.

Sleep: While there are significant differences among different BZDs, in general, they hasten onset of sleep, reduce intermittent awakening and increase total sleep time (specially in those who have a short sleep span). Time spent in stage 2 is increased while that in stage 3 and 4 is decreased. They tend to shorten REM phase, but more REM cycles may occur, so that effect on total REM sleep is less marked than with barbiturates. Nitrazepam has been shown to actually increase REM sleep. Night terrors and body movements during sleep are reduced and stage shifts to stage 1 and 0 are lessened. Most subjects wake up with a feeling of refreshing sleep. Some degree of tolerance develops to the sleep promoting action of BZDs after repeated nightly use.

Muscle relaxant: BZDs produce centrally mediated skeletal muscle relaxation without impairing voluntary activity (*see* Ch. 25). Clonazepam and diazepam have more marked muscle relaxant property. Very high doses depress neuromuscular transmission.

Anticonvulsant: Clonazepam, diazepam, nitrazepam, lorazepam and flurazepam have more prominent anticonvulsant activity than other BZDs. Diazepan and lorazepam are highly effective for short-term use in status-epilepticus, but their utility in long-term treatment of epilepsy is limited by development of tolerance to the anticonvulsant action.

Given i.v., diazepam (but not others) causes analgesia. In contrast to barbiturates, BZDs do not produce hyperalgesia.

Other actions Diazepam decreases nocturnal gastric secretion and prevents stress ulcers. BZDs do not significantly affect bowel movement.

Short-lasting coronary dilatation is produced by i.v. diazepam.

Site and mechanism of action

Benzodiazepines act preferentially on midbrain ascending reticular formation (which maintains wakefulness) and on limbic system (thought and mental functions). Muscle relaxation is produced by a primary medullary site of action and ataxia is due to action on cerebellum.

BZDs act by enhancing presynaptic/postsynaptic inhibition through a specific BZD receptor which is an integral part of the $GABA_A$

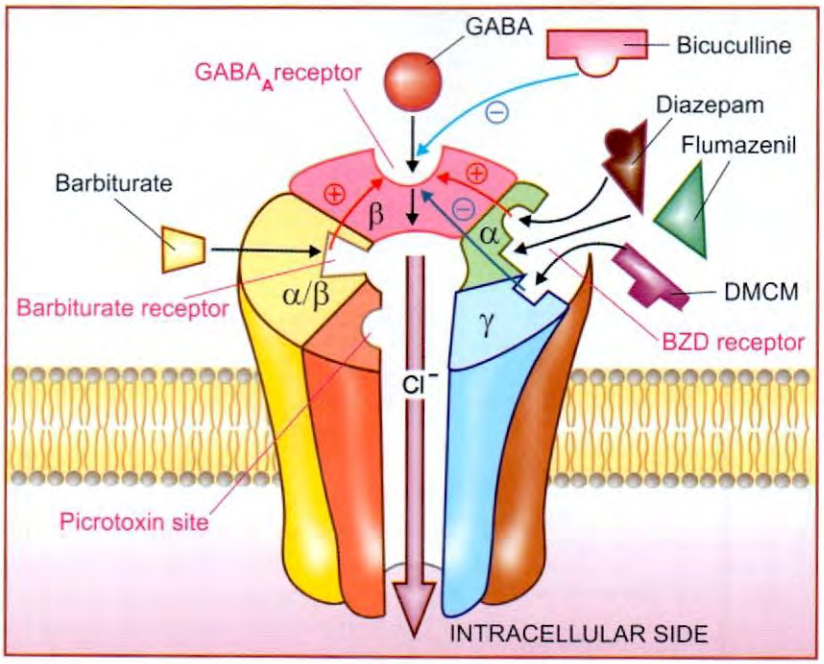


Fig. 29.3: Schematic depiction of GABA$_A$-benzodiazepine receptor-chloride channel complex
The chloride channel is gated by the primary ligand GABA acting on GABA$_A$ receptor located on the β subunit. The benzodiazepine (BZD) receptor located on the interface of α and γ subunits modulates GABA$_A$ receptor in either direction: agonists like diazepam facilitate, while inverse agonists like DMCM hinder GABA mediated Cl$^-$ channel opening, and the BZD antagonist flumazenil blocks the action of both. The barbiturate receptor, located either on α or β subunit also facilitates GABA and is capable of opening Cl$^-$ channel directly as well. Bicuculline blocks GABA$_A$ receptor, while picrotoxin blocks the Cl$^-$ channel directly

receptor–Cl$^-$ channel complex. The subunits of this complex form a pentameric transmembrane anion channel (Fig. 29.3) gated by the primary ligand (GABA), and modulated by secondary ligands which include BZDs. Only the α and β subunits are required for GABA action, and most likely the binding site for GABA is located on the β subunit, while the α/γ subunit interface carrys the BZD binding site. The modulatory BZD receptor increases the frequency of Cl$^-$ channel opening induced by submaximal concentrations of GABA. The BZDs also enhance GABA binding to GABA$_A$ receptor. The GABA$_A$ antagonist bicuculline antagonizes BZD action in a noncompetitive manner. It is noteworthy that the BZDs do not themselves increase Cl$^-$ conductance; have only GABA facilitatory but no GABA mimetic action. This probably explains the lower ceiling CNS depressant effect of BZDs.

The BZD receptor exhibits a considerable degree of constitutive activation. As such, it is capable of fine tuning GABA action in either direction. While the BZD-agonists enhance GABA induced hyperpolarization (due to influx of Cl$^-$ ions), and decrease firing rate of neurones, other compounds called *BZD-inverse agonists* like dimethoxy-ethyl-carbomethoxy-β-carboline (DMCM) inhibit GABA action and are convulsants. The competitive BZD-antagonist flumazenil blocks the sedative action of BZDs as well as the convulsant action of DMCM.

The GABA$_A$-BZD receptor-Cl$^-$ channel complex is composed of five α, β, γ, and in some cases δ, ε, θ or π subunits as well. Several isoforms of α, β and γ subunits have been cloned. The subunit composition of the complex differs at different sites in the brain. Accordingly, there are multiple subtypes of the BZD receptor. The ($\alpha_1 2\ \beta_2 2\ \gamma_2$) pentamer appears to be the most commonly expressed BZD receptor isoform.

Drugs affecting $GABA_A$-receptor gated chloride channel	
• GABA	: Endogenous agonist at $GABA_A$ receptor → promotes Cl^- influx
• Muscimol	: Agonist at $GABA_A$ site
• Bicuculline	: Competitive antagonist at $GABA_A$ receptor
• Picrotoxin	: Blocks Cl^- channel noncompetitively; acts on picrotoxin sensitive site
• Barbiturates	: Agonist at an allosteric site; prolong GABA action; and open Cl^- channel
• Alcohol, Inhalational anaesthetics, Propofol	: Open Cl^- channel directly; allosteric facilitation of GABA
• Benzodiazepines	: Agonist at an allosteric BZD site → facilitate GABA action
• β-Carboline (DMCM)	: Inverse agonist at BZD site → impede GABA action
• Flumazenil	: Competitive antagonist at BZD site

Based on studies conducted in genetically mutated mice, it has been suggested that BZD receptor isoforms containing the α_1 subunit are involved in mediating sedative, hypnotic, and amnesic actions of BZDs, while those containing α_2 subunits mediate anxiolytic and muscle relaxant actions. Diazepam has similar affinity for BZD receptor containing different (α_1 or α_2, or α_3 or α_5) subunits, and has broad spectrum action. Receptor inhomogeneity may provide an explanation for the pharmacological diversity of other BZDs. The newer non-BZD hypnotics zaleplon, Zolpidem, etc. have high affinity for α_1 subunit isoform of BZD receptor and exert selective hypnotic-amnesic effect, but have little antiseizure or muscle relaxant property.

At high concentrations BZDs also potentiate the depressant action of adenosine by blocking its uptake. Certain actions of BZDs are countered by the adenosine antagonist theophylline. Thus, BZDs could be acting through other mechanisms as well.

PHARMACOKINETICS

There are marked pharmacokinetic differences among BZDs, because they differ in lipid-solubility by > 50 fold. These differences are important factors governing their choice for different uses. Oral absorption of some is rapid while that of others is slow. Absorption from i.m. sites is irregular except for lorazepam. Plasma protein binding also varies markedly (flurazepam 10% to diazepam 99%). BZDs are widely distributed in the body. The more lipid soluble members enter brain rapidly and have a two phase plasma concentration decay curve; first due to distribution to other tissues and later due to elimination. A relatively short duration of action is obtained with single dose of a drug that is rapidly redistributed, even though it may have a long elimination t½. Using the elimination t½ alone to predict duration of action may be misleading. However, elimination t½ determines duration of action in case of drugs whose elimination is by far the dominant feature or when the drug is given repeatedly.

Benzodiazepines are metabolized in liver mainly by CYP3A4 and CYP2C19 to dealkylated and hydroxylated metabolites, some of which may be active. The biological effect half-life of drugs with active metabolites may be much longer than the plasma t½ of the administered compound. The phase I metabolites and certain BZDs themselves are conjugated with glucuronic acid. Some BZDs (e.g. diazepam) undergo enterohepatic circulation. BZDs and their phase I metabolites are excreted in urine as glucuronide conjugates. BZDs cross placenta and are secreted in milk.

Drugs with a long t½ or those which generate active metabolites cumulate on nightly use; their action may then extend into the next day. Some features of BZDs used as hypnotic are given in Table 29.1.

HYPNOTIC BENZODIAZEPINES

The salient features of BZDs that are used in the treatment of insomnia are summarized here.

1. Flurazepam It produces an active metabolite which has a long t½. Residual effects are likely next morning; cumulation occurs

TABLE 29.1: Some pharmacokinetic and clinical features of benzodiazepines used as hypnotics

Drug	t½ (hr)*	Redistribution$	Hypnotic dose (mg)	Clinical indications
I. LONG ACTING				
Flurazepam	50–100	–	15–30	Chronic insomnia, short-term insomnia with anxiety; Frequent nocturnal awakening; Night before surgery
Diazepam	30–60	+	5–10	
Nitrazepam	30	±	5–10	
Lorazepam	10–20	–	1–2	
II. SHORT ACTING				
Alprazolam	12	+	0.25–0.5	Individuals who react unfavourably to unfamiliar surroundings or unusual timings of sleep. Sleep onset difficulties.
Temazepam	8–12	+	10–20	
Triazolam	1–3	±	0.125–0.25	

* t½ of elimination phase, including that of active metabolite
$ + indicates that redistribution contributes to termination of action of single dose

on daily ingestion peaking after 3–5 days. It is suitable for patients who have frequent nocturnal awakenings, but not for the elderly due to risk of next day sedation, ataxia and mental confusion.
NINDRAL, FLURAZ 15 mg cap.

2. Diazepam It is the oldest and all purpose BZD, used as anxiolytic, hypnotic, muscle relaxant, premedicant, anaesthetic and for emergency control of seizures due to its broad spectrum activity. Because of rapid oral absorption, it can be used for sleep onset difficulty as well as for sleep maintenance. It generates active metabolites (desmethyl-diazepam, oxazepam). On occasional use it is free of residual effects. With regular use accumulation occurs and prolonged anxiolytic effect may be obtained. It is less likely to cause rebound insomnia on discontinuation of chronic use. Withdrawal phenomena are mild.
VALIUM 2, 5, 10 mg tab., 10 mg/2 ml inj., CALMPOSE 2.5, 5, 10 mg tab, 2 mg/5 ml syr, 10 mg/2 ml inj, PLACIDOX 2, 5, 10 mg tab, 10 mg/2 ml inj.

3. Nitrazepam Dose to dose equipotent as diazepam. Accumulation and residual effects can be avoided only if ingestion is occasional. Good for patients with frequent nocturnal awakenings, when some day time sedation is acceptable.
SEDAMON, HYPNOTEX, NITRAVET 5 mg tab., 5, 10 mg cap.

4. Lorazepam This BZD is absorbed slowly and has prominent sedative-anxiolytic action, because of which it is mainly used to treat anxiety (*see* p. 494). However, it is also employed to promote sleep in anxious and tense patients. Since no active metabolite is produced, cumulative residual drowsiness is not a problem.
ATIVAN, LARPOSE, CALMESE 1, 2 mg tabs.

5. Alprazolam The primary indication of this potent and intermediate duration of action BZD is anxiety disorder (*see* Ch. 33), but it is also being employed as night-time hypnotic due to rapid oral absorption. Its active metabolite has a short half-life. As such, there are few residual effects the next day. Discontinuation after regular use has produced relatively marked withdrawal phenomena.

6. Temazepam It is an intermediate duration BZD. Absorption is slow when taken as tablet but fast when taken in soft gelatin capsule. Good for sleep onset difficulty, free of residual effects because active metabolite has short t½.

7. Triazolam A very potent BZD who's peak effect occurs in < 1 hour; good for sleep induction but poor for maintaining it due to short duration of action. Patient may wake up early in the morning and feel anxious. This may be a withdrawal phenomenon. Rebound insomnia may occur when it is discontinued after a few nights of use. It does not accumulate on repeated nightly use and no residual effects are noted in the morning. However, higher doses can alter sleep architecture, produce anterograde amnesia and anxiety the following day. Some cases of paranoia and other psychiatric disturbances have been noted. For this reason, it has been withdrawn from U.K., but is employed in other countries for elderly patients, shift workers, travellers, etc.

8. Midazolam Extremely rapid absorption—peak in 20 min. It can cause problems in the elderly (ataxia, blackouts), and is more liable for abuse. Therefore, it is not

available now for oral use as a hypnotic. It is mainly used as an i.m. premedicant or an i.v. anaesthetic (*see* p. 411).

ADVERSE EFFECTS

Benzodiazepines are relatively safe drugs. Side effects of hypnotic doses are dizziness, vertigo, ataxia, disorientation, amnesia, prolongation of reaction time—impairment of psychomotor skills (should not drive). Sleep walking, sleep driving and other abnormal sleep behaviours with no memory of these events has been recognized as a possible hazard. Hangover is less common, but may be noted if larger doses are taken, especially of longer acting drugs. Weakness, blurring of vision, dry mouth and urinary incontinence are sometimes complained. Older individuals are more susceptible to psychomotor side effects. Like any hypnotic, BZDs can aggravate sleep apnoea.

Paradoxical stimulation, irritability and sweating may occur in an occasional patient, especially with flurazepam. Some patients, particularly those taking nitrazepam or flurazepam, may experience increase in nightmares and behavioural alterations.

Tolerance to the sedative effects develops gradually, but there is little tendency to increase the dose. Cross tolerance to alcohol and other CNS depressants occurs.

The dependence producing liability of BZDs is low. They are weak reinforcers (less pleasurable) and seldom abused alone. Drug abusers find them rather bland and prefer other CNS depressants. Withdrawal syndrome is generally mild; may be more intense in case of ultrarapid elimination drugs. Anxiety, insomnia, restlessness, malaise, loss of appetite, bad dreams are all that occurs in most cases. Agitation, panic reaction, tremors and delirium are occasional; convulsions are rare. Drug seeking behaviour is not prominent.

An earlier report of increased birth defects on use of diazepam during pregnancy has been disputed. Administration during labour may cause flaccidity and respiratory depression in the neonate.

INTERACTIONS

BZDs synergise with alcohol and other CNS depressants leading to excessive impairment. Concurrent use with sod. valproate has provoked psychotic symptoms.

Drug interactions due to displacement from protein binding or microsomal enzyme induction are not significant.

Since CYP 3A4 isoenzyme plays important role in metabolism of several BZDs, their action can be prolonged by CYP 3A4 inhibitors like ketoconazole, erythromycin and others. Cimetidine, isoniazid and oral contraceptives also retard BZD metabolism.

NON-BENZODIAZEPINE HYPNOTICS

This lately developed group of hypnotics are chemically different from BZDs, but act as agonists on a specific subset of BZD receptors. Their action is competitively antagonized by the BZD antagonist flumazenil, which can be used to treat their overdose toxicity. The non-BZD hypnotics act selectively on α_1 subunit containing BZD receptors and produce hypnotic-amnesic action with only weak antianxiety, muscle relaxant and anticonvulsant effects. They have lower abuse potential than hypnotic BZDs. Given their shorter duration of action, they are being preferred over BZDs for the treatment of insomnia.

Zopiclone This is the first of the non-BZD hypnotics, which acts as an agonist at a subtype of BZD receptor involved in the hypnotic action. The effect on sleep resemble those of BZDs, but it does not alter REM sleep and tends to prolong stages 3 and 4. It is reported not to disturb sleep architecture, but some degree of next morning impairment can occur. Zopiclone has been used to wean off insomniacs taking regular BZD medication. It is metabolized mainly by CYP3A4 with a t½ of 5–6 hours. Dose reduction is needed in the elderly, hepatic impairment and in patients taking CYP3A4 inhibitors.

Zopiclone is indicated for short term (< 2 weeks) treatment of insomnia. Side effects are

metallic or bitter after-taste, impaired judgement and alertness, psychological disturbances, dry mouth and milder dependence. Safety in overdose is similar to BZDs.

ZOPITRAN, ZOPICON, ZOLIUM, 7.5 mg tab, one tab at bedtime for not more than 2–4 weeks (elderly 3.75 mg).

Eszopiclone The active (S) enantiomer of zopiclone has recently been marketed. It increases total sleep time mainly by prolonging stage 2 with minimal effect on sleep architecture. No active metabolite is produced, and t½ is 6 hours. It produces little tolerance and dependence, and is considered suitable for treatment of short-term as well as chronic insomnia.

Dose: 2–3 mg at bed time, elderly and liver disease patient 1 mg:

FULNITE, ZOLNITE 1 mg, 2 mg tabs.

Zolpidem This structurally non-BZD, but selective BZD receptor agonist has pronounced hypnotic effect. Sleep latency is shortened, sleep duration is prolonged in insomniacs, but anticonvulsant, muscle relaxant and antianxiety effects are not evident. The relatively selective hypnotic effect of zolpidem has been ascribed to its preferential action on α_1 subunit containing BZD receptor. Its advantages are: relative lack of effect on slow wave sleep; minimal residual day time sedation or fading of hypnotic action on repeated nightly use; no/little rebound insomnia on discontinuation; low abuse potential combined with safety in overdose like BZDs.

Zolpidem is nearly completely metabolized in liver (t½ 2 hr), and has short duration of action. It is indicated for short-term (1–2 weeks) use in sleep onset insomnia as well as for intermittent awakenings. Because the plasma t½ is short, next day sedation is minimal, but morning sedation or prolongation of reaction-time can occur if it is taken late at night. Side effects are few. Even large doses do not markedly depress respiration. Currently, it is one of the most commonly prescribed hypnotics.

Dose: 5–10 mg (max 20 mg) at bedtime; ½ dose in elderly and liver disease patients.

NITREST, ZOLDEM, DEM 5, 10 mg tabs.

Zaleplon This is the shortest acting of the newer non-BZD hypnotics that selectively act on a subset of BZD receptors containing the α_1 subunit which appear to mediate the hypnotic action. It is rapidly absorbed; oral bioavailability is ~30% due to first pass metabolism; is rapidly cleared by hepatic metabolism with a t½ of 1 hour. No active metabolite is produced. As such, it is effective only in sleep-onset insomnia; does not prolong total sleep time or alter NREM-REM cycles, or reduce the number of awakenings. Because of brevity of action, it can be taken late at night (> 4 hour before waking time) without causing morning sedation. Surprisingly, despite very short action, no day-time anxiety or rebound insomnia has been observed with low doses, and hypnotic effect does not fade on nightly use. However, its use should be limited to 1–2 weeks. The hypnotic efficacy of zaleplon is rated similar to zolpidem. Like the latter, effect on sleep stages and REM sleep are less than that of BZDs. Tolerance and dependence is unusual.

Dose: 5–10 mg (max 20 mg) at bed time.

ZAPLON, ZALEP, ZASO 5, 10 mg tabs.

Etizolam This BZD analogue is a thienotriazolodiazepine derivative, and a BZD receptor agonist which produces the full range of BZD actions. Thus, it has anxiolytic, hypnotic, anticonvulsant and muscle relaxant properties. Actions of etizolam are antagonized by flumazenil which can be used to counteract overdosage. It is absorbed rapidly, peak level is produced in 0.5–2 hours, and it is metabolized by oxidation with a t½ of 3.5 hours.

Chronic intake of etizolam produces tolerance and dependence, and it carries abuse potential, because of which it is a controlled drug in many countries. Etizolam is indicated for the short-term management of anxiety, panic and sleep disorder, but does not appear to offer any specific advantage over the established BZDs.

Dose: For anxiety 0.5–1 mg BD; for insomnia 1–2 mg at bed time.

ETIZOLA, ETILAM, ETIREST 0.5, 1.0 mg tabs.

USES

Currently, BZDs are one of the most frequently prescribed drugs. They have also been combined with many other categories of drugs with a view to improve efficacy by relieving attendant anxiety.

1. As hypnotic A hypnotic should not be casually prescribed for every case of insomnia.

Understanding the pattern and cause of insomnia in the patient is important, and use of a variety of other measures can avoid unnecessary hypnotic medication. When indicated, BZDs or the newer non-BZDs like eszopiclone, zolpidem, zaleplon are the hypnotic of choice. A wide range of compounds are available to suit specific requirements. Some important points are outlined below:

- A hypnotic may be used to shorten sleep latency, to reduce nocturnal awakenings, or to provide anxiolytic effect the next day when insomnia is accompanied with marked element of anxiety.
- In the use of hypnotics, consideration must be given to onset and duration of action of the drug. The most suitable pharmacokinetic profile drug should be chosen for a given case.
- Next morning impairment is largely related to the dose and pharmacokinetic profile of the drug. The next day effects are either due to prolonged sedation (longer acting drugs) or rebound anxiety (shorter acting drugs).
- Any hypnotic (probably except zolpidem-like drugs) becomes ineffective after regular use for a few days; may actually be harmful.
- Though effect of the drug on EEG stages of sleep, including REM sleep, could be physiologically relevant, most important is the subject's own assessment of having slept restfully and waking up feeling fresh with no impairment the following day. The subjective impression that quality of sleep was poor is the major criterion of insomnia.
- Insomnia arises under a variety of circumstances. It could be a long-term (months-years), short-term (weeks) or transient (a day or two, mostly situational) problem.

Chronic insomnia (> 3 weeks) Uncertainty exists about the value of hypnotics in this situation. The patient may have a personality disorder, but often there is no specific stress factor. He may have used hypnotics for long periods or may be alcoholic or have some somatic disease, e.g. gastroesophageal reflux, pain, COPD, etc. which interfere with sleep. Measures like aerobic exercise, training at mental relaxation, avoiding anxiety about past/future performance while in bed, attempting sleep when sleepiness is maximum, avoiding napping at day-time, maintaining regular sleep-wake timings and other sleep-hygiene measures, coffee/alcohol restriction, treatment of concurrent somatic illness, psychotherapy and controlled sleep curtailment may succeed. Good nightly sleep improves the quality of day-time wakefulness. Patients of obstructive sleep apnoea have poor sleep and feel sleepy during the day. All hypnotics aggravate sleep apnoea and are contraindicated.

In selected cases of chronic insomnia intermittent use of a hypnotic, say once every 3 days, may be tried. Risk of tolerance and abuse are maximum among chronic insomniacs. A slowly eliminated drug is preferable because rebound insomnia and withdrawal symptoms are least marked with such drugs.

Short-term insomnia (3–21 days) Emotional problem (occupational stress, bereavement) and physical illness are the usual causes. Patient may have induction difficulty or may be waking up early. Cautious use of low doses of an appropriate drug for the type of sleep disturbance may be made. Generally a hypnotic, free of residual effects should be selected, but when anxiety is a dominant feature, a BZD whose action extends into the next day may be better. Short acting drugs are preferable in the elderly. Intermittent hypnotic use should be limited to 2–3 weeks.

Transient insomnia (1–3 days) Due to alterations in the circumstances of sleep, e.g. unusual noise, on an overnight train, new place, unusual pattern of work, shift workers, intercontinental travel–jetlag, etc. A rapidly eliminated hypnotic or one with marked distribution is to be preferred to avoid residual effects the next morning. Popularity of the newer non-BZD hypnotics has increased due to their rapid onset of action, minimal next-day impairment and absence of cumulation on repeated nightly

use as well as rebound insomnia on stopping. However, night before surgery—a long acting drug is better.

2. Other uses

- As anxiolytic and for day-time sedation (*see* Ch. 33).
- As anticonvulsant, especially emergency control of status epilepticus, febrile convulsions, tetanus, etc. (*see* Ch. 30).
- As centrally acting muscle relaxant for muscle spasms and spasticity (*see* Ch. 25).
- For preanaesthetic medication, i.v. anaesthesia and conscious sedation (*see* Ch. 27).
- Before ECT, electrical cardioversion of arrhythmias, cardiac catheterization, endoscopies, in obstetrics and many minor procedures—diazepam i.v. has gained popularity because of its calming-amnesic-analgesic and muscle relaxant properties and relative safety.
- Alcohol withdrawal in dependent subjects.
- Along with analgesics, NSAIDs, spasmolytics, antiulcer and as adjuvants to treat 'gas' or nonspecific dyspeptic symptoms.

Fixed dose combinations of sedative/hypnotic/anxiolytic drugs with analgesic-antipyretics has been banned in India.

BENZODIAZEPINE ANTAGONIST

Flumazenil It is a BZD analogue which has little intrinsic activity (practically no effect on normal subjects), but competes with BZD agonists as well as inverse agonists for the BZD receptor and reverses their depressant or stimulant effects respectively. Flumazenil abolishes the hypnogenic, psychomotor, cognitive and EEG effects of BZDs.

Flumazenil is absorbed orally, but it is not used orally. Injected i.v., its action starts in seconds and lasts for 1–2 hours; elimination t½ is 1 hr, due to rapid metabolism.

Uses

1. *To reverse BZD anaesthesia* Patients anaesthetized/sedated with a BZD wakeup, get oriented and regain motor control within 1 min of an i.v. injection of 0.3–1 mg of flumazenil. Resedation generally occurs within 1 hour (more with diazepam than with midazolam): supplemental doses of flumazenil may be given. This may allow early discharge of patients after diagnostic procedures and facilitates postanaesthetic management.

2. *BZD overdose* Majority of patients of BZD overdose require only supportive measures like patent airway, maintenance of BP, cardiac and renal function (by fluid transfusion, etc.). In addition, flumazenil 0.2 mg/min may be injected i.v. till the patient regains consciousness. Practically all patients intoxicated with a BZD alone respond within 5 min (maximum total dose 1 mg). However, reversal of respiratory depression is incomplete. Flumazenil blocks the hypnotic effect of zolpidem-like non-BZDs as well. In mixed CNS depressant poisoning, whatever sedation is not abolished by 5 mg of flumazenil should be taken to be due to a non-BZD/non-Zolpidem-like depressant. However, administration of flumazenil may be risky in mixed overdosage with a BZD + a tricyclic antidepressant. It can also be hazardous in BZD-dependent subjects by precipitating severe withdrawal. Thus, use of flumazenil in BZD overdosage requires great caution.

Adverse effects Flumazenil is safe and well tolerated.

Side effects noted during use of flumazenil as a BZD-antagonist are—agitation, discomfort, fearfulness, anxiety, coldness and withdrawal seizures.

ANEXATE 0.5 mg in 5 ml amp.

Triclofos It is an old CNS depressant very similar to chloral hydrate but does not have the acrid odour and burning taste of the latter. Gastric irritation and abdominal side effects are milder. Like chloral hydrate, it is rapidly hydrolysed to trichloroethanol, which is the active metabolite of both. Triclofos is a fast-acting hypnotic; acts in 30 min, action lasts 6–8 hours. Though obsolete, it is some times used to sedate children in distress, and rarely to induce sleep in adults.

Dose: Adult 1–2 g at bed time; child aged 5–10 years 250–500 mg or 15–25 mg/kg.

TRICLORYL, PEDICLORYL 500 mg/5 ml oral soln., 30, 60 ml bottle.

Melatonin It is the principal hormone of the pineal gland secreted at night and has been found to play an important role in entraining (synchronizing) the sleep-wakefulness cycle with the circadian rhythm. Two subtypes of melatonin receptor MT_1 and MT_2 have been identified in the brain. Both are GPCRs and are believed to carry out the function of facilitating sleep onset and fixing its timing in relation to the circadian clock. Though high doses (80 mg) of melatonin administered orally can induce sleep, low doses (2–10 mg) do not depress the CNS, but probably increase the propensity of falling asleep. Started before the flight it has been shown to reduce jet-lag symptoms and to hasten reentrainment with day-night cycle of the new place in intercontinental travellers. Beneficial effects in shift workers and in individuals with delayed sleep phase syndrome have also been reported. Elderly insomniacs have reported subjective improvement in sleep quality. However, melatonin is not a dependable hypnotic; especially in non-elderly insomniacs. Use may therefore be restricted to treatment of jet-lag, shift workers and elderly insomniacs.

Since melatonin secretion declines with age, it has been argued that melatonin supplementation might retard ageing. Though there is no proof of benefit, melatonin (2–5 mg/day) is being consumed as a health food. In India it is marketed as a remedy for disturbed biorhythms and sleep disorders.

MELOSET 3 mg tab, ZYTONIN, ETERNEX melatonin 3 mg + pyridoxine 10 mg tab; one tab at evening daily.

Ramelteon It is a MT_1, MT_2 melatonin receptor agonist introduced as a new class of hypnotic for sleep onset insomnia, that does not alter GABAergic neurotransmission or produce the usual BZD-like side effects. Administered in a dose of 8 mg ½ hour before going to bed, it is shown to hasten sleep onset as well as increase sleep duration, without causing next morning sedation or impairment.

In clinical trial on chronic insomnia patients, continuous nightly treatment with ramelteon maintained its effect to shorten sleep latency and was found to be free of rebound phenomena/withdrawal syndrome on stoppage. No dependence producing potential has been noted so far. It is rapidly absorbed orally, undergoes extensive first pass metabolism in liver by CYP isoenzymes, so that bioavailability is low and elimination t½ is 1–3 hours. Fluvoxamine, ciprofloxacin and fluconazole can inhibit ramelteon metabolism and raise its blood levels, while rifampicin lowers it by inducing its degradation. Side effects are fatigue, sleepiness, and dizziness.

Ramelteon appears to be a promising novel hypnotic, provided its efficacy is established.

ROZEREM, RAMITAX 8 mg tab: 1 tab 1/2 hour before going to bed.

Suvorexant It is the first member of a novel class of insomnia drugs—'dual orexin receptor antagonists' (DORAs). Orexins are neuropeptides found in lateral hypothalamus which promote wakefulness by acting on OX1R and OX2R subtypes of orexin receptors. Observations that orexin levels are high during day time and low at night, and that narcolepsy (episodes of sudden sleep) is associated with loss of orexin neurones, support this role of orexin. Suvorexant blocks both OX1R and OX2R.

In clinical trials, suvorexant has been found to hasten sleep onset, help sleep maintenance and increase total sleep time. With low dose (10 mg) the next-day residual effects were not detected, but higher doses reduced subjective alertness and prolonged reaction time. The dose-related safety concerns expressed by the US-FDA are day-time somnolence, impaired driving, unconscious night-time behaviours (talking in sleep, dream-enacting episodes, sleep walking, weakness in bed and feeling immobilized), narcolepsy-like symptoms and suicidal ideation. However, compared to zolpidem, suvorexant (10 mg) produced minimal neurophysiological disturbances.

Suvorexant is absorbed in 1–2 hours, metabolized mainly by CYP3A4 with t½ of 12 hours, and excreted in faeces. Inhibitors of CYP3A4 may increase its levels producing next-day effects. In the absence of head-to-head comparative studies, the status of suvorexant in relation to other hypnotics is not yet clear. However, it appears not to cause amnesia or ataxia and to have low potential for producing addiction or dependence. It is considered suitable for continuous long-term use with no rebound insomnia on stopping. Thus, it may offer sustained benefit for patients with chronic insomnia. However, elderly patients are more prone to suffer adverse effects which are somnolence, muscle weakness, abnormal dreams and headache. Patients with depression may worsen.

Dose: 10 mg half hour before bed time, higher dose only when lower dose is well tolerated. Internationally marketed as BELSOMRA 5, 10, 15, 20 mg tabs.

☞ PROBLEM DIRECTED STUDY

29.1 A 70-year-old man consults his family physician for the problem of failing to fall asleep occasionally (3–4 times in a month) for the past few months. He usually sleeps well and has a 6–7 hour sleep duration. However, on certain nights he keeps lying in bed for 2–3 hours before getting sleep. Such episodes are unpredictable, and he cannot relate them to any disturbance, anxiety, worry or physical illness. He has tried relaxing, getting up and walking around or reading, but nothing helps. As a result, next day he feels lethargic, impaired, unable to concentrate and has poor creativity. He requests a sleeping pill that he can take occasionally when he fails to fall asleep.

(a) Can he be prescribed a hypnotic for occasional use? If so, which drug would be suitable for late night intake without next morning sedation?

(see Appendix-1 for solution)

Chapter 30 Antiepileptic Drugs

Epilepsies These are a group of disorders of the CNS characterized by paroxysmal cerebral dysrhythmia, manifesting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic body movements (convulsions), sensory or psychiatric phenomena. These episodes are unpredictable and their frequency is highly variable. Epilepsy has a focal origin in the brain, manifestations depend on the site of the focus, regions into which the discharges spread and postictal depression of these regions. Recognised from the dawn of history as 'disease of lightening', it was correctly described by JH Jackson little over a century ago. Epilepsies have been classified variously; major types are described below.

I. Generalised seizures

They have a diffuse origin involving both hemispheres of the brain; manifestations and EEG abnormalities are bilateral.

1. *Generalised tonic-clonic seizures* (GTCS, major epilepsy, grand mal): lasts 1–2 min.
The usual sequence is aura—cry—unconsciousness and patient falls—tonic spasm of all body muscles—clonic jerking followed by prolonged sleep and depression of all CNS functions.

2. *Absence seizures* (minor epilepsy, petit mal): prevalent in children, lasts about 1/2 min.

No or only momentary loss of consciousness, no fall, patient apparently freezes and stares in one direction, no muscular component or minimal bilateral jerking or blinking of eyes, EEG shows characteristic 3 cycles per second spike and wave pattern. Multiple episodes may occur each day. Seizures may remit spontaneously in adolescence.

3. *Atonic seizures* (Akinetic epilepsy): Brief loss of consciousness with relaxation of all muscles due to excessive inhibitory discharges. Patient may fall.

4. *Myoclonic seizures* Shock-like momentary contraction of muscles of a limb or the whole body. Myoclonic jerking may accompany any type of generalised or partial seizures.

5. *Infantile spasms (Hypsarrhythmia)* Seen in infants. Probably not a form of epilepsy. Intermittent muscle spasm and progressive mental deterioration. Diffuse changes in the interseizure EEG are noted.

II. Partial seizures

They have a unilateral localized origin in the brain, but may spread to small or large area, or to the whole brain. Focal origin may be evident clinically, or may be detected in the EEG.

1. *Simple partial seizures* (SPS): There is sudden onset unilateral clonic jerking of a group of muscles or a limb lasting 30–90 sec, or localized sensory disturbances such as pin pricks, visual/auditory hallucinations, etc. depending on the area of the cortex involved. The patient remains conscious and aware of the attack.

2. *Complex partial seizures* (CPS, temporal lobe epilepsy, psychomotor): attacks of bizarre and confused behaviour, dream-like state and purposeless movements, or even walking unaware, emotional changes lasting 1–2 min along with impairment of consciousness. The patient has no recollection of the attack. An aura often precedes. The seizure focus is located in the temporal lobe.

3. *Simple partial or complex partial seizures secondarily generalized* The partial seizure occurs first and evolves into generalized tonic-clonic seizures with loss of consciousness.

Most of the cases of epilepsy are primary (idiopathic), some may be secondary to trauma/surgery on the head, intracranial tumour,

tuberculoma, cysticercosis, cerebral ischaemia, etc. Treatment is symptomatic, depends mostly on the seizure type, but not on the etiology of seizure or whether it is primary or secondary.

Experimental models These models for testing antiepileptic drugs have also shed light on the etiopathogenesis of epilepsy.

1. *Maximal electroshock seizures* Brief high intensity shock is applied to the head of a rodent (just as in ECT): produces tonic flexion—tonic extension—clonic convulsions. The tonic phase (especially extensor) is selectively abolished by drugs effective in GTCS and complex partial seizures. Activity in this model represents action on spread of seizure discharge.

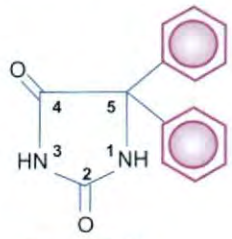
2. *Pentylenetetrazol (PTZ) clonic seizures* Injection of PTZ in rats or mice produces clonic convulsions which are prevented by drugs effective in absence and myoclonic seizures. Activity in this model represents action on seizure focus itself.

3. *Chronic focal seizures* Produced by application of alumina cream on the motor cortex of monkey.

4. *Kindled seizures* Brief bursts of weak electrical impulses are applied to the brain (especially amygdala) intermittently over days. After-discharges increase progressively and tonic-clonic seizures are produced after 10–15 shocks. With time spontaneous seizures set in, usually after >100 shocks. This indicates that seizures have a self perpetuating and reinforcing effect: more neuronal circuits are facilitated and recruited in the seizure process. Kindling is probably involved in the genesis of complex partial seizures and GTCS.

Phenytoin (Diphenylhydantoin)

It was synthesized in 1908 as a barbiturate analogue, but shelved due to poor sedative property. Its anticonvulsant activity was specifically tested in 1938 in the newly developed electroshock seizure model, and till recently it was a major antiepileptic drug.



PHENYTOIN

Phenytoin is not a global CNS depressant; only mild sedation occurs at therapeutic doses. The most prominent action is abolition of tonic phase of maximal electroshock seizures, with no effect on or prolongation of clonic phase. It limits spread of seizure activity. Threshold for PTZ convulsions is not raised.

Mechanism of action Phenytoin prevents repetitive detonation of normal brain cells. This

ANTIEPILEPTIC DRUGS

Barbiturate	Hydantoin	Succinimide	Benzodiazepines	Newer drugs
Phenobarbitone	Phenytoin Fosphenytoin	Ethosuximide	Clonazepam Diazepam Lorazepam Clobazam	Topiramate Levetiracetam Zonisamide Vigabatrin Tiagabine Lacosamide

Deoxybarbiturate	Iminostilbene	Aliphatic carboxylic acid	Phenyltriazine	Cyclic GABA analogues
Primidone	Carbamazepine Oxcarbazepine Eslicarbazepine	Valproate sod (Valproic acid) Divalproex	Lamotrigine	Gabapentin Pregabalin

Perampanel, retigabine, stiripentol, rufinamide and few other newer antiseizure drugs have been introduced in some countries as second line/add-on drugs for refractory partial seizures.

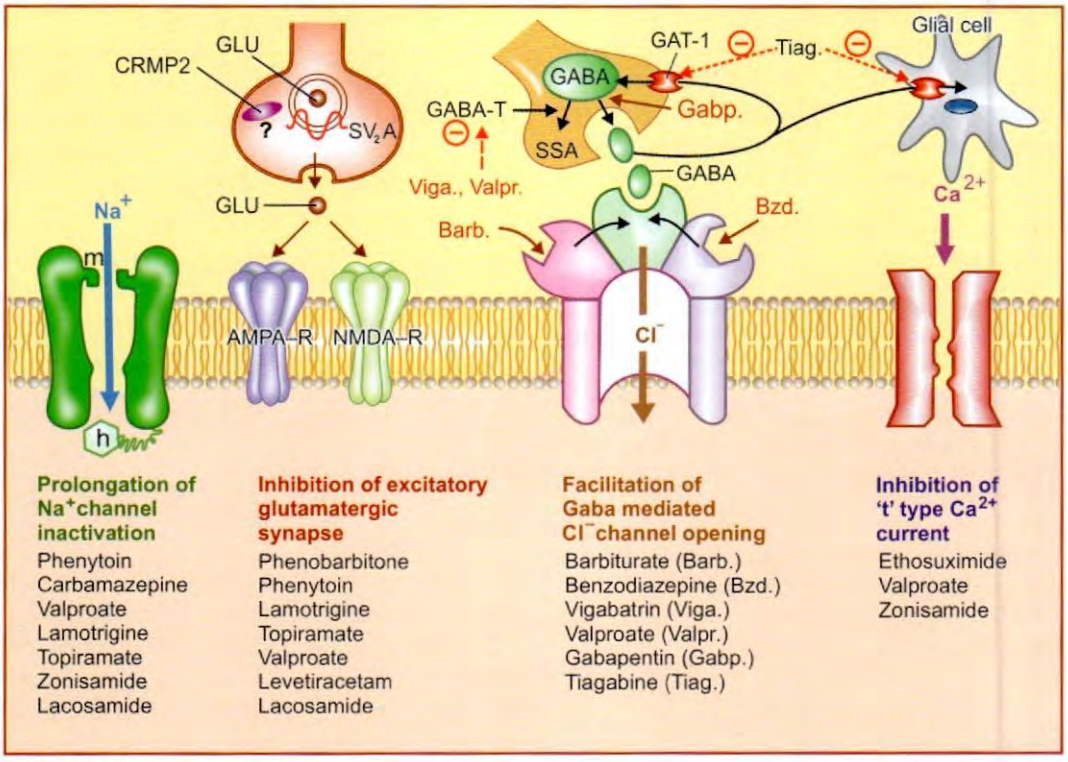


Fig. 30.1: Major mechanisms of anticonvulsant action
m—Activation gate; h—Inactivation gate; GABA-T—GABA transaminase; SSA—Succinic semialdehyde; GAT-1—GABA transporter; GLU—Glutamate; SV_2A—Synaptic vesicular protein 2A; CRMP2—collapsin-response mediator protein; NMDA-R—N-methyl D-aspartate receptor; AMPA-R—α aminohydroxy methyl isoxazole propionic acid receptor

is achieved by prolonging the inactivated state of voltage sensitive neuronal Na^+ channel (Fig. 30.1) that governs the refractory period of the neurone. As a result high frequency discharges are inhibited with little effect on normal low frequency discharges. This effect has been noted at therapeutic concentration of phenytoin. It also depresses presynaptic release of glutamate (excitatory transmitter), facilitates GABA (inhibitory transmitter) release and reduces Ca^{2+} influx. However, these actions require higher concentration and their contribution to the therapeutic response is uncertain. Intracellular accumulation of Na^+ that occurs during repetitive firing is also prevented.

Therapeutic concentrations of phenytoin have no effect on resting membrane potential: normal synaptic transmission is not impaired. Phenytoin, in contrast to phenobarbitone and valproate, does not interfere with kindling. Its ability to selectively suppress high frequency firing confers efficacy in trigeminal neuralgia and cardiac arrhythmias as well.

Pharmacokinetics Absorption of phenytoin by oral route is slow, mainly because of its poor aqueous solubility. Bioavailability of different market preparations may differ. Phenytoin is metabolized in liver by hydroxylation involving CYP2C9 and 2C19 as well as by glucuronide conjugation. The kinetics of metabolism is *capacity limited*; changes from first order to zero order over the therapeutic range. As a result small increments in dose produce disproportionately high plasma concentrations. The t½ (12–24 hours at therapeutic levels), progressively increases (upto 60 hr) when plasma concentration rises above 10 µg/ml because metabolizing enzymes get saturated. Monitoring of plasma concentration is very helpful in adjusting dosage.

Adverse effects After prolonged use numerous side effects are produced at therapeutic plasma concentration:

- Gum hypertrophy: Commonest (20% incidence), more in younger patients. It is due to overgrowth of gingival collagen fibres. This can be minimized by maintaining oral hygiene.
- Hirsutism, coarsening of facial features (troublesome in young girls), acne.
- Hypersensitivity reactions are—rashes, DLE, lymphadenopathy; neutropenia is rare but requires discontinuation of therapy.
- Megaloblastic anaemia and osteomalacia can occur on long term use due to interference with folate absorption and vit. D activation respectively.
- Administered during pregnancy, phenytoin can produce *'foetal hydantoin syndrome'* (hypoplastic phalanges, cleft palate, harelip, microcephaly), which is probably caused by its arene-oxide metabolite.

Over dose toxicity due to higher plasma concentration of phenytoin produces:

(a) Cerebellar and vestibular manifestations: ataxia, vertigo, diplopia, nystagmus.
(b) Drowsiness, behavioural alterations, mental confusion, hallucinations, disorientation and rigidity.
(c) Epigastric pain, nausea and vomiting.
(d) Intravenous injection of phenytoin sodium can cause local vascular injury → intimal damage and thrombosis of the vein → edema and discolouration of the injected limb. Tissue necrosis occurs if the solution extravasates.
(e) Fall in BP and cardiac arrhythmias occur only on i.v. injection which, therefore, must be given under continuous ECG monitoring.

Interactions Phenytoin is a potent inducer of CYP2C8/9, CYP3A4/5 isoenzymes. It competitively inhibits CYP2C9/19.

- Phenobarbitone competitively inhibits phenytoin metabolism, while by enzyme induction both enhance each other's degradation—unpredictable overall interaction.
- Carbamazepine and phenytoin induce each other's metabolism.
- Valproate displaces protein bound phenytoin and decreases its metabolism: plasma level of unbound phenytoin increases.
- Chloramphenicol, isoniazid, cimetidine and warfarin inhibit phenytoin metabolism—can precipitate its toxicity.
- Phenytoin competitively inhibits warfarin metabolism.
- Phenytoin induces microsomal enzymes and increases degradation of steroids (failure of oral contraceptives), doxycycline, theophylline.
- Sucralfate binds phenytoin in g.i. tract and decreases its absorption.

Uses Phenytoin has been the standard drug for GTCS and partial seizures, but is now used only when better tolerated newer drugs cannot be used. It produces frequent side effects and numerous drug interactions. Due to nonlinear clearance, small increase in dose causes marked rise in plasma concentration and toxicity. It can exacerbate absence and myoclonic seizures. For status epilepticus, phenytoin sod. i.v. is used only when fosphenytoin is not available.

In trigeminal neuralgia, it is a second choice drug to carbamazepine.

Dose: Start with 100 mg BD, maximum 400 mg/day. Children 5–8 mg/kg/day.

DILANTIN 25 mg, 100 mg cap., 100 mg/4 ml oral suspension, 100 mg/2 ml inj; EPSOLIN 100 mg tab, 100 mg/2 ml inj; EPTOIN 50, 100 mg tab, 25 mg/ml syr; FENTOIN-ER 100 mg extended release cap.

Fosphenytoin This water soluble prodrug of phenytoin has been introduced to overcome the difficulties in i.v. administration of phenytoin, which it has replaced for use in status epilepticus. In the body, it is rapidly converted to phenytoin; its doses are expressed as phenytoin equivalents (PE). On i.v. injection it is less damaging to the intima; only minor vascular complications are produced and it can be injected at a faster rate (150 mg/min), but like phenytoin sod., it requires ECG monitoring. While phenytoin cannot be injected in a drip of glucose solution (because it gets precipitated), fosphenytoin can be injected with both saline and glucose.

FOSOLIN 50 mg/ml in 2 ml, 10 ml inj.

Carbamazepine

Chemically related to imipramine, it was introduced in the 1960s for trigeminal neuralgia, but soon became a first line drug for partial seizures as well as GTCS. Its pharmacological actions resemble those of phenytoin, but important differences have been noted in experimental studies. Carbamazepine modifies maximal electroshock seizures as well as raises threshold to PTZ and electroshock convulsions. High frequency neuronal discharges are inhibited, and presynaptic action may decrease transmitter release. It also inhibits kindling. Action on Na^+ channels (prolongation of inactivated state) is similar to phenytoin.

Carbamazepine exerts a lithium-like therapeutic effect in mania and bipolar mood disorder. It also has antidiuretic action, probably by enhancing ADH action on renal tubules.

Pharmacokinetics Oral absorption of carbamazepine is slow and variable because of poor water solubility. It is 75% bound to plasma proteins and metabolized in liver by oxidation to an active metabolite (10–11 epoxy carbamazepine), as well as by hydroxylation and conjugation to inactive ones. It is a substrate as well as inducer of CYP3A4 and CYP2C9. Initially its plasma t½ is 20–40 hours but, decreases to 10–20 hr on chronic medication due to autoinduction of metabolism.

Adverse effects Carbamazepine produces dose-related neurotoxicity—sedation, dizziness, vertigo, diplopia and ataxia. Use of extended release oral tablets helps to avoid high peaks in plasma concentration and the resultant neurologic symptoms. Vomiting, diarrhoea, worsening of seizures are also seen with higher doses. Acute intoxication causes coma, convulsions and cardiovascular collapse.

Hypersensitivity reactions are rashes, photosensitivity, hepatitis, lupus like syndrome, rarely agranulocytosis and aplastic anaemia. Mild leucopenia due to hypersensitivity is more common.

Water retention and hyponatremia can occur in the elderly because carbamazepine enhances ADH action.

Increased incidence of minor foetal malformations has been reported. Its combination with valproate doubles teratogenic frequency.

Interactions Carbamazepine is an enzyme inducer; can reduce efficacy of haloperidol, oral contraceptives, lamotrigine, valproate and topiramate. Metabolism of carbamazepine is induced by phenobarbitone, phenytoin, and *vice versa*. Erythromycin, fluoxetine, isoniazid inhibit metabolism of carbamazepine.

Uses Carbamazepine is the most effective drug for CPS and is very commonly used for GTCS and SPS. However, it can exacerbate myoclonic, absence and atonic seizures.

Trigeminal and related neuralgias: Carbamazepine is the drug of choice. These neuralgias are characterized by attacks of high intensity electric shock-like or stabbing pain set off by even trivial stimulation of certain trigger zones in the mouth or on the face. Drugs benefit by interrupting temporal summation of afferent impulses (by a selective action on high frequency nerve impulses). Carbamazepine is not an analgesic, but has a specific action (almost diagnostic) in these neuralgias. About 60% patients respond well. Phenytoin, lamotrigine and baclofen are less efficacious alternatives. Gabapentin can be tried in nonresponders.

Carbamazepine is not useful in diabetic, traumatic and other forms of neuropathic pain.

Manic depressive illness and acute mania: as an alternative to lithium (*see* Ch. 32).

Dose: 200–400 mg TDS; Children 15–30 mg/kg/day.

TEGRETOL, MAZETOL 100, 200, 400 mg tab, 100 mg/5 ml syr; CARBATOL 100, 200, 400 mg tab.

MAZETOL SR, TEGRITAL CR 200, 400 mg sustained release/continuous release tabs. to avoid high peaks and low troughs in plasma concentration. These are the preferred formulations.

Oxcarbazepine

This newer congener of carbamazepine is rapidly converted to an active metabolite that is only glucuronide conjugated but not oxidized. Toxic effects due to the epoxide metabolite are avoided. Drug interactions and autoinduction of own metabolism are less marked, because it is a weak enzyme inducer. Risk of hepatotoxicity is estimated to be lower than with carbamazepine; but that of hyponatraemia is more. Indications are the same as for carbamazepine, but it may be better tolerated. Dose to dose it is 1½ times less potent.

OXETOL, OXCARB, OXEP 150, 300, 600 mg tabs.

Eslicarbazepine This (S)+ enantiomer prodrug is very rapidly converted in liver to the same active metabolite as is oxcarbazepine. As such, it has the same range of therapeutic and toxic effects, but is suitable for once daily dosing. It is approved as add-on drug for partial seizure with or without generalization only in adults.

Dose: Initially 400 mg/day; increase if needed upto 1200 mg OD.

ESLIFY 200, 400, 600, 800 mg tabs; NORMICTAL, ZEFRETOL 400, 800 mg tabs.

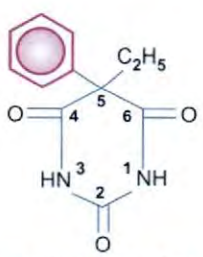
Phenobarbitone (*see* Ch. 29)

Phenobarbitone was the first efficacious antiepileptic introduced in 1912. The mechanism of CNS depressant action of barbiturates is described on p. 426. The same may apply to anticonvulsant action. Enhancement of $GABA_A$ receptor mediated synaptic inhibition appears to be most important mechanism. However, conferred probably by its 5-phenyl substitution, phenobarbitone has specific anticonvulsant activity which is not entirely dependent on general CNS depression. Quantitative differences in the different facets of action (GABA-facilitatory, GABA-mimetic, antiglutamate, Ca^{2+} entry reduction) have been noted for phenobarbitone compared to the hypnotic barbiturates. The higher anticonvulsant: hypnotic activity ratio of phenobarbitone may be due to its minimal effect on Ca^{2+} channels and glutamate release compared to hypnotic barbiturates. With continued use of phenobarbitone sedation wanes off but not anticonvulsant action. It has a wide spectrum of anticonvulsant property—raises seizure threshold as well as limits spread and suppresses kindled seizures.

Phenobarbitone has slow oral absorption and a long plasma t½ (80–120 hours), is metabolized in liver as well as excreted unchanged by kidney. Steady-state concentrations are reached after 2–3 weeks.

Phenobarbitone competitively inhibits as well as induces phenytoin and imipramine metabolism; effect on their plasma concentration is unpredictable. Sod. valproate tends to raise phenobarbitone levels when given concurrently.

The major drawback of phenobarbitone as an antiepileptic is its sedative action. Long term administration (as needed in epilepsy) may produce additional side effects like—behavioural abnormalities, diminution of intelligence, impairment of learning and memory, hyperactivity in children, mental confusion in older people.



PHENOBARBITONE

Uses Phenobarbitone is effective in generalized tonic-clonic (GTC), simple partial (SP) and complex partial (CP) seizures in a dose of 60 mg 1–3 times a day in adults; in children (3–5 mg/kg/day). However, it is infrequently used now because of its dulling and behavioural side effects.

Status epilepticus: Phenobarbitone sod. may be injected i.m. or i.v. but response is slow to develop.

It is not effective in absence and atonic seizures.

GARDENAL 30, 60 mg tabs, 20 mg/5 ml syr; LUMINAL 30 mg tab, PHENOBARBITONE SODIUM 200 mg/ml inj.

Primidone A deoxybarbiturate, which is converted by liver to phenobarbitone and phenylethyl malonamide (PEMA). Its antiepileptic activity is mainly due to these active metabolites because t½ of primidone (6–14 hr) is less than that of its active metabolites. About 1/3 primidone is excreted unchanged by kidney. Dose to dose primidone is less potent, but antiepileptic efficacy is similar to phenobarbitone. It is seldom used now in GTCS and partial epilepsy, mainly as an adjuvant to phenytoin or carbamazepine.

Adverse effects are similar to phenobarbitone. In addition, anaemia, leukopenia, psychotic reaction and lymph node enlargement occur rarely.

Dose: Start with 250 mg OD, then 250–500 mg BD, children 10–20 mg/kg/day.

MYSOLINE 250 mg tab.

Ethosuximide

The most prominent action of ethosuximide is suppression of PTZ induced clonic seizures at doses which produce no other discernable effect. It raises seizure threshold but does not modify maximal electroshock seizures or inhibit kindling. Clinically it is effective only in absence seizures.

The primary action appears to be exerted on the thalamocortical system which is involved in the generation of absence seizures. The EEG in absence seizures shows characteristic bilaterally synchronous 3 Hz spike and wave rhythm generated by reciprocal activation and oscillation of impulses between thalamus and neocortex through reverberatory synaptic connections. Thalamic neurones exhibit prominent 'T' (transient) current which is low threshold Ca^{2+} current (due to inward flow of Ca^{2+} through T type Ca^{2+} channels) that acts as the pacemaker and amplifies repetitive spikes. Ethosuximide selectively suppresses T current without affecting other types of Ca^{2+} or Na^+ currents. This correlates well with its selective action in absence seizures.

Ethosuximide is rather slowly absorbed, largely metabolized in liver and excreted in urine. Plasma t½ averages 48 hours in adults and 32 hours in children.

Adverse effects Dose-related side effects are gastrointestinal intolerance, tiredness, mood changes, agitation, headache, drowsiness and inability to concentrate.

Hypersensitivity reactions like rashes, DLE and blood dyscrasias occur rarely.

Use The primary indication for ethosuximide is absence seizures; but valproate is more commonly used. Ethosuximide is also approved for use in myoclonic seizures.

Dose: 20–30 mg/kg/day; ZARONTIN, ETHOSUXIMIDE 250 mg/5 ml syr.

Valproic acid (Sodium valproate)

It is a branched chain aliphatic carboxylic acid with a broad spectrum anticonvulsant action. Valproate is more potent in blocking PTZ seizures than in modifying maximal electroshock, but phenytoin-like suppression of high frequency neuronal firing has been demonstrated at therapeutic concentrations. Establishment of chronic experimental seizure foci and kindling are also prevented. Remarkably, at anticonvulsant doses, valproate produces little sedation or other central effects. Likewise, it is effective in partial seizures and GTCS, as well as in absence, myoclonic and atonic seizures.

Valproate appears to act by multiple mechanisms:

- A phenytoin-like frequency-dependent prolongation of Na^+ channel inactivation.
- Weak attenuation of Ca^{2+} mediated 'T' current (ethosuximide like).
- Enhanced release of inhibitory transmitter GABA due to inhibition of its degradation (by GABA-transaminase) as well as probably by increasing its synthesis from glutamic acid.
- Blockade of excitatory NMDA glutamate receptors.

Pharmacokinetics Oral absorption of valproic acid is good. It is 90% bound to plasma proteins; completely metabolized in liver by oxidation, mainly by CYP2C9 and 2C19 (some metabolites are active) and glucuronide conjugation, and then excreted in urine. Plasma t½ is 10–15 hours; but anticonvulsant effects are longer lasting.

Adverse effects The toxicity of valproate is relatively low.

Anorexia, vomiting, loose motions and heart burn are common but mild. Drowsiness, ataxia and tremor occur at high doses. However, cognitive and behavioural effects are not prominent. Alopecia, curling of hair, weight gain and increased bleeding tendency have been observed. Rashes and thrombocytopenia are infrequent hypersensitivity phenomena.

Asymptomatic rise in serum transaminase is often noted; monitoring of liver function is advised.

A rare but serious adverse effect is fulminant hepatitis; occurs only in children (especially below 3 yr). Those with hepatic disease or who receive other anticonvulsant or hepatotoxic drug are at greater risk.

Administered during pregnancy, it has produced spina bifida and other neural tube defects in the offspring; should be avoided.

Dose: Adults—start with 200 mg TDS, maximum 600 mg TDS; children—15–30 mg/kg/day.

VALPARIN CHRONO 100, 200, 300, 500 mg tabs, 200 mg/5 ml syr; ENCORATE 200, 300, 500 mg regular and controlled release tabs, 200 mg/5 ml syr, 100 mg/ml inj.

VALPROL-CR 200, 300, 500 mg controlled release tab, 200 mg/5 ml syrup, 100 mg/ml inj.

Uses Valproic acid is the drug of choice for absence seizures. Because of good tolerability it is also one of the Ist line drugs for partial seizures and GTCS.

Valproate is the most effective drug for myoclonic seizures. It is also useful in atonic seizures, in which control is often incomplete, but valproate is the drug of choice.

Mania and bipolar illness: Very commonly used as alternative to lithium (*see* Ch. 32). It has also been used for panic attacks.

Valproate has some prophylactic efficacy in migraine.

Interactions

- Valproate increases plasma levels of phenobarbitone and lamotrigine by inhibiting their metabolism.
- It displaces phenytoin from protein binding site and decreases its metabolism; phenytoin toxicity may occur.
- Valproate inhibits hydrolysis of active epoxide metabolite of carbamazepine.
- Concurrent administration of clonazepam and valproate is contraindicated because absence status may be precipitated.

- Foetal abnormalities are more common if valproate and carbamazepine are given concurrently.

Divalproex (Semisodium valproate) It is the coordination compound of valproic acid with sodium valproate (1:1). Oral absorption is slower, but bioavailability is the same. Gastric tolerance may be better. Divalproex is primarily used in mania and bipolar illness, but may be employed in epilepsy in the same way as valproic acid.

DIPROEX, VALANCE, 125, 250, 500 mg tabs; DEPAKOTE 250, 500 mg tabs.

Clonazepam

It is a benzodiazepine with prominent anticonvulsant properties: blocks PTZ seizures at doses which produce mild sedation. Efficacy in modifying maximal electroshock seizures is low and it is singularly ineffective in GTCS. Production of generalized seizures by kindling is suppressed, but local after-discharges persist.

Benzodiazepines potentiate GABA induced Cl^- influx to produce sedation and the same mechanism has been held responsible for the anticonvulsant property, but the locus of action in the brain may be different. At large doses, high frequency discharges are inhibited akin to phenytoin.

Pharmacokinetics Oral absorption of clonazepam is good. It is 85% bound to plasma proteins, completely metabolized in liver and excreted in urine; t½ averages 24 hours confering long duration of action. It does not produce any active metabolite.

Adverse effects The most important side effect of clonazepam is sedation and dullness. This can be minimized by starting at low dose; some tolerance develops with chronic therapy. Lack of concentration, irritability, temper and other behavioural abnormalities may occur in children. Motor disturbances and ataxia are dose-related adverse effects. Salivation and increased respiratory secretions may be complained of.

Uses Clonazepam has been primarily employed in absence seizures. It is also useful as an adjuvant in myoclonic and akinetic epilepsy and may afford some benefit in infantile spasms. However, its value is limited by development of tolerance to the therapeutic effect within six months or so. Clonazepam is also used to suppress acute mania.

Dose: adults 0.5–5 mg TDS, children 0.02–0.2 mg/kg/day.

LONAZEP, CLONAPAX, RIVOTRIL 0.5, 1.0, 2.0 mg tab.

Clobazam It is a 1,5 benzodiazepine (diazepam and others are 1,4 benzodiazepines), found to possess useful antiepileptic efficacy in partial, secondarily generalized tonic-clonic as well as in absence and atonic seizures, including some refractory cases. Sedation and psychomotor retardation are less prominent, but side effect profile is similar to other BZDs. It appears to act by facilitating GABA action.

Oral bioavailability of clobazam is ~90% and elimination t½ 18 hrs, but an active metabolite is produced which has longer t½ (>35 hr). It is generally used as adjuvant to other antiepileptic drugs like carbamazepine or valproate or lamotrigine when monotherapy is inadequate.

Dose: start with 10–20 mg at bedtime, can be increased upto 40 mg/day;

FRISIUM, LOBAZAM, CLOZAM, 5, 10, 20 mg cap.

Diazepam (*see* Ch. 29)

It has anticonvulsant activity in a variety of models, including maximal electroshock, but is not used for long term therapy of epilepsy because of prominent sedative action and rapid development of tolerance to the antiepileptic effect. However, it is a first line drug for emergency control of convulsions, e.g. status epilepticus, tetanus, eclampsia, convulsant drug poisoning, etc.

For this purpose 0.2–0.3 mg/kg slow i.v. injection is followed by small repeated doses as required; maximum 100 mg/day. However, thrombophlebitis of the injected vein is common. Marked fall in BP and respiratory depression can occur; resuscitative measures should be at hand before the drug is injected.

Rectal instillation of diazepam is now the preferred therapy for febrile convulsions in children.

Lorazepam 0.1 mg/kg injected i.v. at a rate not exceeding 2 mg/min is better suited than diazepam in status epilepticus or for emergency control of convulsions of other etiology, because of lesser local thrombophlebitic complications and more sustained action than that of diazepam which is rapidly redistributed.

Lamotrigine A newer anticonvulsant having carbamazepine-like action profile: modifies maximal electroshock and decreases electrically

evoked as well as photic after-discharge duration. Prolongation of Na^+ channel inactivation and suppression of high frequency firing has been demonstrated. In addition, it may directly block voltage sensitive Na^+ channels, thus stabilizing the presynaptic membrane and preventing release of excitatory neurotransmitters, mainly glutamate and aspartate. This may account for its broader-spectrum of antiseizure efficacy. However, it does not antagonize PTZ seizures or block NMDA type of glutamate receptors.

Lamotrigine is a broad-spectrum antiepileptic. Initially found useful as add-on therapy in refractory cases of partial seizures and GTCS, it has now been shown effective as monotherapy as well. It is a first line drug now for these types of epilepsy. Absence and myoclonic or akinetic epilepsy cases have also been successfully treated. Reduction in seizure frequency or complete control is obtained as frequently as with carbamazepine. Some cases of neuralgic pain also respond.

Lamotrigine is well absorbed orally and metabolized completely in liver. Its t½ is 24 hr, but is reduced to ~16 hrs in patients receiving phenytoin, carbamazepine or phenobarbitone. On the contrary valproate inhibits glucuronidation of lamotrigine and doubles its blood level, but valproate levels are lowered by lamotrigine. The dose of lamotrigine should be reduced to half in patients taking valproate. However, metabolism of other anticonvulsants and oral contraceptives is not altered.

Side effects are sleepiness, dizziness, diplopia, ataxia and vomiting. In some comparative trials lamotrigine has been found to be better tolerated than carbamazepine or phenytoin. Negative effect on cognitive function is not reported. Rash may be a severe reaction, particularly in children, requiring withdrawal.

Dose: 50 mg/day initially, increase upto 300 mg/day as needed; not to be used in children.

LAMETEC, LAMITOR, LAMIDUS 25, 50, 100 mg tabs.

Gabapentin This lipophilic GABA derivative crosses to the brain and enhances GABA release, but does not act as agonist at $GABA_A$ receptor. It modifies maximal electroshock as well as inhibits PTZ induced clonic seizures.

Gabapentin and its newer congener pregabalin exert a specific analgesic effect in neuropathic pain. Recently they have been found to modulate a subset of neuronal voltage sensitive Ca^{2+} channels which contain $\alpha 2\delta$-1 subunits. It is postulated that decreased entry of Ca^{2+} into the presynaptic neurone through these channels could reduce glutamate release, lowering neuronal excitability. However, whether $\alpha 2\delta$-1 Ca^{2+} channel modulation or the GABA enhancing action, or both are responsible for the anticonvulsant/analgesic effect of gabapentin and pregabalin, is not known.

Added to a first line drug, gabapentin reduces seizure frequency in refractory partial seizures with or without generalization. Though gabapentin monotherapy is also effective in SPS and CPS, it is mostly employed as add-on drug. Gabapentin is considered to be a first line drug for neuralgic pain due to diabetic neuropathy and postherpetic neuralgia. It has some prophylactic effect in migraine and is an alternative drug for phobic states.

Gabapentin is well absorbed orally and excreted unchanged in urine with a t½ of 6 hrs. No drug interactions have been noted, and no change in dose of primary antiepileptic drug is required when gabapentin is added. Side effects are mild sedation, tiredness, dizziness, tremor and unsteadiness.

Dose: Start with 300 mg OD, increase to 300–600 mg TDS as required; NEURONTIN 300 mg, 400 mg cap, GABANTIN, GABAPIN 100, 300, 400 mg cap.

Pregabalin This newer congener of gabapentin has similar pharmacodynamic, pharmacokinetic properties and clinical indications in seizure disorders. It has been particularly used for neuropathic pain, such as diabetic neuropathy, postherpetic neuralgia, complex regional pain syndrome (CRPS) and certain other types of chronic pain. Sedative side effects are claimed to be less prominent, but poor concentration, rashes and allergic reactions have been complained.

Dose: 75–150 mg BD, max 600 mg/day

PREGABA, NEUGABA, TRUEGABA 75, 150 mg caps. PREGALIN-X-SR 75 mg SR tab.

Levetiracetam A unique anticonvulsant which suppresses kindled seizures, but is ineffective against maximal electroshock or PTZ. Clinical efficacy has been demonstrated both as adjuvant medication as well as monotherapy in refractory partial seizures with or without generalization. The mechanism of action is not known. None of the major anticonvulsant mechanisms appear to be applicable. However, levetiracetam binds selectively to a synaptic vesicular protein 'SV_2A', and this may alter release of glutamate and/or GABA across the synapse, thereby exerting anti-seizure effect (*see* Fig. 30.1). It also inhibits N-type calcium channels which may affect intracellular Ca^{2+} release.

Levetiracetam is completely absorbed orally, partly hydrolysed, but mainly excreted unchanged in urine with a t½ of 6–8 hours. It is neither oxidized by CYP enzymes nor induces or inhibits them. As such, it is free of drug interactions. Few side effects like sleepiness, dizziness, weakness and rarely behavioural changes are reported. Driving may be impaired. Because of good tolerability, levetiracetam is being increasingly used in partial seizures, and myoclonic epilepsy, mainly as add-on drug. For GTCS and absence seizures it is a second-line adjunctive drug. It is not approved for use in children below 4 years.

Dose: 0.5 g BD, increase upto 1.0 g BD (max 3 g/day), children 4-15 year 10–30 mg/kg/day.

LEVOREXA, TORLEVA, LEVTAM 0.25, 0.5, 1.0 g tabs.

Topiramate This weak carbonic anhydrase inhibitor has broad spectrum anticonvulsant activity in maximal electroshock, PTZ induced clonic seizures and in kindling model. It appears to act by multiple mechanisms, *viz.* phenytoin like prolongation of Na^+ channel inactivation, suppression of repetitive neuronal firing, GABA potentiation by a postsynaptic effect, antagonism of certain glutamate receptors and neuronal hyperpolarization through K^+ channels.

Topiramate is indicated as monotherapy as well as for supplementing primary antiepileptic drug in refractory SPS, CPS and GTCS. Promising results have been obtained in myoclonic epilepsy and as add-on drug in absence seizures. Topiramate is readily absorbed orally and mainly excreted unchanged in urine with an average t½ of 24 hours. Adverse effects are impairment of attention, sedation, ataxia, word finding difficulties, poor memory, weight loss, paresthesias and renal stones.

Topiramate has been approved for prophylaxis of migraine; may be used when β blockers/other prophylactics are contraindicated or are not effective.

Dose: Initially 25 mg OD or BD; increase weekly upto 100–200 mg BD as required.

TOPEX, EPITOP, TOPAMATE, NEXTOP 25, 50, 100 mg tabs.

Zonisamide Another newer anticonvulsant with weak carbonic anhydrase inhibitory action that modifies maximal electroshock seizures and inhibits kindled seizures, but does not antagonize PTZ. Prolongation of Na^+ channel inactivation resulting in suppression of repetitive neuronal firing has been observed. It has also been found to suppress T-type of Ca^{2+} currents in certain neurones.

Zonisamide is well absorbed orally and mainly excreted unchanged in urine with a t½ of > 60 hours. A small fraction is oxidized and conjugated with glucuronic acid. It is indicated both as monotherapy and as add-on drug in refractory partial seizures with or without generalization, and has been tried in absence seizures. Side effects are somnolence, dizziness, headache, irritability and anorexia. Metabolic acidosis and renal stones can occur. Zonisamide is to be avoided in patients sensitive to sulfonamides. No drug interactions have been observed.

Dose: 25–100 mg BD. Not to be given to children.

ZONISEP, ZONICARE, ZONIT 50, 100 mg cap.

Lacosamide This recently introduced antiseizure drug is indicated in adults only for add-on therapy of partial seizures with or without generalization. It acts by enhancing Na^+ channel inactivation and suppressing repetitive firing of neurones. Lacosamide is metabolized by CYP2C19 and excreted in urine with t½ ~ 12 hours. No alteration in dose of companion antiepileptic drug is needed, because it neither

induces nor inhibits drug metabolizing enzymes. Adverse effects are ataxia, vertigo, diplopia, tremor, depression and cardiac arrhythmia.

Dose: Initially 50 mg BD, increase upto 200 mg BD.

LACASA 50, 100, 150, 200 mg tabs, LACOSAM, LACOPSY 50, 100 mg tab.

Tiagabine This newer anticonvulsant potentiates GABA mediated neuronal inhibition by blocking GABA transporter GAT-1 which removes synaptically released GABA into neurones and glial cells (*see* Fig. 30.1). Kindled seizures are suppressed with less marked effect on maximal electroshock. Currently it is approved only for add-on therapy of partial seizures with or without secondary generalization, when not adequately controlled by standard antiepileptic drugs alone. Side effects are mild sedation, nervousness, asthenia, amnesia, dermatitis and abdominal pain.

Tiagabine is well absorbed, partly metabolized and excreted mainly in faeces. The t½ is 6 hours.

Dose: 4–16 mg TDS

TIGATEL 2,4,12,16 mg tabs.

Vigabatrin (γ vinyl GABA) It is an inhibitor of GABA-transaminase, the enzyme which degrades GABA. Anticonvulsant action may be due to increase in synaptic GABA concentration. It is effective in many patients with refractory epilepsy, especially CPS with or without generalization, and in infantile spasms. It is approved only for adjuvant medication.

Visual field contraction, alteration of colour vision, paresthesias and production of behavioural changes, depression or psychosis has restricted its use to only as a reserve drug.

*D*ose: Adults 0.5–1.5 g BD, for infantile spasms 50–150 mg/kg/day in divided doses.

SABNIL 0.5 g tab.

TREATMENT OF EPILEPSIES

Antiepileptic drugs suppress seizures, but do not cure the disorder; the disease may fadeout though after years of successful control. The aim of drugs is to control and totally prevent all seizure activity at an acceptable level of side effects. With the currently available drugs, this can be achieved in about half of the patients. Another 20–30% attain partial control, while the rest remain refractory. The cause of epilepsy should be searched in the patient; if found and treatable, an attempt to remove it should be made. Some general principles of symptomatic treatment with antiepileptic drugs are:

1. Choice of drug (Table 30.1) and dose is according to the seizure type(s) and need of the individual patient. There is a trend to prefer the newer antiepileptic drugs, because they are less sedating, produce few side effects and drug interactions are insignificant. However, the newer drugs are less well studied.
2. Initiate treatment early, because each seizure episode increases the propensity to further attacks, probably by a process akin to kindling. Start with a single drug, preferably at low dose—gradually increase dose till full control of seizures or side effects appear. If full control is not obtained at maximum tolerated dose of one drug, substitute another drug. For changing one antiepileptic drug to another, dose of the first drug should be gradually reduced and that of the second drug gradually increased till the second drug regimen is fully established.
3. Use combinations only when all reasonable monotherapy fails. Combining drugs with different mechanisms of action, such as those which prolong Na^+ channel inactivation with those facilitating GABA appears more appropriate. Pharmacokinetic interactions among anticonvulsants are common; dose adjustment guided by therapeutic drug monitoring is warranted.
4. When therapy with two drugs fails to achieve adequate control, addition of a third drug generally does not improve the response, unless the patient suffers from more than one seizure types.
5. A single tonic-clonic seizure in a subject with no predisposing factor for development of epilepsy (history of head injury, family history of epilepsy, neurological abnormality, abnormal EEG or brain scan) may not merit initiation of antiepileptic therapy.
6. Therapeutic regimen should be as simple as possible. A seizure diary should be maintained.
7. All drug withdrawals should be gradual (except in case of toxicity). Abrupt stoppage of therapy without introducing another effective drug can precipitate status epilepticus.

Table 30.1: Choice of antiseizure drugs

Type of seizure	*First line drugs*	*Alternative/Add-on drugs*	*Reserve/Add-on drugs*
1. *Partial seizures* (SPS, CPS) with or without generalization	Carbamazepine, Lamotrigine, Valproate, Oxcarbazepine	Levetiracetam, Clobazam, Phenytoin Gabapentin, Topiramate	Lacosamide, Phenobarbitone, Zonisamide, Tiagabine
2. *Generalized seizures* • Tonic-clonic	Valproate, Lamotrigine, Carbamazepine	Clobazam, Oxcarbazepine Phenytoin	Levetiracetam, Topiramate Phenobarbitone
• Absence	Valproate, Ethosuccimide	Lamotrigine, Clobazam, Clonazepam	Levetiracetam Topiramate Zonisamide
• Myoclonic	Valproate	Topiramate Levetiracetam	Clobazam, Clonazepam
• Atonic	Valproate	Lamotrigine	Topiramate Clonazepam
3. *Febrile seizures*	Diazepam (rectal)	–	–
4. *Status epilepticus*	Lorazepam (i.v.) Diazepam (i.v.)	Fosphenytoin (i.v.)	Phenobarbitone (i.m.)

Prolonged therapy (may be life-long, or at least 3 years after the last seizure) is needed. Stoppage of therapy may be attempted in selected cases. Features favourable to withdrawal are:
- childhood epilepsy,
- absence of family history,
- primary generalized tonic-clonic epilepsy,
- recent onset at start of treatment,
- absence of cerebral disorder and normal inter-seizure EEG.

Even with these features recurrence rates of 12–40% have been reported.

8. Dose regulation may be facilitated by monitoring of steadystate plasma drug levels. Monitoring is useful because:
   (a) Therapeutic range of concentrations has been defined for many drugs.
   (b) There is marked individual variation in the plasma concentration attained with the same daily dose.
   (c) Compliance among epileptic patients is often poor.

Plasma levels given in Table 30.2 are to serve as rough guides.

9. When women on antiepileptic therapy conceive, antiepileptic drugs should not be stopped. Though, most antiseizure drugs increase the incidence of birth defects, discontinuation of therapy carries a high risk of status epilepticus. Fits occurring during pregnancy themselves increase birth defects and may cause mental retardation in the offspring (anoxia occurs during seizures). An attempt to reduce the dose of drugs should be cautiously made. It may be advisable to substitute valproate by another drug.

   Prophylactic folic acid supplementation in 2nd and 3rd trimester along with vit. K in the last month of pregnancy is recommended, particularly in women receiving antiepileptic drugs to minimise neural tube defects and bleeding disorder respectively in the neonate.

10. A seizure episode does not require any drug treatment. During an attack of tonic-clonic seizures, the first priority is to prevent injury due to fall or biting. The patient should be put in prone or lateral position. The head should be turned and patency of airway ensured. The attack usually passes off in 2–3 min, but the patient may not be roadworthy for a couple of hours.

Table 30.2: Plasma half life, therapeutic and toxic plasma concentration range of some important antiepileptic drugs

Drug	*Half life (hr)*	*Plasma concentration (μg/ml)*	
		Therapeutic	*Toxic*
Phenobarbitone	80–120	10–30	> 30 mild, > 60 severe
Phenytoin	12–36	10–20	> 20 mild, > 35 severe
Carbamazepine	10–40	5–10	> 12
Ethosuximide	30–50	50–100*	>200
Valproate	10–15	40–100*	–
Clonazepam	20–40	0.01–0.1*	–

* Poorly correlated with response.

Febrile convulsions Some children, especially under 5 years age, develop convulsions during fever. Seizures may recur every time with fever and few may become chronic epileptics. Every attempt should be made to see that they do not develop fever, but when they do, temperature should not be allowed to rise by using paracetamol and external cooling.

The best treatment of febrile convulsions is rectal diazepam 0.5 mg/kg given at the onset of convulsions. The i.v. preparation can be used where the rectal formulation is not available. A rectal solution (5 mg in 2.5 ml) in tubes is available in the UK and some other countries. Seizures generally stop in 5 min; if not, another dose may be given. The drug is repeated 12 hourly for 4 doses. If fever is prolonged a gap of 24–48 hr is given before starting next series of doses.

In recurrent cases or those at particular risk of developing epilepsy—intermittent prophylaxis with diazepam (oral or rectal) started at the onset of fever is recommended. Chronic prophylaxis with phenobarbitone advocated earlier has been abandoned, because of poor efficacy and behavioural side effects.

Infantile spasms (hypsarrhythmia) Therapy of this condition is unsatisfactory, antiepileptic drugs are generally useless. Corticosteroids afford symptomatic relief but cannot be used for long-term due to adverse effects. Clonazepam, valproate and vigabatrin may afford some relief.

Status epilepticus When seizure activity occurs for >30 min, or two or more seizures occur without recovery of consciousness, the condition is called *status epilepticus*. Recurrent tonic-clonic convulsions without recovery of consciousness in between is an emergency; fits have to be controlled as quickly as possible to prevent death and permanent brain damage.

- The first priority is to maintain patient airway. This is followed by 20–50 ml of 50% dextrose injected i.v. to correct hypoglycaemia, in case that is responsible for the seizures.
- *Lorazepam* 4 mg (0.1 mg/kg in children) injected i.v. at the rate of 2 mg/min, repeated once after 10 min if required, is the first choice drug now. It is effective in 75–90% cases and produces a more sustained anticonvulsant effect (lasting 6–12 hours) than diazepam, because of lower lipid solubility and slower redistribution. Moreover, thrombophlebitis of injected vein is less likely with lorazepam.
- *Diazepam* 10 mg (0.2–0.3 mg/kg) injected i.v. at 2 mg/min, repeated once after 10 min if required, has been the standard therapy till recently. However, its anticonvulsant effect starts fading after 20 min, and many supplemental doses may be required. It is also more damaging to the injected vein.
- *Fosphenytoin* 100–150 mg/min i.v. infusion to a maximum of 1000 mg (15–20 mg/kg) under continuous ECG monitoring is a slower acting drug which should be given

subsequently irrespective of response to lorazepam. This may suppress seizures that have not responded to lorazepam, and pave the way for long-term seizure treatment.

- *Phenytoin sod.* It should be used only when fosphenytoin is not available, because it can be injected only at the rate of 25–50 mg/min and causes more marked local vascular complications.
- *Phenobarbitone sod.* 50–100 mg/min i.v. injection to a maximum of 10 mg/kg is another slower acting drug which can be used as alternative to fosphenytoin or when the latter is ineffective. It is also employed to maintain seizure free state over short term before definitive oral therapy is instituted.
- Refractory cases who fail to respond to lorazepam and fosphenytoin within 40 min of seizure onset may be treated with i.v. midazolam/propofol/thiopentone anaesthesia, with or without curarization and full intensive care.
- General measures, including maintenance of airway (intubation if required), oxygenation, fluid and electrolyte balance, BP, normal cardiac rhythm, euglycaemia and care of the unconscious must be taken.

☞ PROBLEM DIRECTED STUDY

30.1 A young lady aged 25 years comes for consultation along with her husband for having suffered two episodes of fits lasting 2–3 min each over the past one week. Just before each fit, she experienced flickering in her right arm. Description of the fit given by the husband corresponds to tonic-clonic seizures. She gave the history of having met a car accident about one year back in which she received head injury. There is no family history of epilepsy. General physical and neurological examination revealed no abnormality. Investigations, including EEG and MRI scan of the brain, were ordered.

(a) What instructions should be given to the husband regarding care to be taken, if and when, the next fit occurs?

(b) Should antiepileptic drug/drugs be started right away, or therapy be delayed till findings of the investigations become available or till more fits occur?

(c) In case antiseizure therapy has to be started right away, should a single drug or a combination of drugs be given? Which drug(s) would be the most appropriate for this patient? (see Appendix-1 for solution)

Chapter 31 Antiparkinsonian Drugs

These are drugs that have a therapeutic effect in parkinsonism.

Parkinsonism It is an extrapyramidal motor disorder characterized by *rigidity, tremor* and *hypokinesia* with secondary manifestations like defective posture and gait, mask-like face and sialorrhoea; dementia may accompany. If untreated the symptoms progress over several years to end-stage disease in which the patient is rigid, unable to move, unable to breathe properly; succumbs mostly to chest infections/embolism.

Parkinson's disease (PD) is a progressive degenerative disorder, mostly affecting older people, first described by James Parkinson in 1817. Majority of the cases are idiopathic, some are arteriosclerotic while postencephalitic are now rare. Wilson's disease (hepatolenticular degeneration) due to chronic copper poisoning, is a rare cause.

The most consistent lesion in PD is degeneration of neurones in the substantia nigra pars compacta (SN-PC) and the nigrostriatal (dopaminergic) tract. This results in deficiency of dopamine (DA) in the striatum which controls muscle tone and coordinates movements. An imbalance between dopaminergic (inhibitory) and cholinergic (excitatory) system in the striatum occurs giving rise to the motor defect. Though the cholinergic system is not primarily affected, its suppression (by anticholinergics) tends to restore balance.

The cause of selective degeneration of nigrostriatal neurones is not precisely known, but appears to be multifactorial. Ageing, genetic predisposition, oxidative generation of free radicals, N-methyl-4-phenyl tetrahydropyridine (MPTP)-like environmental toxins and excitotoxic neuronal death due to NMDA-receptor (excitatory glutamate receptor) mediated Ca^{2+} overload have all been held responsible.

Drug-induced reversible parkinsonism due to neuroleptics, metoclopramide (dopaminergic blockers) is now fairly common, while that due to reserpine (DA depleter) is historical.

Belladonna alkaloids had been empirically used in Parkinson's disease (PD). A breakthrough was made in 1967 when *levodopa* was found to produce dramatic improvement. Its use was based on sound scientific investigations made in the preceding 10 years that:

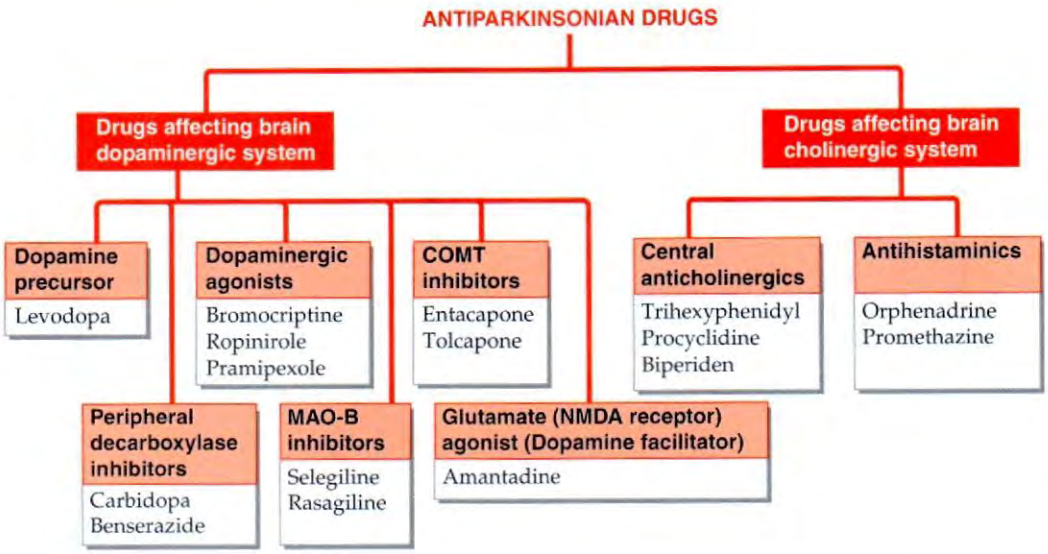
- DA is present in the brain;
- it (along with other monoamines) is depleted by reserpine;
- reserpine induced motor defect is reversed by DOPA (the precursor of DA);
- striatum of patients dying of PD was deficient in DA.

Thus, parkinsonism was characterized as a DA deficiency state and levodopa was used to make good this deficiency, because DA itself does not cross the blood-brain barrier. In the subsequent years, a number of levodopa potentiators and DA agonists have been developed as adjuvants/alternatives.

None of the drugs alter course of the disease in PD, but improve quality of life for a few years.

LEVODOPA

Levodopa has a specific salutary effect in PD: efficacy exceeding that of any other drug used alone. It is inactive by itself, but is the immediate precursor of the transmitter DA. More than 95% of an oral dose is decarboxylated in the peripheral tissues (mainly gut and liver). DA thus formed is further metabolized, and



the remaining acts on heart, blood vessels, other peripheral organs and on CTZ (though located in the brain, i.e. floor of IV ventricle, it is not bound by blood-brain barrier). About 1–2% of administered levodopa crosses to the brain, is taken up by the surviving dopaminergic neurones, converted to DA which is stored and released as a transmitter. This is supported by the finding that brains of parkinsonian patients treated with levodopa till death had higher DA levels than those not so treated. Further, those patients who had responded well had higher DA levels than those who had responded poorly.

ACTIONS

1. CNS Levodopa hardly produces any effect in normal individuals or in patients with other neurological diseases. Marked symptomatic improvement occurs in parkinsonian patients. Hypokinesia and rigidity resolve first, later tremor as well. Secondary symptoms of posture, gait, handwriting, speech, facial expression, mood, self care and interest in life are gradually normalized. Therapeutic benefit is nearly complete in early disease, but declines as the disease advances.

The effect of levodopa on behaviour has been described as a 'general alerting response'. In some patients this progresses to excitement—frank psychosis may occur. Embarrassingly disproportionate increase in sexual activity has also been noted. Dementia, if present, does not improve; rather it predisposes to emergence of psychiatric symptoms.

Levodopa has been used to produce a non-specific 'awakening' effect in hepatic coma.

Two subtypes of DA receptors (D1, D2) were originally described. Three more (D3, D4, D5) have now been identified and cloned. All are G protein coupled receptors and are grouped into two families:

D1 like (D1, D5) Are excitatory: act by increasing cAMP formation and PIP_2 hydrolysis thereby mobilizing intracellular Ca^{2+} and activating protein kinase C through IP_3 and DAG.

D2 like (D2, D3, D4) Are inhibitory: act by inhibiting adenylyl cyclase/opening K^+ channels/depressing voltage sensitive Ca^{2+} channels.

The various subtypes of DA receptors are differentially expressed in different areas of the brain, and appear to play distinct roles. Both D1 and D2 receptors are present in the striatum and are involved in the therapeutic response to levodopa. They respectively regulate the activity of two pathways having opposite effects on the thalamic input to the motor cortex (Fig. 31.1). Thus, stimulation of excitatory D1 as well as inhibitory D2 receptors in the striatum achieves the same net effect of smoothening movements and reducing muscle tone.

Dopamine receptor in SN-PC and in pituitary is also of D2 type. The D3 receptors predominate in nucleus accumbans and hypothalamus, but are sparse in caudate and putamen, while D4 and D5 are mostly distributed in neocortex, midbrain, medulla and hippocampus.

2. CVS The peripherally formed DA can cause tachycardia by acting on β adrenergic receptors. Though DA can stimulate vascular adrenergic receptors as well, rise in BP is not seen. Instead, postural hypotension is quite common. This may be a central action. Excess DA and NA formed in the brain decrease sympathetic outflow; also DA formed in autonomic ganglia can impede ganglionic transmission.

Gradual tolerance develops to both cardiac stimulant and hypotensive actions.

3. CTZ Dopaminergic receptors are present in this area and DA acts as an excitatory transmitter. The DA formed peripherally gains access to the CTZ without hindrance—elicits nausea and vomiting. Tolerance develops gradually to this action.

4. Endocrine DA acts on pituitary mammotropes to inhibit prolactin release and on

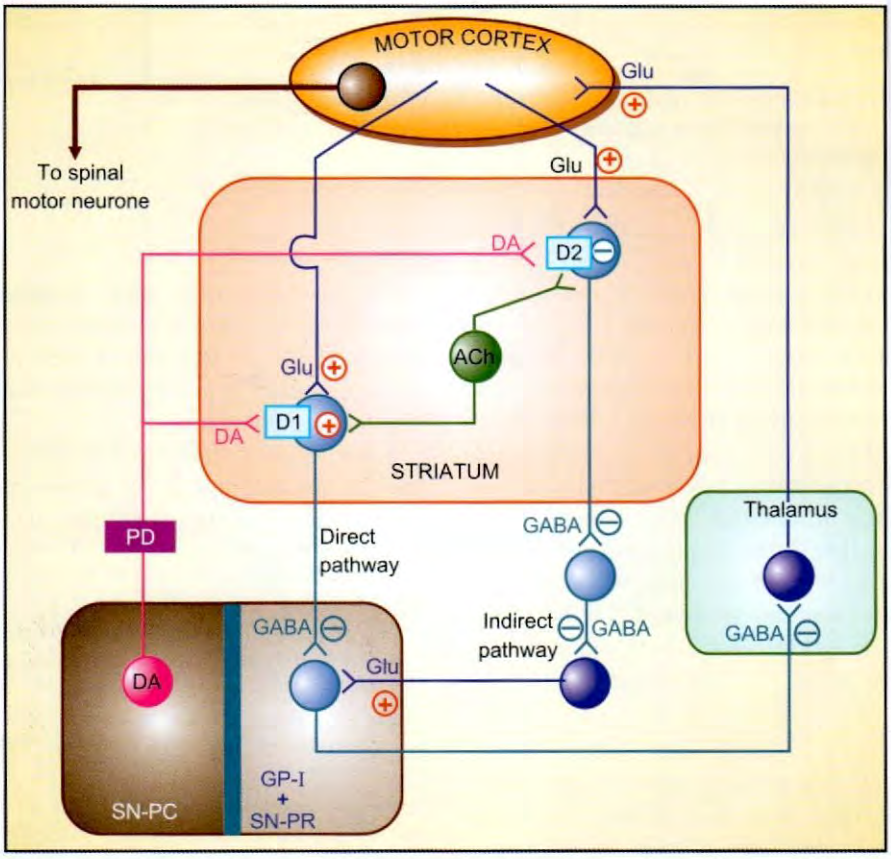


Fig. 31.1: Simplified scheme of side loop circuits in the basal ganglia that provide modulatory input to the motor cortex. The striatal GABAergic neurones receive side-loop excitatory glutamatergic (Glu) input from the motor cortex and modulatory dopaminergic (DA) projections from the substantia nigra pars compacta (SN-PC). There are also balancing cholinergic (ACh) interneurones. The striatal neurones express both excitatory D1 and inhibitory D2 receptors. The output from the striatum to substantia nigra pars reticulata (SN-PR) and internal globus pallidus (GP-I) follows a direct and an indirect pathway. The direct pathway modulated by DI receptors releases inhibitory transmitter GABA, while the dominant indirect pathway modulated by D2 receptors has two inhibitory (GABAergic) relays and an excitatory (glutamatergic) terminal. Due to this arrangement, dopaminergic action in the striatum exerts inhibitory influence on SN-PR and GP-I *via* both the pathways. The output neurones from SN-PR and GP-I feedback on the motor cortex through the thalamus using an inhibitory GABAergic link and an excitatory glutamatergic terminal. The basal ganglia modulatory loop serves to smoothen output to the spinal motor neurone and reduce basal tone.

The degenerative lesion (in SN-PC) of Parkinson's disease (PD) decreases dopaminergic input to the striatum, producing an imbalance between DA and ACh, resulting in hypokinesia, rigidity and tremor.

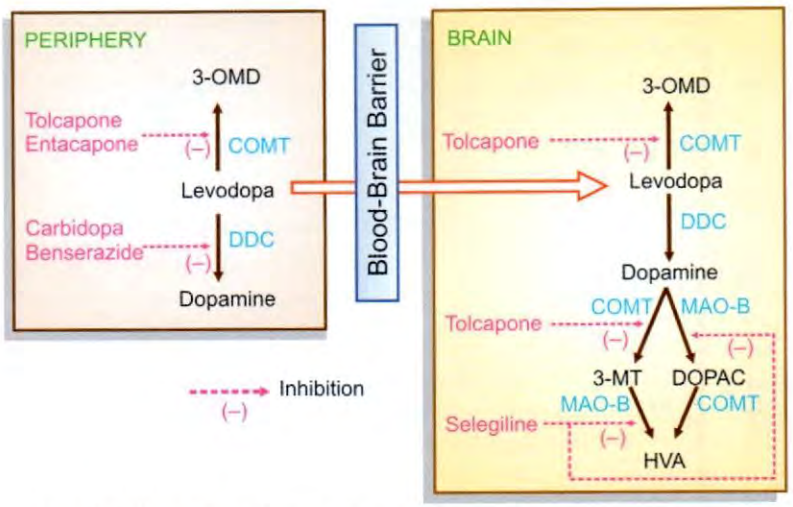


Fig. 31.2: Metabolic pathways of levodopa in the periphery and the brain.
3-OMD—3-O-methyldopa; COMT—Catechol-O-methyl transferase; MAO—monoamine oxidase; 3-MT—3-methoxytyramine; DOPAC—3,4 dihydroxy phenylacetic acid; HVA—Homovanillic acid (3-methoxy-4-hydroxy phenylacetic acid), DDC—Dopa decarboxylase

somatotropes to increase GH release. Though prolactin levels in blood fall during levodopa therapy, increased GH levels are not noted in parkinsonian patients. Probably the mechanisms regulating GH secretion are altered in these patients.

PHARMACOKINETICS

Levodopa is rapidly absorbed from the small intestines by utilizing the active transport process meant for aromatic amino acids. Bioavailability of levodopa is affected by:

(i) Gastric emptying: if slow, levodopa is exposed to degrading enzymes present in gut wall and liver for a longer time—less is available to penetrate blood-brain barrier.

(ii) Amino acids present in food compete for the same carrier for absorption: blood levels are lower when taken with meals.

Levodopa undergoes high first pass metabolism in g.i. mucosa and liver. The peripheral and central pathway of metabolism of levodopa is depicted in Fig. 31.2.

About 1% of administered levodopa that enters brain, aided by amino acid carrier mediated active transport across brain capillaries, also undergoes the same transformation. The plasma t½ of levodopa is 1–2 hours. Pyridoxal is a cofactor for the enzyme dopa-decarboxylase. The metabolites are excreted in urine mostly after conjugation.

ADVERSE EFFECTS

Side effects of levodopa therapy are frequent and often troublesome. Most are dose-related and limit the dose that can be administered, but are usually reversible. Some are prominent in the beginning of therapy while others appear late.

At the initiation of therapy These side effects can be minimized by starting with a low dose.

1. *Nausea and vomiting* It occurs in almost every patient. Tolerance gradually develops and then the dose can be progressively increased.

2. *Postural hypotension* It occurs in about 1/3 of patients, but is mostly asymptomatic; some patients experience dizziness, few have fainting attacks. It is more common in patients receiving antihypertensives. Tolerance develops with continued treatment and BP normalizes.

3. *Cardiac arrhythmias*
4. *Exacerbation of angina*

} Due to β adrenergic action of peripherally formed DA; more in patients with pre-existing heart disease.

5. *Alteration in taste sensation*

After prolonged therapy

1. *Abnormal movements (dyskinesias)* Facial tics, grimacing, tongue thrusting, choreoathetoid movements of limbs start appearing after a few months of use of levodopa at optimum therapeutic dose. These dyskinesias worsen with time and practically all patients get involved after few years. Their intensity corresponds with levodopa levels. No tolerance develops to this adverse effect, but dose reduction decreases severity. Abnormal movements may become as disabling as the original disease itself, and are the most important dose-limiting side effects.

2. *Behavioural effects* They range from mild anxiety, nightmares, etc. to severe depression, mania, hallucinations, mental confusion or frank psychosis. Excessive DA action in the limbic system is probably responsible (antidopaminergic drugs are antipsychotic). Levodopa is contraindicated in patients with psychotic illness.

3. *Fluctuation in motor performance* After 2–5 years of therapy, the level of control of parkinsonian symptomatology starts showing fluctuation. 'End of dose' deterioration (wearing off) which is initially gradual, develops into rapid 'switches' or 'on-off' effect. With time 'all or none' response develops, i.e. the patient is alternately well and disabled. Abnormal movements may jeopardise even the 'on' phase. This is probably a reflection of progression of the disorder. With progressive degeneration of DA neurones the ability to regulate storage and release of DA may be largely lost: DA is then synthesized in the striatum on a moment-to-moment basis resulting in rapid and unpredictable fluctuations in motor control. Dose fractionation and more frequent administration tends to diminish these fluctuations for a time.

Cautious use of levodopa is needed in the elderly; patients with ischaemic heart disease; cerebrovascular, psychiatric, hepatic and renal disease; peptic ulcer (risk of bleeding is increased); glaucoma and gout.

Dose: Start with 0.25 g BD after meals, gradually increase till adequate response is obtained. Usual dose is 2–3 g/day.

LEVOPA, BIDOPAL 0.5 g tab.

Interactions

1. Pyridoxine: Abolishes the therapeutic effect of levodopa (if it is not combined with carbidopa) by enhancing its peripheral decarboxylation so that less of it remains available to cross to the brain.
2. Phenothiazines, butyrophenones, metoclopramide reverse the therapeutic effect of levodopa by blocking DA receptors. The antidopaminergic domperidone blocks levodopa induced nausea and vomiting without abolishing its antiparkinsonian effect, because domperidone does not cross blood-brain barrier, but reaches CTZ. Domperidone can be used to allay vomiting due to levodopa. Reserpine abolishes levodopa action by preventing entry of DA into synaptic vesicles.
3. Nonselective MAO inhibitors: prevent degradation of DA and NA that is synthesized in excess from the administered levodopa at peripheral sites. This may cause hypertensive crisis.
4. Antihypertensive drugs: postural hypotension caused by levodopa is accentuated in patients receiving antihypertensive drugs; reduce their dose if levodopa is started.
5. Atropine, and antiparkinsonian anticholinergic drugs have additive therapeutic action with low doses of levodopa, but retard its absorption—more time is available for peripheral degradation—efficacy of levodopa may be reduced (not when combined with carbidopa).

PERIPHERAL DECARBOXYLASE INHIBITORS

Carbidopa and *benserazide* are extracerebral dopa decarboxylase inhibitors; they do not penetrate blood-brain barrier and do not inhibit conversion of levodopa to DA in the brain.

Administered along with levodopa, they increase its t½ in the periphery and make more of it available to cross blood-brain barrier and reach its site of action.

Benefits of the combination are—

1. The plasma t½ of levodopa is prolonged and its dose is reduced to approximately 1/4th.
2. Systemic concentration of DA is reduced, nausea and vomiting are minimized—therapeutic doses of levodopa can be attained more quickly.
3. Cardiac complications are reduced.
4. Pyridoxine reversal of levodopa effect does not occur.
5. 'On-off' effect is minimized since cerebral DA levels are more sustained.
6. Degree of improvement may be higher; some patients, not responding adequately to levodopa alone, also improve.

Problems not resolved or accentuated are—

1. Involuntary movements
2. Behavioural abnormalities

} may even be more pronounced and appear earlier.

3. Excessive day time sleepiness in some patients.
4. Postural hypotension.

Currently, levodopa is practically always used along with a decarboxylase inhibitor, except in patients who develop marked involuntary movements with the combination.

Combination of levodopa with carbidopa has been given the name 'Co-careldopa'.

Preparations and dose

	Carbidopa		*Levodopa*
	(per tab/cap)		
TIDOMET-LS, SYNDOPA-110,	10 mg	+	100 mg
SINEMET, DUODOPA-110	10 mg	+	100 mg
TIDOMET PLUS, SYNDOPA PLUS	25 mg	+	100 mg
TIDOMET FORTE, SYNDOPA-275	25 mg	+	250 mg

BENSPAR, MADOPAR: Benserazide 25 mg + levodopa 100 mg cap.

Usual daily maintenance dose of levodopa is 0.4–0.8 g along with 75–100 mg carbidopa or 100–200 mg benserazide, given in 3–4 divided doses. Therapy is started at a low dose and suitable preparations are chosen according to the needs of individual patients, increasing the dose as required.

DOPAMINERGIC AGONISTS

The DA agonists can act on striatal DA receptors even in advanced patients who have largely lost the capacity to synthesize, store and release DA from the administered levodopa. Moreover, they are longer acting, can exert subtype selective activation of DA receptors involved in parkinsonism and not share the concern expressed about levodopa of contributing to dopaminergic neuronal damage by oxidative metabolism.

Bromocriptine (*see* Ch. 17) It is an ergot derivative which acts as potent agonist on D2 receptors, but as partial agonist or antagonist on D1 receptors. Improvement in parkinsonian symptoms occurs within ½–1 hr of an oral dose of bromocriptine and lasts for 6–10 hours. If used alone, doses needed in parkinsonism are high, and often produce intolerable side effects, especially vomiting, hallucinations, hypotension, nasal stuffiness, conjunctival injection. Marked fall in BP with the 'first dose' has occurred in some patients, especially those on antihypertensive medication.

Bromocriptine has been largely replaced by the newer DA agonists ropinirole and pramipexole.

Dose: Initially 1.25 mg once at night, increase as needed upto 5 mg TDS.

PROCTINAL, SICRIPTIN, PARLODEL, 1.25, 2.5 mg tabs, ENCRIPT 2.5, 5 mg tabs.

Ropinirole and Pramipexole These are two nonergoline, selective D2/D3 receptor agonists with negligible affinity for D1 and nondopaminergic receptors. Pramipexole has relatively greater affinity for D3 receptors. The therapeutic effect in PD as well as side effect profile is similar to bromocriptine, but they are better tolerated with fewer g.i. symptoms. Consequently dose titration for maximum improvement can be achieved in 1–2 weeks, while the same may take several months with bromocriptine. However, behavioural side effects have been noted.

Ropinirole and pramipexole are now frequently used for monotherapy in early PD as well as to supplement levodopa-carbidopa in advanced cases. Trials have found them to afford symptom relief nearly comparable to levodopa. The Parkinson Study Group and other multicentric trials have noted lower incidence

of dyskinesias and motor fluctuations among patients treated with these drugs than those treated with levodopa. There is some indirect evidence that use of ropinirole/pramipexole in place of levodopa-carbidopa may be associated with slower rate of neuronal degeneration. Such encouraging findings along with less marked dyskinesias and molor fluctuations have established the nonergoline DA agonists as effective alternatives to levodopa and may afford longer symptom-free life to PD patients. They are also useful supplementary drugs to levodopa.

Ropinirole is rapidly absorbed orally, 40% plasma protein bound, extensively metabolized, mainly by hepatic CYP1A2, to inactive metabolites, and eliminated with a terminal t½ of 6 hrs. It is thus longer acting than levodopa, useful in the management of motor fluctuations and reducing frequency of on-off effect.

Side-effects are nausea, dizziness, hallucinations, and postural hypotension. Behavioural side effects like impulsive shopping, betting, gambling and inappropriate sexual overactivity have been observed. Overall, psychiatric side effects are more with DA agonists than with levodopa. Episodes of day time sleep have been noted with ropinirole as well as pramipexole. The higher incidence of hallucinations and sleepiness may disfavour their use in the elderly. Patients should be advised not to drive if they suffer this side effect.

Ropinirole is FDA approved for use in 'restless leg syndrome'.

Ropinirole: Starting dose is 0.25 mg TDS, titrated to a maximum of 4–8 mg TDS. Early cases generally require 1–2 mg TDS.

ROPITOR, ROPARK, ROPIN, ROPEWAY 0.25, 0.5, 1.0, 2.0 mg tabs.

Pramipexole: It is twice as potent as ropinirole, but comparable in efficacy and tolerability. Starting dose 0.125 mg TDS, titrate to 0.5–1.5 mg TDS.

PRAMIPEX 0.125, 0.25, 0.5, 1 mg tab; PARPEX 0.5, 1.0, 1.5 mg tabs, PRAMIROL 0.125, 0.25, 0.5, 1.0, 1.5 mg tabs.

Restless legs syndrome (RLS): It is a peculiar sensorymotor disorder affecting the legs during periods of relaxation, especially sleep. The affected subject feels an irresistable urge to constantly move the legs, usually associated with tingling, itching, discomfort, aching or cramps. The symptoms abate by walking and do not appear during activity. The disorder may be mild and go unnoticed. In some cases, symptoms are severe and disrupt sleep, resulting in day-time sleepiness. The disorder may be primary (idiopathic) or secondary to iron deficiency anaemia, folate or other vitamin deficiencies, varicose veins, peripheral neuropathy (diabetic/uraemic, etc.), or be associated with pregnancy. A genetic basis and mild dopaminergic hypofunction in the brain have been implicated.

The nonergot dopaminergic agonists are the most effective drugs. Relatively low doses: ropinirole (0.25–1.0 mg) or pramipexole (0.125–0.5 mg) taken 2–3 hours before bedtime each day afford dramatic relief in many cases. Other drugs used are benzodiazepines, gabapentin or pregabalin, but these are mostly reserved for nonresponsive cases.

MAO-B INHIBITOR

Selegiline (Deprenyl) It is a selective and irreversible MAO-B inhibitor. Two isoenzyme forms of MAO, termed MAO-A and MAO-B are recognized; both are present in peripheral adrenergic structures and intestinal mucosa, while the latter predominates in the brain and blood platelets. MAO-B preferentially oxidizes DA. Unlike nonselective MAO inhibitors, selegiline in low doses (10 mg/day) does not interfere with peripheral metabolism of dietary amines; Accumulation of CAs and hypertensive reaction does not develop, while intracerebral degradation of DA is retarded (Fig. 31.2). This is responsible for the therapeutic effect in parkinsonism. Higher doses can produce hypertensive interactions with levodopa and indirectly acting sympathomimetic amines.

Selegiline alone has mild antiparkinsonian action in early cases. Administered with levodopa, it prolongs and enhances levodopa action, attenuates motor fluctuations and decreases 'wearing off' effect. As an adjuvant to levodopa, it is beneficial in 50–70% patients and permits 20–30% reduction in levodopa dose. However, advanced cases with 'on-off' effect are not improved and the peak dose levodopa side effects such as dyskinesias, mental confusion or hallucinations may be worsened. Moreover, clinical benefits derived from selegiline are short lived (6–26 months).

Based on the hypothesis that oxidation of DA and/or environmental toxins (MPTP-like) in the striatum by MAO to free radicals was

causative in parkinsonism, it was proposed that early therapy with selegiline might delay progression of the disorder. However, no difference in the course of the disease has been detected on follow up of selegiline treated patients in large multicentric studies. Nevertheless, there is some recent data supporting a neuroprotective effect of rasagiline, another MAO-B inhibitor, in parkinsonism.

Adverse effects Postural hypotension, nausea, confusion, accentuation of levodopa induced involuntary movements and psychosis. Selegiline is partly metabolized by liver into amphetamine which sometimes causes insomnia and agitation. Selegiline is contraindicated in patients with convulsive disorders.

Selegiline interacts with pethidine possibly by favouring its metabolism to norpethidine which causes excitement, rigidity, hyperthermia, respiratory depression. It may also interact with tramadol, dextromethorphan, tricyclic antidepressants and selective serotonin reuptake inhibitors.

ELDEPRYL 5, 10 mg tab; SELERIN, SELGIN 5 mg tab;
Dose: 5 mg with breakfast and with lunch, either alone (in early cases) or with levodopa/carbidopa. Reduce by 1/4th levodopa dose after 2–3 days of adding selegiline.

Rasagiline Another newer selective MAO-B inhibitor with selegiline-like therapeutic effect in parkinsonism. However, it is 5 times more potent, longer acting and not metabolized to amphetamine. It is therefore given once a day in the morning, and does not produce excitatory side effects or insomnia. Because of the above mentioned advantages, it is now preferred over selegiline.

Dose: 1 mg OD in the morning.
RELGIN, RASALECT 0.5, 1.0 mg tabs, RASIPAR 1 mg tab.

COMT INHIBITORS

Two selective, potent and reversible COMT inhibitors *Entacapone* and *Tolcapone* have been introduced as adjuvants to levodopa-carbidopa for advanced PD. When peripheral decarboxylation of levodopa is blocked by carbidopa/benserazide, it is mainly metabolized by COMT to 3-O-methyldopa (*see* Fig. 31.2). Blockade of this pathway by entacapone/tolcapone prolongs the t½ of levodopa and allows a larger fraction of administered dose to cross to brain. Because 3-OMD competes with levodopa for active transport across blood-brain barrier, lowering 3-OMD level in blood itself may improve entry of levodopa in the brain. Since COMT plays a role in the degradation of DA in brain as well, COMT inhibitors could preserve DA formed in the striatum and supplement the peripheral effect (Fig. 31.2). However, entacapone acts only in the periphery (probably because of short duration of action ~2 hr). For tolcapone also, the central action is less important.

Both entacapone and tolcapone enhance and prolong the therapeutic effect of levodopa-carbidopa in advanced PD with motor fluctuations. They may be used to smoothen 'wearing off', increase 'on' time, decrease 'off' time, improve activities of daily living and allow levodopa dose to be reduced. They are not indicated in early PD cases.

Entacapone: 200 mg with each dose of levodopa-carbidopa, max. 1600 mg/day.
ADCAPON, COMTAN 200 mg tab.
Tolcapone: 100–200 mg BD or TDS.

Worsening of levodopa adverse effects such as nausea, vomiting, dyskinesia, postural hypotension, hallucinations, etc. occurs often when a COMT inhibitor is added. However, this can be minimised by adjustment of levodopa dose, which should be reduced by 20–30%. Other prominent side effect is diarrhoea in 10–18% patients (less with entacapone) and yellow-orange discolouration of urine.

Because of reports of acute fatal hepatitis and rhabdomyolysis, tolcapone has been suspended in Europe and Canada, while in USA its use is allowed only after patient's informed consent, in those not responding to entacapone. Entacapone is not hepatotoxic.

GLUTAMATE (NMDA Receptor) ANTAGONIST (Dopamine Facilitator)

Amantadine Developed as an antiviral drug for prophylaxis of influenza A_2 (*see* Ch. 59), it was found serendipitiously to benefit parkinsonism. It acts rapidly but has lower efficacy

than levodopa, and may be equivalent to anticholinergics. About 2/3rd patients derive some benefit. However, tolerance develops over weeks or months and the efficacy is gradually lost. The mechanism of action of amantadine is not clear. It promotes presynaptic synthesis and release of DA in the brain and has an antagonistic action on NMDA type of glutamate receptors, through which the striatal dopaminergic system exerts its influence.

Amantadine can be used in milder cases, or in short courses to supplement levodopa for advanced cases. In the latter situation, it serves to suppress motor fluctuations and abnormal movements. Fixed dose of 100 mg BD is used (not titrated according to response). The effect of a single dose lasts 8–12 hours;
AMANTREL, COMANTREL 100 mg tab.

Side effects These are insomnia, restlessness, confusion, nightmares, anticholinergic effects and rarely hallucinations.

A characteristic side effect due to local release of CAs resulting in postcapillary vasoconstriction is *livedo reticularis* (bluish discolouration) and edema of ankles.
Side effects are accentuated when amantadine is combined with anticholinergics.

CENTRAL ANTICHOLINERGICS

These are drugs having a higher central : peripheral anticholinergic action ratio than atropine, but the pharmacological profile is similar. Certain H_1 antihistaminics also have significant central anticholinergic property. There is little to choose clinically among these drugs, though individual preferences vary.

The central anticholinergics act by reducing the unbalanced cholinergic activity in the striatum of parkinsonian patients. These drugs produce 10–25% improvement in parkinsonian symptoms lasting 4–8 hours after a single dose. Generally, tremor is benefited more than rigidity; hypokinesia is improved the least. Sialorrhoea is controlled by their peripheral action. The overall efficacy is much lower than levodopa. However, they are inexpensive and produce less side effects than levodopa. They may be used alone in mild cases or when levodopa is contraindicated. In others, they can be combined with levodopa in an attempt to lower levodopa dose.

Anticholinergics are the only drugs effective in drug (phenothiazines, other D2 antagonists) induced parkinsonism.

The side effect profile is similar to atropine. Impairment of memory and cognition, organic confusional states and blurred vision are more common in the elderly. Urinary retention is possible in elderly males. The antihistaminics are less efficacious than anticholinergics, but are better tolerated by older patients. Their sedative action also helps. Orphenadrine has mild euphoriant action.

Trihexyphenidyl It is the most commonly used drug. Start with the lowest dose in 2–3 divided portions per day and gradually increase till side effects are tolerated.

1. Trihexyphenidyl (benzhexol): 2–10 mg/day; PACITANE, PARBENZ 2 mg tab.
2. Procyclidine: 5–20 mg/day; KEMADRIN 2.5, 5 mg tab.
3. Biperiden: 2–10 mg/day oral, i.m. or i.v.: DYSKINON 2 mg tab., 5 mg/ml inj.
4. Orphenadrine: 100–300 mg/day; DISIPAL, ORPHIPAL 50 mg tab.
5. Promethazine: 25–75 mg/day; PHENERGAN 10, 25 mg tab.

Some general points

1. None of the above drugs alter the basic pathology of PD—the disease continues to progress. Drugs only provide symptomatic relief and give most patients an additional 5–10 years of happier and productive life.

Considering that oxidative metabolism of DA generates free radicals which may rather hasten degeneration of nigrostriatal neurones, it has been argued that levodopa therapy might accelerate progression of PD. There is no proof yet for this, and controlled prospective studies have not detected any difference in the progression of disease due to levodopa therapy. However, appearance of dyskinesias is related to dose and duration of levodopa therapy. Thus, it may be prudent to delay use of levodopa and begin with anticholinergics/a MAO-B inhibitor or a nonergot DA agonist in early/mild/younger patients. Two or more drugs together may be needed as the disease progresses.

2. Many authorities consider it prudent to delay the initiation of antiparkinsoniam drugs till symptoms impact patient's lifestyle. When drug therapy becomes imperative but disease is mild, only anticholinergics or selegiline/rasagiline may be sufficient. However, anticholinergics are often not tolerated by elderly patients, especially

males. Monotherapy with the newer DA agonists ropinirole or pramipexole is generally started first when the above drugs become inadequate, especially in younger patients, because of fewer motor complications. However, behavioural psychotic side effects and sudden onset sleep may necessitate switching over to levodopa-carbidopa therapy.

3. Combination of levodopa with a decarboxylase inhibitor increases efficacy and reduces early, but not late complications. It is now the standard therapy, and has replaced levodopa alone. Slow and careful initiation over 2–3 months, increasing the dose as tolerance to early side effects develops and then maintenance at this level with frequent evaluation gives the best results. Full benefit lasts for about 2–3 years, then starts declining.

4. Subsequently the duration of benefit from a levodopa dose progressively shortens—end of dose 'wearing off' effect is seen. Dyskinesias appear, mostly coinciding with the peak of levodopa action after each dose. Relief of parkinsonian symptoms gets linked to the production of dyskinesias. Still later (4–8 years) the 'on-off' phenomena and marked dyskinesias may become so prominent that the patient is as incapacitated with the drug as without it. However, discontinuation of levodopa or dopamine agonists, particularly when higher doses have been employed, may precipitate marked rigidity hampering even respiratory excursions, hyperthermia, mental deterioration and a state resembling the 'neuroleptic malignant syndrome'.

5. Levodopa alone is now used only in those patients who develop intolerable dyskinesias with a levodopa-decarboxylase inhibitor combination.

6. A MAO-B inhibitor, especially rasagiline, given alone often produces adequate symptom relief in early/mild cases, and may retard disease progression. It is also used as adjuvant therapy in advanced cases who have response fluctuation. The MAO-B inhibitor serves to prolong and smoothen levodopa-carbidopa effect.

7. The direct DA agonists, like ropinirole/pramipexole are commonly used as the first dopaminergic drug in early cases, as well as to supplement levodopa in late cases to smoothen 'on off' phenomenon, to reduce levodopa dose and possibly limit dyskinesias.

8. In advanced cases, the COMT inhibitor entacapone may be added to levodopa-carbidopa to prolong its action and subdue 'on off' fluctuation. It can be given to patients receiving rasagiline or DA agonists as well.

9. 'Drug holiday' (withdrawal of levodopa for 4–21 days) to reestablish striatal sensitivity to DA by increasing dopaminergic receptor population is no longer practiced.

PROBLEM DIRECTED STUDY

31.1 A 70-year-old man has been under treatment for Parkinson's disease for the last 5 years. He is currently receiving Tab. levodopa 100 mg + carbidopa 25 mg two tablets in the morning, afternoon and night. He now suffers stiffness, shaking and difficulty in getting up from bed in the morning. These symptoms decrease about ½ hour after taking the medicine, but again start worsening by noon. He notices one-sided twitching of facial muscles which is more frequent 1–2 hour after each dose of levodopa-carbidopa.

(a) Should his levodopa-carbidopa medication be stopped/replaced by another drug or the dose be increased further? Alternatively, can another drug be added to his ongoing medication? If so, should levodopa-carbidopa dose be changed or left unaltered?

(see Appendix-1 for solution)

Chapter 32 Drugs Used in Mental Illness: Antipsychotic and Antimanic Drugs

The psychopharmacological agents or psychotropic drugs are those having primary effects on *psyche* (mental processes) and are used for treatment of psychiatric disorders.

During the past 70 years psychiatric treatment has witnessed major changes due to the advent of drugs which can have specific salutary effect in mental illnesses. Before 1950s psychiatric treatment was mostly confined to providing custodial care in mental asylums, which has changed to aiming at restoring the patient to his place in the community. All that could be done before 1952 was to dope and quieten agitated and violent patients. The introduction of *chlorpromazine* (CPZ) in that year has transformed the lives of schizophrenics; most of them can now be rehabilitated to productive life. *Reserpine* was discovered soon after. Though it is a powerful pharmacological tool to study monoaminergic systems in brain and periphery, its clinical use in psychiatry lasted only few years. Next came the *tricyclic* and *MAO inhibitor antidepressants* in 1957–58 and covered another group of psychiatric patients. Many novel and atypical antipsychotics, selective serotonin reuptake inhibitors (SSRIs) and other antidepressants have been introduced since the 1980s. These are now more frequently used. Meprobamate (1954) aroused the hope that anxiety could be tackled without producing marked sedation. This goal has been realised more completely by the development of *Chlordiazepoxide* (1957) and other *benzodiazepines* in the 1960s. *Buspirone* is a significant later addition.

Little attention was paid to Cade's report in 1949 that *Lithium* could be used for excitement and mania: its effective use started in the 1960s and now it has a unique place in psychiatry. Interestingly, some antiepileptics like, valproate and lamotrigine as well as some atypical antipsychotics are now first line drugs in mania and bipolar disorders.

Categorization of psychiatric disorders is often not clear cut. The criteria adopted overlap in individual patients. Nevertheless, broad divisions have to be made, primarily on the basis of predominant manifestations, to guide the use of drugs. The principal categories are:

Psychoses These are severe psychiatric illness with serious distortion of thought, behaviour, capacity to recognise reality and of perception (delusions and hallucinations). There is inexplicable misperception and misevaluation; the patient may be unable to meet the ordinary demands of life.

(a) *Acute and chronic organic brain syndromes (cognitive disorders)* Such as delirium and dementia with psychotic features; some toxic or pathological basis can often be defined. Prominent features are confusion, disorientation, defective memory, disorganized thought and behaviour.

(b) *Functional disorders* No underlying cause can be defined; memory and orientation are mostly retained but emotion, thought, reasoning and behaviour are seriously altered.

- *Schizophrenia* (split mind), i.e. splitting of perception and interpretation from reality—hallucinations, inability to think coherently with little impairment of alertness and intellect.
- *Paranoid states* with marked persecutory or other kinds of fixed delusions (false beliefs) and loss of insight into the abnormality.
- *Mood (affective) disorders* The primary symptom is change in mood state; may manifest as:

Mania—elation or irritable mood, reduced sleep, hyperactivity, uncontrollable thought and speech, may be associated with reckless or violent behaviour, or

Depression—sadness, loss of interest and pleasure, worthlessness, guilt, physical and mental slowing, melancholia, self-destructive ideation.

A common form of mood disorder is *bipolar disorder* with cyclically alternating manic and depressive phases. Two major categories of bipolar disorder are recognized:
Type I: Mania episodes only or both manic and depressive phases.

Type II: Cycles of hypomania alternating with major depression, but no mania episodes.

Neuroses These are less serious; ability to comprehend reality is not lost, though the patient may undergo extreme suffering. Depending on the predominant feature, it may be labelled as:

(a) *Anxiety* An unpleasant emotional state associated with uneasiness, worry, tension and concern for the future.

(b) *Phobic states* Fear of the unknown or of some specific objects, person or situations.

(c) *Obsessive-compulsive disorder* Limited abnormality of thought or behaviour; recurrent intrusive thoughts or ritual-like behaviours which the patient realizes are abnormal or stupid, but is not able to overcome even on voluntary effort. The obsessions generate considerable anxiety and distress.

(d) *Reactive depression* due to physical illness, loss, blow to self-esteem or bereavement, but is excessive or disproportionate.

(e) *Post-traumatic stress disorder* Varied symptoms following distressing experiences like war, riots, earthquakes, etc.

(f) *Hysterical* Dramatic symptoms resembling serious physical illness, but situational, and always in the presence of others; the patient does not feign, but actually undergoes the symptoms, though the basis is only psychic and not physical.

Pathophysiology of mental illness is not clear, though some ideas have been formed, e.g. dopaminergic overactivity in the limbic system may be involved in schizophrenia and mania, while monoaminergic (NA, 5-HT) deficit may underlie depression. Treatment is empirical, symptom oriented and not disease specific. However, it is highly effective in many situations. Depending on the primary use, the psychotropic drugs may be grouped into:

1. *Antipsychotic* (neuroleptic, ataractic, major tranquilizer) useful in all types of functional psychosis, especially schizophrenia.

(The term 'Neuroleptic' is applied to chlorpromazine/haloperidol-like conventional antipsychotic subclass of drugs which have potent D2 receptor blocking activity and produce psychic indifference, emotional quietening with extrapyramidal symptoms, but without causing ataxia or cognitive impairment.)

2. *Antimanic* (mood stabiliser) used to control mania and to break into cyclic affective disorders.

3. *Antidepressants* used for minor as well as major depressive illness, phobic states, obsessive-compulsive behaviour, and certain anxiety disorders.

4. *Antianxiety* (anxiolytic-sedative, minor tranquilizer) used for anxiety and phobic states.

5. *Psychotomimetic* (psychedelic, psychodysleptic, hallucinogen). They are seldom used therapeutically, but produce psychosis-like states. Majority of them are drugs of abuse, e.g. cannabis, LSD.

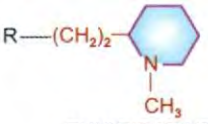
Tranquilizer It is an old term meaning "a drug which reduces mental tension and produces calmness without inducing sleep or depressing mental faculties." This term was used to describe the effects of reserpine or chlorpromazine. However, it has been interpreted differently by different people; some extend it to cover both chlorpromazine-like and antianxiety drugs, others feel that it should be restricted to the antianxiety drugs only. Their division into *major* and *minor* tranquilizers is not justified, because the 'minor tranquilizers' (diazepam-like drugs) are not less important drugs: they are more frequently prescribed and carry higher abuse liability than the 'major tranquilizers' (chlorpromazine-like drugs). The term tranquilizer is, therefore, best avoided.

ANTIPSYCHOTIC DRUGS (Neuroleptics)

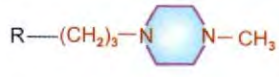
These are drugs having a salutary therapeutic effect in psychoses.



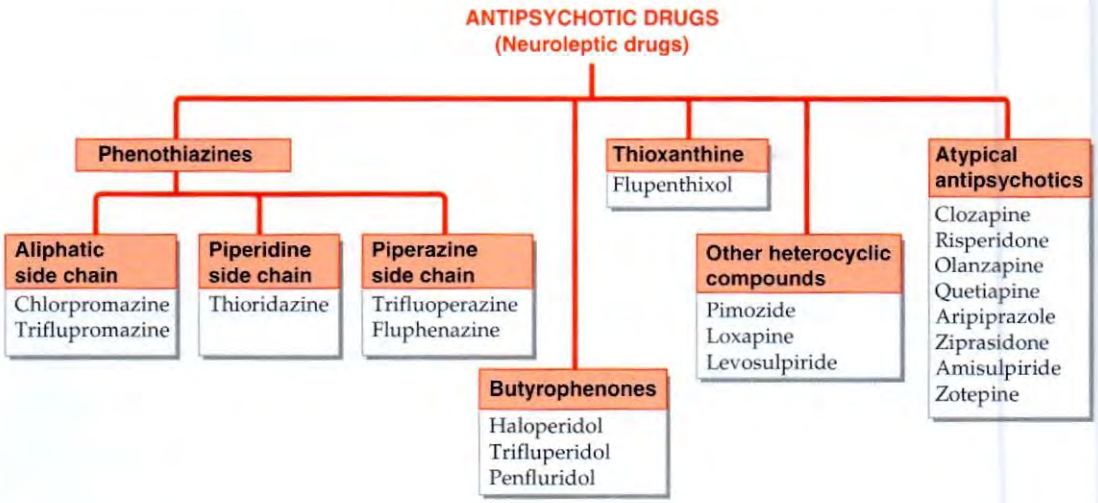
CHLORPROMAZINE
(aliphatic side chain)



THIORIDAZINE
(piperidine side chain)



TRIFLUOPERAZINE
(piperazine side chain)



SECTION 7

Many more drugs have been marketed in other countries but do not deserve special mention. Pharmacology of chlorpromazine (CPZ) is described as prototype; others only as they differ from it. Their comparative features are presented in Table 32.1.

PHARMACOLOGICAL ACTIONS

1. CNS Effects differ in normal and psychotic individuals.

In nonpsychotic individuals CPZ produces indifference to surroundings, paucity of thought, psychomotor slowing, emotional quietening, reduction in initiative and tendency to go off to sleep from which the subject is easily arousable. Spontaneous movements are minimized but slurring of speech, ataxia or motor incoordination does not occur. This is mostly perceived to be unpleasant, and has been referred to as the 'neuroleptic syndrome'. The typical antipsychotic drugs have potent dopamine D2 receptor blocking property and produce extrapyramidal motor side effects. As such, they are called *'Neuroleptic drugs'*.

In a psychotic CPZ reduces irrational behaviour, agitation and aggressiveness and controls psychotic symptomatology. Disturbed thought and behaviour are gradually normalized, anxiety is relieved. Hyperactivity, hallucinations and delusions are suppressed.

All phenothiazines, thioxanthenes and butyrophenones have the same antipsychotic efficacy, but potency differs in terms of equieffective doses. The aliphatic and piperidine side chain phenothiazines (CPZ, triflupromazine, thioridazine) have low potency, produce more sedation and cause greater potentiation of hypnotics, opioids, etc. The sedative effect is produced promptly, while antipsychotic effect takes weeks to develop. Moreover, tolerance develops to the sedative but not to the antipsychotic effect. Thus, the two appear to be independent actions.

Performance and intelligence are relatively unaffected, but vigilance is impaired. Extrapyramidal motor disturbances (*see* adverse effects) are intimately linked to the antipsychotic effect, but are more prominent in the high potency compounds and least in thioridazine, clozapine and other atypical antipsychotics. A predominance of lower frequency waves occurs in the EEG and arousal response is dampened. However, no consistent effect on sleep architecture has been noted. The disturbed sleep pattern in a psychotic is normalized.

Chlorpromazine lowers seizure threshold and can precipitate fits in untreated epileptics. The piperazine side chain compounds have a

lower propensity for this action. Temperature control is knocked off at relatively higher doses rendering the individual poikilothermic. Body temperature falls if surroundings are cold. The medullary respiratory and other vital centres are not affected, except at very high doses. It is very difficult to produce coma with overdose of these drugs. Phenothiazines and butyrophenones, except thioridazine, have potent antiemetic action exerted through the CTZ. However, they are ineffective in motion sickness.

Mechanism of action All antipsychotics (except clozapine-like atypical ones) have potent dopamine D2 receptor blocking action (*see* p. 453 for dopamine receptor subtypes). Antipsychotic potency has shown good correlation with their capacity to bind to D2 receptor. Phenothiazines and thioxanthenes also block D1, D3 and D4 receptors, but there is no correlation of such blockade with their antipsychotic potency. Blockade of dopaminergic projections to the temporal and prefrontal areas constituting the 'limbic system' and in mesocortical areas is probably responsible for the antipsychotic action. This contention is strengthened by the observation that drugs which increase DA activity (amphetamines, levodopa, bromocriptine) induce or exacerbate schizophrenia. Moreover, the dopamine receptor population has been found to be greater in the brains of untreated psychotics, and higher DA levels have been detected in the nucleus accumbens, caudate nucleus and putamen of schizophrenics. A *'dopamine hypothesis of schizophrenia'* has been propounded envisaging DA overactivity in limbic area to be responsible for the disorder. Accordingly, blockade of DA overactivity in limbic area produces the antipsychotic effect, while that in basal ganglia produces the parkinsonian adverse effects. The delayed onset of these effects may be explained by initial adaptive increase in the firing of DA neurones and DA turnover, which gradually subsides and a state of persistent inactivation supervenes as the drug is continued, corresponding to the emergence of the therapeutic effect as well as the extrapyramidal side effects.

However, DA overactivity in the limbic area is not the only abnormality in schizophrenia. Other monoaminergic (5-HT) as well as amino-acid (glutamate) neurotransmitter systems may in addition be affected. That LSD and other indole hallucinogens are $5HT_2$ receptor agonists points to a role of brain serotonergic system in schizophrenia. It has been found that DA activity in prefrontal cortex is actually diminished in schizophrenia; but this has been correlated to the cognitive impairment and other negative symptoms. Only the positive symptoms (hallucinations, aggression, etc.) appear to be closely linked to DA overactivity in mesolimbic areas, but not the negative symptoms (apathy, cognitive deficit, social withdrawal, etc). There is some evidence that hypofunction of NMDA glutamate receptors in the brain could also be contributing to schizophrenia. Not withstanding the above, reduction of dopaminergic neurotransmission is the major mechanism of antipsychotic action.

The DA hypothesis fails to explain the antipsychotic activity of clozapine and other atypical antipsychotics which have weak D2 blocking action. However, these drugs have significant $5\text{-}HT_2$ and α_1 adrenergic blocking action, and some are relatively selective for D4 receptors. Thus, antipsychotic property may depend on a specific profile of action of the drugs on several neurotransmitter receptors. Positron emission tomography (PET) studies of D2 and other receptor occupancy in brains of antipsychotic drug treated patients have strengthened this concept.

Dopaminergic blockade in pituitary lactotropes causes hyperprolactinemia, while that in CTZ is responsible for the antiemetic action.

2. ANS Neuroleptics have varying degrees of α adrenergic blocking activity which may be graded as:

CPZ = triflupromazine = thioridazine > fluphenazine > haloperidol > trifluoperazine > pimozide, i.e. more potent compounds have lesser α blocking activity.

Anticholinergic property of neuroleptics is weak and may be graded as:

thioridazine > CPZ > triflupromazine > trifluoperazine = haloperidol.

The phenothiazines have weak H_1-antihistaminic and anti-5-HT actions as well.

3. Local anaesthetic Chlorpromazine is as potent a local anaesthetic as procaine. However, it is not used for this purpose because of its irritant action. Other antipsychotic drugs have weaker/no membrane stabilizing action.

4. CVS Neuroleptics produce hypotension (primarily postural) by a central as well as peripheral action on sympathetic tone. The hypotensive action is more marked after parenteral administration and roughly parallels the α adrenergic blocking potency. Hypotension is not prominent in psychotic patients, but is accentuated by hypovolemia. Partial tolerance to the hypotensive action develops after chronic use. Reflex tachycardia accompanies hypotension.

High doses of CPZ directly depress the heart and produce ECG changes (Q-T prolongation and suppression of T wave). CPZ exerts some antiarrhythmic action, probably due to membrane stabilization. Arrhythmia may occur in overdose, especially with thioridazine.

5. Endocrine Neuroleptics consistently increase prolactin release by blocking the inhibitory action of DA on pituitary lactotropes. This may result in galactorrhoea and gynaecomastia.

Secretion of pituitary hormones including GH, gonadotropins and ADH is reduced by CPZ, and ACTH response to stress is subdued. However, clinically significant consequences are infrequent.

Though in general, antipsychotic drugs do not affect blood sugar level, CPZ and few others have the potential to impair glucose tolerance or aggravate diabetes, as well as elevate serum triglycerides. This is often associated with weight gain, which may be a causative factor along with accentuation of insulin resistance.

Tolerance and dependence

Tolerance to the sedative and hypotensive actions develops within days or weeks, but maintenance doses for therapeutic effect in most psychotics remain fairly unchanged over years, despite increased DA turnover in the brain. The antipsychotic, extrapyramidal and other actions based on DA antagonism do not display tolerance.

Neuroleptics are hedonically (pertaining to pleasure) bland drugs, lack reinforcing effect so that chronic recipients do not exhibit drug seeking behaviour. Physical dependence is probably absent, though some manifestations on discontinuation have been considered withdrawal phenomena.

PHARMACOKINETICS

Oral absorption of CPZ is somewhat unpredictable and bioavailability is low. More consistent effects are produced after i.m. or i.v. administration. It is highly bound to plasma as well as tissue proteins; brain concentration is higher than plasma concentration. Volume of distribution, therefore, is large (20 L/kg). It is metabolized in liver, mainly by CYP 2D6 into a number of metabolites.

The acute effects of a single dose of CPZ generally last for 6–8 hours. The elimination t½ is variable, but mostly is in the range of 18–30 hours. The drug cumulates on repeated administration, and it is possible to give the total maintenance dose once a day. Some metabolites are active. Moreover, the duration of clinical benefit is much longer relative to the elimination t½; probably because of tight binding to the D2 receptors. The metabolites are excreted in urine and bile for months after discontinuing the drug.

The broad features of pharmacokinetics of other neuroleptics are similar.

Dose: 10–100 mg TDS, oral/i.m; max 800 mg/day.

CHLORPROMAZINE, LARGACTIL 10, 25, 50, 100 mg tab, 5 mg/5 ml and 25 mg/ 5 ml syr., 50 mg/2 ml inj.

DISTINCTIVE FEATURES OF NEUROLEPTICS

Antipsychotic drugs differ in potency and in their propensity to produce different effects. This is summarized in a comparative manner in Table 32.1.

Table 32.1: Comparative properties of antipsychotic drugs

Drug	Antipsychotic dose (mg/day)	Relative activity			
		Extrapyramidal	Sedative	Hypotensive	Antiemetic
1. Chlorpromazine	100–800	++	+++	+++	++
2. Triflupromazine	50–200	++±	+++	++	+++
3. Thioridazine	100–400	+	+++	+++	±
4. Trifluoperazine	2–20	+++	+	+	+++
5. Fluphenazine	1–10	+++	+	+	+++
6. Haloperidol	2–20	+++	+	+	+++
7. Trifluperidol	1–8	+++	+	+	+++
8. Flupenthixol	3–15	+++	+	+	+
9. Pimozide	2–6	+++	+	+	+
10. Loxapine	20–50	++	+	++	+
11. Clozapine	100–300	–	++	++	–
12. Risperidone	2–8	++	+	+	–
13. Olanzapine	2.5–20	±	++	+	–
14. Quetiapine	50–400	±	+++	++	–
15. Aripiprazole	5–30	±	±	±	–
16. Ziprasidone	40–160	±	+	±	–

+ to +++ indicates increasing intensity of that action;
– indicates absence of that action

1. *Triflupromazine* An aliphatic side chain phenothiazine, somewhat more potent than CPZ. Used mainly as antiemetic; it frequently produces acute muscle dystonias in children; especially when injected.

SIQUIL 10 mg tab, 10 mg/ml inj.

2. *Thioridazine* A low potency phenothiazine having marked central anticholinergic action. Incidence of extrapyramidal side effects is very low. Cardiac arrhythmias and interference with male sexual function are more common. Risk of eye damage limits long-term use.

Dose: 25–100 mg 1–3 times a day.

MELOZINE, MELLERIL, THIORIL 25, 50, 100 mg tabs.

3. *Trifluoperazine, fluphenazine* These are high potency piperazine side chain phenothiazines. They have minimum autonomic actions. Hypotension, sedation and lowering of seizure threshold are not significant. They are less likely to impair glucose tolerance, cause jaundice or hypersensitivity reactions. However, extrapyramidal side effects and tardive dyskinesia are marked.

Trifluoperazine: TRINICALM, NEOCALM 1, 5, 10 mg tab.
Fluphenazine: ANATENSOL 1 mg tab, 2.5 mg/5 ml elixir

Fluphenazine decanoate can be given as a depot i.m. injection every 2–4 weeks in uncooperative psychotics.

ANATENSOL DECANOATE, PROLINATE 25 mg/ml inj.

4. *Haloperidol* It is the most commonly used typical antipsychotic; has high potency and pharmacological profile resembling that of piperazine substituted phenothiazines. It produces few autonomic effects, is less epileptogenic, does not cause weight gain, jaundice is rare. Haloperidol is the preferred drug for acute schizophrenia, Huntington's disease and Gilles de la Tourette's syndrome. Parenteral formulation for i.m. use in acute cases is available. It is metabolised by CYP3A4 and 2D6 both. Elimination t½ averages 24 hours.

Dose: 1–10 mg BD.

SERENACE, SENORM 1.5, 5, 10 mg tab, 5 mg/ml inj., HALOPIDOL 2, 5, 10, 20 mg tab, 2 mg/ml oral liq, 10 mg/ml drops.

5. *Trifluperidol* It is similar to but slightly more potent than haloperidol.

Dose: 0.5 mg/day initially increase up to 8 mg/day.

TRIPERIDOL 0.5 mg tab, 2.5 mg/ml inj.

6. *Penfluridol* An exceptionally long acting neuroleptic, recommended for chronic schizophrenia, affective withdrawal and social maladjustment.

Dose: 20–60 mg oral (max 120 mg) once weekly; SEMAP, FLUMAP, PENFLUR 20 mg tab.

7. *Flupenthixol* This thioxanthine is less sedating than CPZ; indicated in schizophrenia and other psychoses, particularly in withdrawn and apathetic patients, but not in those with psychomotor agitation or mania. Infrequently used now.

FLUANXOL 0.5, 1, 3 mg tab, FLUANXOL DEPOT 20 mg/ml inj.

8. *Pimozide* It is a selective DA antagonist with little α adrenergic or cholinergic blocking activity. Because of long duration of action (several days; elimination t½ 48–60 hours) after a single oral dose, it is considered good for maintenance therapy but not when psychomotor agitation is prominent. Incidence of dystonic reactions is low, but it tends to prolong myocardial APD and carries risk of arrhythmias. It has been particularly used in Gilles de la Tourett's syndrome and in ticks.

Dose: 2–6 mg/day.

ORAP, NEURAP, PIMODAC 2, 4 mg tab.

9. *Loxapine* A dibenzoxazepine having CPZ like DA blocking and antipsychotic activity. The actions are quick and short lasting (t½ 8 hr). No clear cut advantage over other antipsychotics has emerged.

Dose: 10–50 mg BD.

LOXAPAC 10, 25, 50 mg caps, 25 mg/5 ml liq.

10. *Levosulpiride* This substituted benzamide is chemically related to the prokinetic drug cisapride, but has selective D2 receptor blocking activity. In addition to being an antipsychotic, it retains prokinetic property. Levosulpiride is indicated in schizophrenia, anxiety, as well as in gastroesophageal reflux, irritable bowel syndrome and peptic ulcer.

Dose: 25–100 mg OD–TDS

LESURIDE 25 mg tab; 75 mg SR tab; 25 mg/2 ml inj; NEXIPRIDE 25, 50, 100 mg tab; 75, 150 mg SR tab; 25 mg/2 ml inj.

ATYPICAL (Second generation) ANTIPSYCHOTICS

These are newer (second generation) antipsychotics that have weak D2 blocking but potent 5-HT_2 antagonistic activity. Extrapyramidal side effects are minimal, and atypical antipsychotics tend to improve the impaired cognitive function in psychotics.

1. *Clozapine* It is the first atypical antipsychotic; pharmacologically distinct from CPZ and related drugs in that it has only weak D2 blocking action, produces few/no extrapyramidal symptoms; tardive dyskinesia is rare and prolactin level does not rise. Both positive and negative symptoms of schizophrenia are improved and clozapine is the most effective drug in refractory schizophrenia, i.e. patients not responding to typical neuroleptics may respond to it. The differing pharmacological profile may be due to its relative selectivity for D4 receptors (which are sparse in basal ganglia) and additional 5-HT_2 as well as α adrenergic blockade. It is quite sedating, moderately potent anticholinergic, but paradoxically induces hypersalivation. Significant H_1 blocking property is present.

Clozapine is metabolized by CYP1A2, CYP2C19 and CYP3A4 into active and inactive metabolites with an average t½ of 12 hours. Its major limitation is higher incidence of agranulocytosis (0.8%) and other blood dyscrasias: weekly monitoring of leucocyte count is required. Metabolic complication like weight gain, hyperlipidemia and precipitation of diabetes is another major limilation. High dose can induce seizures even in nonepileptics. Other side effects are sedation, unstable BP, tachycardia and urinary incontinence. Few cases of myocarditis have been reported which start like flu but may progress to death. Because of the above risks, clozapine is used as a reserve drug in refractory schizophrenia.

Dose: 25–100 mg/day, max 300 mg/day.

LOZAPIN, SIZOPIN, SKIZORIL 25, 50, 100 mg tabs.

2. *Risperidone* Another compound whose antipsychotic activity has been ascribed to a combination of D2 + 5-HT_2 receptor blockade. In addition, it has high affinity for α_1, α_2 and H_1 receptors: blockade of these may contribute to efficacy as well as side effects like postural hypotension. However, BP can rise if it is given with a SSRI. Risperidone is more potent D2 blocker than clozapine; extrapyramidal side

effects are less only at low doses (<6 mg/day). Prolactin levels rise disproportionately during risperidone therapy, but it is less epileptogenic than clozapine, though frequently causes agitation. Weight gain and incidence of new-onset diabetes is less than with clozapine and it is often selected as the first line drug in schizophrenia now. Caution has been issued about increased risk of stroke in the elderly.

Dose: 1–3 mg BD.

RESPIDON, SIZODON, RISPERDAL 1, 2, 3, 4 mg tabs, 1 mg/ml oral liq.

3. *Olanzapine* This atypical antipsychotic; resembles clozapine in blocking multiple monoaminergic (D2, 5-HT_2, α_1, α_2) as well as muscarinic and H_1 receptors. Both positive and negative symptoms of schizophrenia are improved. A broader spectrum of efficacy covering schizo-affective disorders has been demonstrated, and it is approved for use in mania.

Olanzapine is a potent antimuscarinic, produces dry mouth and constipation. Weaker D2 blockade results in few extrapyramidal side effects and little rise in prolactin levels, but is more epileptogenic than high potency phenothiazines. It causes weight gain and carries a higher risk of impairing glucose tolerance or worsening diabetes as well as elevating serum triglyceride. These metabolic complications have discouraged its use. Incidence of stroke may be increased in the elderly. Agranulocytosis has not been reported. Olanzapine is metabolized by CYP1A2 and glucuronyl transferase. The t½ is 24–30 hours.

Dose: 5–20 mg/day.

OLEANZ 2.5, 5, 7.5, 10 and 20 mg tab, 10 mg/amp inj, OLACE, OZAP 2.5, 5, 7.5 mg tab.

4. *Quetiapine* This new short-acting (t½ 6 hours) atypical antipsychotic requires twice daily dosing. It blocks 5-HT_{1A}, 5-HT_2, D2, α_1, α_2 and H_1 receptors in the brain, but D2 blocking activity is low: extrapyramidal and hyperprolactinaemic side effects are minimal. However, it is quite sedating (sleepiness is a common side effect), and major portion of daily dose is given at night. This may help psychotic patients who are unable to sleep well. Postural hypotension can occur, especially during dose titration. Urinary retention/incontinence are reported in few patients. Weight gain and rise in blood sugar are moderate, and it causes some degree of QTc prolongation, risking arrhythmia only at high doses. There is evidence of efficacy of quetiapine in acute mania as well as in bipolar depression, because of which it is frequently selected for maintenance therapy. It is metabolized mainly by CYP3A4; can interact with macrolides, antifungals, anticonvulsants, etc.

Dose: Initially 50 mg/day, increase gradually as needed upto 400 mg/day.

QUTIPIN 25, 50, 100, 200 mg tabs, 50, 100, 200, 400 mg SR tabs., SEROQUIN, SOCALM 25, 50, 100, 200 mg tabs.

5. *Aripiprazole* This atypical antipsychotic is unique in being a partial agonist at D2 and 5-HT_{1A} receptor, but antagonist at 5-HT_2 receptor. The high affinity but low intrinsic activity of aripiprazole for D2 receptor impedes dopaminergic transmission by occupying a large fraction of D2 receptors but activating them minimally. It is not sedating, may even cause insomnia. Extrapyramidal side effects, hyperprolactinaemia and hypotension are not significant. Little tendency to weight gain and rise in blood sugar has been noted. A moderate prolongation of Q-Tc interval occurs at higher doses. Frequent side effects are nausea, dyspepsia, constipation and light-headedness, but not antimuscarinic effects.

Aripiprazole is quite long-acting (t½ ~ 3 days); dose adjustments should be done after 2 weeks treatment. It is metabolized by CYP3A4 as well as CYP2D6; dose needs to be halved in patients receiving ketoconazole or quinidine, and doubled in those taking carbamazepine. Aripiprazole is indicated in schizophrenia with positive and negative symptoms. It is also useful in treatment resistant depression as an augmenting agent, and as maintenance drug in bipolar disorder.

Dose: Initially 10 mg OD, increase upto 30 mg OD.

ARPIZOL, ARIVE 10, 15, 20, 30 mg tabs, ARILAN 15, 30 mg tabs.

6. *Ziprasidone* Another atypical antipsychotic with combined D2 + 5-$HT_{2A/2C}$ + H_1 + α_1 blocking activity. Antagonistic action at 5-HT_{1D} + agonistic activity at 5-HT_{1A} receptors along

with moderately potent inhibition of 5-HT and NA reuptake indicates some anxiolytic and antidepressant property as well. Like other atypical antipsychotics, ziprasidone has low propensity to cause extrapyramidal side effects or hyperprolactinaemia. It is mildly sedating, causes modest hypotension and is less likely to cause weight gain or blood sugar elevation. Nausea and vomiting are the common side effects but it lacks antimuscarinic effects. More importantly, a dose-related prolongation of Q-T interval occurs imparting potential to induce serious cardiac arrhythmias, especially in the presence of predisposing factors/drugs.

The t½ of ziprasidone is ~8 hours; needs twice daily dosing. In comparative trials, its efficacy in schizophrenia has been rated equivalent to haloperidol. It is also indicated in mania.

Dose: 20–40 mg twice daily, max 160 mg/day.

AZONA, ZIPSYDON 20, 40, 80 mg tabs.

7. *Amisulpiride* This congener of *Sulpiride* is categorized with the atypical antipsychotics because it produces few extrapyramidal side effects and improves many negative symptoms of schizophrenia as well. However, similar to typical neuroleptics it retains high affinity for D2 (and D3) receptors and has low-affinity for 5-HT_2 receptors. It also produces hyperpolactinemia. Amisulpiride is not a sedative. Rather, insomnia, anxiety and agitation are common side effects, and antidepressant property has been noted. Risk of weight gain and metabolic complications is low, but Q-T prolongation has been observed, especially in predisposed elderly patients. Amisulpiride is absorbed orally and mainly excreted unchanged in urine with a t½ of 12 hours.

Dose: 50–300 mg/day in 2 doses for schizophrenia with predominant negative symptoms. Also for acute psychosis 200–400 mg BD.

SULPITAC, SKIZOTUS, AMAZEO 50, 100, 200 mg tabs.

8. *Zotepine* Another atypical antipsychotic with dopamine D2+D1, 5-HT_2, α_1 adrenergic and histamine H_1 receptor blocking activities. It also inhibits NA reuptake. Like other drugs of the class, it benefits both positive and negative symptoms of schizophrenia, but is rated less effective than clozapine. Extrapyramidal side effects are less prominent than with typical neuroleptics, but more than clozapine. Hyperprolactinemia is noted. Zotepine lowers seizure threshold and incidence of seizures is increased at high doses. Weight gain, hyperglycaemia and dyslipidemia are likely as with clozapine. Common side effects are weakness, headache, and postural hypotension.

Absorption after oral ingestion is good but first pass metabolism is extensive. The elimination t½ is 14 hours. Zotepine is approved for use in schizophrenia, but does not offer any specific advantage. It has been discontinued in the U.K.

Dose: Initially 25 mg TDS; increase upto 100 mg TDS.

ZOLEPTIL, NIPOLEPT 25, 50 mg tabs.

Asenapine and *Iloperidone* are other atypical antipsychotics with no specific advantage.

ADVERSE EFFECTS

Antipsychotics are very safe drugs in single or infrequent doses: deaths from overdose are almost unknown. However, side effects are common and often limit their use.

I. Based on pharmacological actions (dose related)

1. *CNS* Drowsiness, lethargy, mental confusion; more with low potency typical antipsychotics and some atypical ones like quetiapine and clozapine. Tolerance to sedative effect may develop. Other side effects are increased appetite and weight gain (not with haloperidol); aggravation of seizures in epileptics; even nonepileptics may develop seizures with high doses of some antipsychotics like clozapine and occasionally olanzapine. However high potency, phenothiazines, risperidone, quetiapine, aripiprazole and ziprasidone have little effect on seizure threshold.

2. *CVS* Postural hypotension, palpitation, inhibition of ejaculation (especially with thioridazine) are due to α adrenergic blockade; more common with low potency phenothiazines. Q-T prolongation and cardiac arrhythmias are a risk of overdose with thioridazine, pimozide and ziprasidone.

3. *Anticholinergic* Dry mouth, blurring of vision, constipation, urinary hesitancy in elderly males (thioridazine has the highest propensity); absent in high potency agents. Dry mouth and constipation is common with olanzapine. Some like clozapine induce hypersalivation despite anticholinergic property, probably due to central action.

4. *Endocrine* Hyperprolactinemia (due to D2 blockade) is common with typical neuroleptics and risperidone. This can lower Gn levels, but amenorrhoea, infertility, galactorrhoea and gynaecomastia occur infrequently after prolonged treatment. The atypical antipsychotics, except risperidone, do not appreciably raise prolactin levels.

5. *Metabolic effects* Elevation of blood sugar and triglyceride levels as a consequence of chronic therapy with certain antipsychotics is a major concern now. Low potency phenothiazines (CPZ, thioridazine) and some atypical antipsychotics, particularly olanzapine and clozapine have high risk of precipitating diabetes or worsening it. High potency drugs like trifluperazine, fluphenazine, haloperidol and atypical antipsychotics like risperidone, aripiprazole and ziprasidone have low/no risk. The mechanism of this effect is not clear; may be due to weight gain and/or accentuation of insulin resistance.

Raised triglyceride level is another consequence of insulin resistance. Cardiovascular mortality among schizophrenics is higher; increased use of atypical antipsychotics may be a contributory factor.

6. *Extrapyramidal disturbances* These are the major dose-limiting side effects; more prominent with high potency drugs like fluphenazine, haloperidol, pimozide, etc., least with thioridazine, clozapine, and all other atypical antipsychotics, except higher dose of risperidone. The extrapyramidal effects may be categorized into:

(a) *Parkinsonism* with typical manifestations—rigidity, tremor, hypokinesia, mask like face, shuffling gait; appears between 1–4 weeks of therapy and persists unless dose is reduced. If that is not possible, one of the anticholinergic antiparkinsonian drugs may be given concurrently. Changing the antipsychotic, especially to an atypical agent, may help. Though quite effective, routine combination of the anticholinergic from the start of therapy in all cases is not justified, because they tend to worsen memory and impair intellect, in addition to dry mouth and urinary retention. Levodopa is not effective since D2 receptors are blocked.

A rare form of extrapyramidal side effect is perioral tremors 'rabbit syndrome' that generally occurs after a few years of therapy. It often responds to central anticholinergic drugs.

(b) *Acute muscular dystonias* Bizarre muscle spasms, mostly involving linguo-facial muscles —grimacing, tongue thrusting, torticollis, locked jaw; occurs within a few hours of a single dose or at the most in the first week of therapy. It is more common in children below 10 years and in girls, particularly after parenteral administration; overall incidence is 2%. It lasts for one to few hours and then resolves spontaneously. One of the central anticholinergics, promethazine or hydroxyzine injected i.m. clears the reaction within 10–15 min.

(c) *Akathisia* Restlessness, feeling of discomfort, apparent agitation manifested as a compelling desire to move about, but without anxiety, is seen in some patients between 1–8 weeks of therapy: upto 20% incidence. It may be mistaken for exacerbation of psychosis. The mechanism of this complication is not understood; no specific antidote is available. A central anticholinergic may reduce the intensity in some cases; but a benzodiazepine like clonazepam or diazepam is the first choice treatment of the motor restlessness. Propranolol is more effective; may be given to non-responsive cases. Most patients respond to reduction in dose of the neuroleptic or changeover to an atypical antipsychotic like quetiapine.

(d) *Malignant neuroleptic syndrome* It occurs rarely with high doses of potent agents. The patient develops marked rigidity, immobility, tremor, hyperthermia, semiconsciousness, fluctuating BP and heart rate; myoglobin may be present in blood. The syndrome lasts 5–10 days after drug withdrawal and may be fatal. The neuroleptic must be stopped promptly and symptomatic treatment instituted. Though,

antidopaminergic action of the neuroleptic may be involved in the causation of this syndrome; anticholinergics are of no help. Intravenous dantrolene may benefit. Bromocriptine in large doses has been found useful.

(e) *Tardive dyskinesia* It occurs late in therapy, sometimes even after withdrawal of the neuroleptic: manifests as purposeless involuntary facial and limb movements like constant chewing, pouting, puffing of cheeks, lip licking, choreoathetoid movements. It is more common in elderly women, and is a manifestation of progressive neuronal degeneration along with supersensitivity to DA. It is accentuated by anticholinergics and temporarily suppressed by high doses of the neuroleptic (this should not be tried except in exceptional circumstances). An incidence of 10–20% has been reported after long term treatment. This reaction is uncommon with clozapine, quetiapine and other atypical antipsychotics. The dyskinesia may subside months or years after withdrawal of therapy, or may be lifelong. There is no satisfactory solution of the problem.

Recently two vesicular monoamine transporter 2 (VMAT2) inhibitors *Deutetrabenazine* and *Valbenazine* have been approved by US-FDA for symptomatic treatment of tardive dyskinesia. They act by depleting presynaptic stores of DA.

7. *Miscellaneous* *Weight gain* often occurs due to long-term antipsychotic therapy, sugar and lipids may tend to rise. *Blue pigmentation* of exposed skin, *corneal and lenticular opacities, retinal degeneration* (more with thioridazine) occur rarely after long-term use of high doses of phenothiazines.

II. Hypersensitivity reactions These are not dose related.

1. *Cholestatic jaundice* with portal infiltration; 2–4% incidence; occurs between 2–4 weeks of starting therapy. It calls for withdrawal of the drug; resolves slowly. More common with low potency phenothiazines; rare with haloperidol.

2. *Skin rashes, urticaria, contact dermatitis, photosensitivity* (more with CPZ).

3. *Agranulocytosis* is rare; more common with clozapine.

4. *Myocarditis* Few cases have occurred with clozapine.

INTERACTIONS

1. Neuroleptics potentiate all CNS depressants —hypnotics, anxiolytics, alcohol, opioids and antihistaminics. Overdose symptoms may occur.
2. Neuroleptics block the actions of levodopa and direct DA agonists in parkinsonism.
3. Antihypertensive action of clonidine and methyldopa is reduced, probably due to central α_2 adrenergic blockade.
4. Phenothiazines and others are poor enzyme inducers—no significant pharmacokinetic interactions occur. Enzyme inducers (barbiturates, anticonvulsants) can reduce blood levels of neuroleptics.

USES

1. Psychoses

Schizophrenia The antipsychotics are used primarily in functional psychoses. They have an indefinable but definite therapeutic effect in all forms of schizophrenia: produce a wide range of symptom relief. There is no difference in the efficacy of typical and atypical antipsychotics against positive symptoms (hallucinations, delusions, disorganized thought, restlessness, insomnia, anxiety, fighting, aggression) but for negative symptoms (apathy, loss of insight and volition, emotional blunting, affective flattening, poverty of speech, social withdrawal) the atypical ones are more effective. Antipsychotics also tend to restore affective and motor disturbances and help upto 90% patients to lead a near normal life in the society. However, intellect and cognition are little benefited. Some patients do not respond, and virtually none responds completely. Antipsychotics are only symptomatic treatment, do not remove the cause of illness; long-term (even life-long) treatment may be required. Judgement, memory and orientation are only marginally improved. Patients with recent onset of illness and acute exacerbations respond better. The goal of therapy is to relieve symptoms and functionally rehabilitate the patient.

Choice of drug is largely empirical, guided by the presenting symptoms, associated features and mood state, and on the type of side effect that is more acceptable in a particular patient. In general, the atypical antipsychotics are better tolerated and more commonly used now than the older typical ones. Individual patients differ in their response to different antipsychotics; there is no way to predict which patient will respond better to which drug. The following may help drug selection:

- Agitated, combative and violent—haloperidol, quetiapine, CPZ.
- Withdrawn and apathetic—trifluoperazine, fluphenazine, aripiprazole, ziprasidone.
- Patient with mainly negative symptoms and resistant cases—clozapine is the most effective; alternatives are olanzapine, risperidone, aripiprazole, ziprasidone.
- Patient with mood elevation, hypomania—haloperidol, fluphenazine, quetiapine, olanzapine.
- If extrapyramidal side effects and risk of tardive dyskinesia must be avoided —thioridazine, clozapine or any other atypical antipsychotic.
- Elderly patients who are more prone to sedation, mental confusion and hypotension—a high potency phenothiazine, haloperidol or aripiprazole.

Currently, the newer atypical antipsychotics are tried first and are more commonly prescribed. Though, there is no convincing evidence of higher efficacy, they produce fewer side effects and neurological complications. They are preferable for long-term use in chronic schizophrenia due to low risk of tardive dyskinesia. Of the older, typical neuroleptics, the high potency agents, especially haloperidol, are preferred over the low potency ones.

Gilles de la Tourette syndrome This disorder characterized by multiple motor or phonic tics (which may be awkward or obscene) prevalent mostly among children is treated symptomatically with behavioural therapy and training, often supplemented by typical antipsychotic drugs, especially haloperidol or pimozide. Atypical antipsychotics like risperidone and aripiprazole have also been found to help overcome the compulsive tics.

Acute mania Antipsychotics are required in high doses for rapid control of acute mania. Fortunately, manic patients tolerate them very well. Haloperidol or olanzapine may be given i.m.; beneficial effects become evident in 1–3 days. Lithium or valproate may be started simultaneously or after the acute phase. Such combination therapy is more effective. The antipsychotic may be continued for months or may be withdrawn gradually after 1–3 weeks when lithium or its substitute has stabilized the mood state. For mania patients who are to be treated orally, the current trend is to use one of the atypical antipsychotics *viz.* olanzapine/risperidone/aripiprazole or quetiapine to avoid extrapyramidal side effects.

Bipolar disorder Some atypical antipsychotics (olanzapine, aripiprazole, quetiapine) alone or in combination with lithium/valproate, are also now being used in the maintenance therapy of bipolar disorder (*see* p. 478).

Organic brain syndromes Antipsychotic drugs have limited efficacy in dementia and delirium associated with psychotic features. They may be used in low doses on a short-term basis. One of the potent drugs is preferred to avoid mental confusion, hypotension and precipitation of seizures. Moreover, low potency drugs (CPZ, thioridazine) have significant antimuscarinic property which may worsen delirium and dementia. Haloperidol, risperidone, aripiprazole or ziprasidone are mostly selected.

General comments The dose of antipsychotic drugs has to be individualized by titration with the symptoms and kept at minimum. In chronic schizophrenia maximal therapeutic effect is seen after 2–4 months therapy. However, injected neuroleptics control aggressive symptoms of acute schizophrenia over hours or a few days. Combination of two or more antipsychotics is not advantageous. However, a patient on maintenance therapy with a nonsedative drug may be given additional CPZ or haloperidol

by i.m. injection to control exacerbations or violent behaviour.

In a *depressed psychotic*, a tricyclic/SSRI antidepressant may be combined with relatively lower dose of an antipsychotic. One of the atypical agents is mostly used because they are effective in bipolar disorder. Quetiapine is the preferred drug, because it is effective as monotherapy as well. Benzodiazepines may be added for brief periods in the beginning.

Low dose maintenance or intermittent regimens of antipsychotics have been tried in relapsing cases. Depot injections, e.g. fluphenazine/haloperidol decanoate given at 2–4 week intervals are preferable in many cases.

2. Anxiety Antipsychotics have antianxiety action but should not be used for simple anxiety because they produce psychomotor slowing, emotional blunting, autonomic and extrapyramidal side effects. Benzodiazepines are the primary drugs used in anxiety. However, low dose of quetiapine, risperidone or olanzepine have been found useful as adjuvants to SSRIs in generalized anxiety disorder.

3. As antiemetic The typical neuroleptics are potent antiemetics. They control a wide range of drug and disease induced vomiting at doses much lower than those needed in psychosis. However, they should not be given unless the cause of vomiting has been identified. Though effective in morning sickness, they should not be used for this condition. Neuroleptics are not effective in motion sickness: probably because dopaminergic pathway through the CTZ is not involved. With the availability of 5-HT_3 antagonists and other antiemetics, use of neuroleptics for control of vomiting has declined.

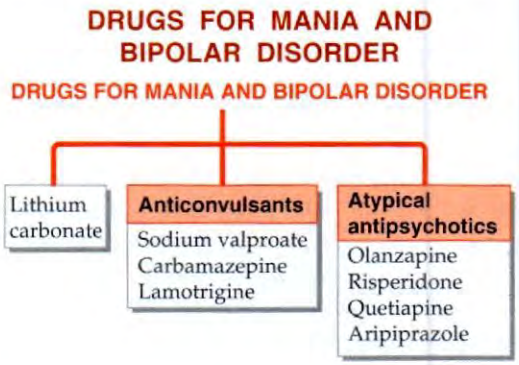
4. Other uses

(a) *To potentiate hypnotics, analgesics and anaesthetics:* such use is rarely justified now.

(b) *Intractable hiccough:* may respond to parenteral CPZ.

(c) *Tetanus:* CPZ is an alternative drug to relieve skeletal muscle spasm.

(d) *Alcoholic hallucinosis* and *Huntington's disease* are the other indications.



LITHIUM CARBONATE

Lithium is a small monovalent cation. In 1949, it was found to be sedative in animals and to exert beneficial effects in manic patients.

In the 1960s and 1970s the importance of maintaining a narrow range of serum lithium concentration was realized and unequivocal evidence of its clinical efficacy was obtained. Lithium is a drug of its own kind to suppress mania and to exert a prophylactic effect in bipolar (manic) disorder at doses which have no overt CNS effects. Lithium is established as the standard antimanic and mood stabilizing drug. However, over the past 2–3 decades, several anticonvulsants and atypical antipsychotics have emerged as equally effective and more manageable alternatives to lithium.

Actions and mechanism

1. *CNS* Lithium has practically no acute effects in normal individuals as well as in bipolar patients. It is neither sedative nor euphorient; but on prolonged administration, it acts as a mood stabiliser in bipolar disorder. Given to patients in acute mania, it gradually suppresses the episode taking 1–2 weeks; continued treatment prevents cyclic mood changes. The markedly reduced sleep time of manic patients is normalized.

The mechanism of antimanic and mood stabilizing action of lithium is not known. However, the following mechanisms have been proposed:

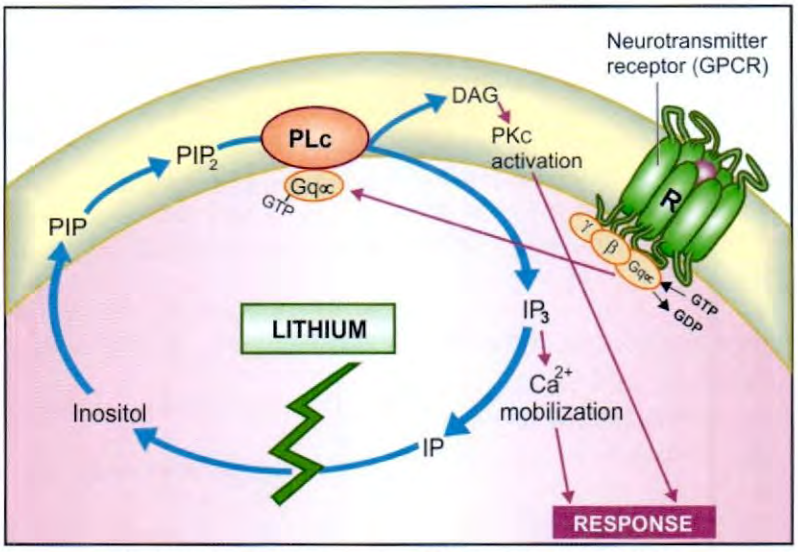


Fig. 32.1: Proposed mechanism of antimanic action of lithium

PIP—Phosphatidyl inositol phosphate; PIP_2—Phosphatidyl inositol bisphosphate; IP_3—Inositol trisphosphate; IP—Inositol-1-phosphate; PLc—Phospholipase C; DAG—Diacylglycerol; PKc—Protein Kinase C; Gq—Coupling Gq protein; R—Neurotransmitter receptor

- Li^+ partly replaces body Na^+ and is nearly equally distributed inside and outside the cells (contrast Na^+ and K^+ which are unequally distributed); this may affect ionic fluxes across brain cells or modify the property of cellular membranes. However, relative to Na^+ and K^+ concentration, the concentration of Li^+ associated with therapeutic effect is very low.
- Lithium decreases the presynaptic release of NA and DA in the brain of treated animals without affecting 5-HT release. This may correct any imbalance in the turnover of brain monoamines.
- The above hypothesis cannot explain why Li^+ has no effect on people not suffering from mania. An attractive hypothesis has been put forward based on the finding that lithium in therapeutic concentration range inhibits hydrolysis of inositol-1-phosphate by inositol monophosphatase. As a result, the supply of free inositol for regeneration of membrane phosphatidyl-inositides, which are the source of IP_3 and DAG, is reduced (Fig. 32.1). The hyperactive neurones involved in the manic state may be preferentially affected, because supply of inositol from extracellular sources is meagre. Thus, lithium may ignore normally operating receptors, but 'search out' and selectively, though indirectly, dampen signal transduction in the overactive receptors functioning through phosphatidyl inositol hydrolysis. In support of this hypothesis, it has been recently demonstrated that valproate, which has Li^+ like effect in mania and bipolar disorder, also reduces intraneuronal concentration of inositol in human brain by inhibiting *de novo* inositol synthesis.

Several other mechanisms involving elements of neuronal signalling like PKc, glutamate, arachidonate, etc. have also been proposed to explain lithium action.

2. *Other actions* Lithium inhibits the action of ADH on distal tubules in the kidney and causes a diabetes insipidus like state.

An insulin-like action on glucose metabolism is exerted.

Leukocyte count is increased by lithium therapy. Lithium inhibits release of thyroid hormones resulting in feedback stimulation of thyroid through pituitary. Majority of Li^+ treated patients remain in a state of compensated euthyroidism, but few get decompensated and become clinically hypothyroid.

Pharmacokinetics and control of therapy

Lithium is well absorbed orally (peak level in 2–3 hours) and is neither protein bound nor metabolized. It first distributes in extracellular water, then gradually enters cells and penetrates into brain, ultimately attaining a rather uniform distribution in total body water. The CSF concentration of Li^+ is about half of plasma concentration. Apparent volume of distribution at steady-state averages 0.8 L/kg.

Lithium is handled by the kidney in much the same way as Na^+. Nearly 80% of the filtered Li^+ is reabsorbed in the proximal convoluted tubule. When Na^+ is restricted, a larger fraction of filtered Na^+ is reabsorbed, so is Li^+, tending to raise serum Li^+. After a single dose of Li^+, its urinary excretion is rapid for 10–12 hours, followed by a much slower phase lasting several days. The t½ of the latter phase is 16–30 hours. Renal clearance of lithium is 1/5 of creatinine clearance. On repeated medication, steady-state plasma concentration is achieved in 5–7 days. Levels are higher in older patients and in those with renal insufficiency.

There is marked individual variation in the rate of lithium excretion. Thus, with the same daily dose, different individuals attain widely different plasma concentrations. However, in any individual the clearance remains fairly constant over time. Since the margin of safety is narrow, monitoring of serum lithium concentration is essential for optimising therapy; 0.5–0.8 mEq/L is considered optimum for maintenance therapy in bipolar disorder, while 0.8–1.2 mEq/L is required for episodes of acute mania. Toxicity symptoms occur frequently when serum levels exceed 1.5 mEq/L.

Lithium is excreted in sweat and saliva as well, and secreted in breast milk. Mothers on lithium should not breastfeed.

Adverse effects Side effects are common, but are mostly tolerable. Toxicity occurs at levels only marginally higher than therapeutic levels.

- Nausea, vomiting and mild diarrhoea occur initially, can be minimized by starting at lower doses.
- Thirst and polyuria are experienced by most patients
- Fine tremors may occur even at therapeutic concentrations.
- CNS toxicity manifests as plasma concentration rises producing coarse tremors, giddiness, ataxia, motor incoordination, nystagmus, mental confusion, slurred speech, hyper-reflexia. Overdose symptoms are regularly seen at plasma concentration above 2 mEq/L producing muscle twitchings, drowsiness, delirium, coma and convulsions. Vomiting, severe diarrhoea, albuminuria, hypotension and cardiac arrhythmias are the other features of Li^+ toxicity.

  Treatment It is symptomatic. There is no specific antidote. Osmotic diuretics and sod. bicarbonate infusion promote Li^+ excretion. Haemodialysis is indicated if serum levels are > 4 mEq/L.
- On long-term use, some patients develop renal diabetes insipidus. Most patients gain some body weight.
- Goiter has been reported in about 4%. This is due to interference with release of thyroid hormone → fall in circulating T_3, T_4 levels → TSH secretion from pituitary → enlargement (goiter) and stimulation of thyroid. Many patients remain euthyroid, few become hypothyroid. Lithium induced goiter and hypothyroidism does not warrant discontinuation of therapy; can be easily managed by thyroid hormone supplementation.
- Lithium is contraindicated during pregnancy: foetal goiter and other congenital

abnormalities, especially cardiac, can occur; the newborn is often hypotonic.

- At therapeutic levels, Li^+ can cause reduction of T-wave amplitude. At higher levels, SA node and A-V conduction may be depressed, but arrhythmias are infrequent. Lithium is contraindicated in sick sinus syndrome.
- Lithium can cause dermatitis and worsen acne.

Interactions

1. Diuretics (thiazide, furosemide) by causing Na^+ loss promote proximal tubular reabsorption of Na^+ as well as Li^+ → plasma levels of lithium rise. Potassium sparing diuretics cause milder Li^+ retention.
2. Tetracyclines, NSAIDs and ACE inhibitors can also cause lithium retention.
3. Lithium reduces pressor response to NA.
4. Lithium tends to enhance insulin/sulfonylurea induced hypoglycaemia.
5. Neuroleptics, including haloperidol, have been frequently used along with lithium without problem. However, sometimes, the combination of haloperidol and lithium produces marked tremor and rigidity.

Use

Lithium is used as its carbonate salt because this is less hygroscopic and less gastric irritant than LiCl. Lithium citrate is used in syrup formulations.

LICAB, LITHOSUN 300 mg tab, 400 mg SR tab.

It is generally started at 300–600 mg/day and gradually increased to yield therapeutic plasma levels;

1. *Acute mania* (inappropriate cheerfulness or irritability, motor restlessness, high energy level, nonstop talking, racing thoughts, flight of ideas, little need for sleep and progressive loss of contact with reality; sometimes violent behaviour). Though lithium is effective in controlling acute mania, response is slow and control of plasma levels is difficult during the acute phase. Most psychiatrists prefer to use an atypical antipsychotic orally or by i.m. injection (*see* p. 473), with or without a potent BZD like clonazepam/lorazepam, and start lithium after the episode is under control. Maintenance lithium therapy is generally given for 6–12 months to prevent recurrences.

2. *Bipolar disorder* Lithium has proven efficacy in bipolar disorder: is gradually introduced and maintained at plasma concentration between 0.5–0.8 mEq/L. Such treatment lengthens the interval between cycles of mood swings: episodes of mania as well as depression are attenuated, if not totally prevented in upto 70% patients. However, because of frequent side effects and problems in maintaining narrow range of serum Li^+ levels, valproate and other alternative drugs are more frequently used now.

Recurrent *unipolar depression* also responds to lithium therapy. Combination of antidepressant + lithium is often used.

3. Lithium is being sporadically used in many other *recurrent neuropsychiatric illness*, cluster headache and as adjuvant to antidepressants in resistant nonbipolar *major depression.*

ALTERNATIVES TO LITHIUM

Approximately 30% patients of mania and bipolar disorder (especially rapidly cycling cases) show incomplete or poor response to lithium. Many do not tolerate it, or are at special risk of toxicity. Strong evidence of efficacy of some anticonvulsants and atypical antipsychotics in different phases of the disorder is now available.

1. *Sodium valproate* Relatively high dose oral valproate is a first line treatment for mania. It acts faster than lithium but slower than antipsychotics ± a BZD. Valproate has a better safety profile than lithium. *Divalproex*, a complex of valproic acid, is more commonly used due to better gastric tolerance. A combination of valproate with an atypical antipsychotic has high efficacy in acute mania.

Valproate is also an effective prophylactic in bipolar disorder, and can be useful in those not responding to lithium or not tolerating

it. Patients with rapid cycling pattern may particularly benefit from valproate therapy. A combination of lithium and valproate may succeed in cases resistant to monotherapy with either drug.

2. *Carbamazepine* Another antiepileptic, carbamazepine (CBZ) was found to control mania and to prolong remission in bipolar disorder. However, it is less effective than lithium or valproate in acute mania. Moreover, acute mania requires rapidly acting drug, while effective doses of carbamazepine have to be gradually built up. Initiation of therapy with high doses needed for efficacy produce neurotoxicity and are poorly tolerated. Compared to lithium and valproate, efficacy of carbamazepine for long-term prophylaxis of bipolar disorder is less well established, though some non-responsive cases may respond to it, especially the rapidly cycling ones. Due to strong enzyme inducing property, CBZ has many drug interactions causing problems in the use of other drugs. Nevertheless, it is a valuable alternative to lithium.

3. *Lamotrigine* There is now strong evidence of efficacy of this newer anticonvulsant for prophylaxis of depression in bipolar disorder. Lamotrigine is not effective for treatment as well as prevention of mania. It is now extensively used in the maintenance therapy of type II bipolar disorder (major depressive episodes alone or alternating with hypomania), because in this condition risk of inducing mania is minimal. Lamotrigine can be combined with lithium to improve its efficacy. The tolerability profile of lamotrigine is favourable.

4. *Atypical antipsychotics* Lately, several studies have testified to the efficacy of atypical antipsychotics in acute mania. *Olanzapine*, *risperidone*, *aripiprazole*, *quetiapine*, with or without a BZD, are now the first line drugs for control of acute mania, except cases requiring urgent parenteral therapy, for which i.m. olanzapine or haloperidol are the most effective. Aripiprazole has recently emerged as the favoured drug for treatment of mania in bipolar I disorder, both as monotherapy as well as adjuvant to lithium or valproate. Maintenance therapy with aripiprazole prevents mania. Lack of metabolic effects favours its long-term use.

Olanzapine is also approved for maintenance therapy of bipolar disorder. Though both manic and depressive phases are suppressed, it is not considered suitable for long-term therapy due to higher risk of weight gain, hyperglycaemia, etc. Strong evidence of efficacy of quetiapine has emerged in bipolar depression. Combination of an atypical antipsychotic with valproate or lithium has demonstrated high efficacy in acute phases as well as for maintenance therapy of bipolar disorder.

HALLUCINOGENS (Psychotomimetics, Psychedelics, Psychodysleptics, Psychotogens)

These are drugs which alter mood, behaviour, thought and perception in a manner similar to that seen in psychosis. Many natural products having hallucinogenic property have been discovered and used by man since prehistoric times. A number of synthetic compounds have also been produced. The important ones are briefly introduced below.

INDOLE AMINES

1. Lysergic acid diethylamide (LSD) Synthesized by Hofmann (1938) who was working on the chemistry of ergot alkaloids, and himself experienced its hallucinogenic effect. It is the most potent psychedelic, 25–50 µg produces all the effects. In addition to the mental effects, it produces pronounced central sympathetic stimulation. The hallucinogenic and other behavioural effects of LSD probably involve agonistic action on $5HT_2$ receptors in the brain serotonergic system.

2. Lysergic acid amide A close relative of LSD but 10 times less potent; found in morning glory (*Ipomoea violace*) seeds.

3. Psilocybin Found in a Mexican mushroom *Psilocybe mexicana*; it has been used by Red Indian tribals during religious rituals.

4. Harmine It is present in a vine *Banisteriopsis caapi*, found in the Amazon region. The Brazilian natives have used it as a snuff.

5. Bufotenin It was isolated from the skin of a toad (*Bufo marinus*). It is also found in 'Cohaba Snuff' and in the mushroom *Amanita muscaria*.

The above are all *Indolealkylamines* related chemically to 5-HT. A number of other synthetic derivatives like Dimethyltryptamine (DMT) are also hallucinogenic.

PHENYLALKYL AMINES

Mescaline From Mexican 'Peyote cactus' *Lophophora williamsi*. It is a low potency hallucinogen used by natives during rituals. It is a phenylalkylamine but does not have marked sympathomimetic effects.

Ecstasy Methylene dioxy methamphetamine (MDMA, or tenamphetamine) is an amphetamine-like synthetic compound with stimulant and hallucinogenic properties, that has been abused as a recreational and euphoriant drug, especially by college students under the name *'Ecstasy'*. Fear of neurotoxicity has reduced its popularity.

Yaba This is a combination of methamphetamine with another stimulant methylhexanamine or caffeine. Popular as a 'street drug' in Thailand and Myanmar, it has spread to many countries including India, as a 'party drug' among the youth. Users claim it to be an aphrodisiac and that it produces a 'high'. The risk of neurotoxicity is similar to amphetamine.

Other synthetic phenylalkylamines with hallucinogenic property are—Dimethoxymethyl amphetamine (DOM) and Methylene dioxyamphetamine (MDA). High doses and repeated use of amphetamine can also cause psychosis.

ARYLCYCLOHEXYL AMINES

Phencyclidine It is an anticholinergic, which activates σ (sigma) receptors in the brain causing disorientation, distortion of body image, hallucinations and an anaesthetic like state. Ketamine is a closely related compound with lower hallucinogenic potential and is used in anaesthesia. Mixed with drinks, ketamine has been abused as a 'rape drug', because of its fast and strong depressant-amnesic action.

CANNABINOIDS

$^{9}\Delta$ Tetrahydrocannabinol ($^{9}\Delta$ THC) It is the active principle of *Cannabis indica* (Marijuana), which has been the most popular recreational and ritualistic intoxicant used for millennia. Its use has spread worldwide. The following are the various forms in which it is used.

Bhang the dried leaves—it is generally taken by oral route after grinding and making a paste. It acts slowly.

Ganja the dried female inflorescence—it is more potent and is smoked: effects are produced almost instantaneously.

Charas it is the dried resinous extract from the flowering tops and leaves—most potent and is usually smoked along with tobacco; also called 'hashish'.

Cannabis is the drug of abuse having the lowest acute toxicity. Even habitual use is not clearly associated with neurotoxicity or damage to any organ system. Though, personality and psychiatric problems are more common among cannabis users, it is not definite whether such traits led to cannabis use or cannabis caused them. Young abusers may exhibit 'amotivational syndrome', i.e. loss of interest in work or self-improvement activities.

Considerable insight has been obtained in cannabinoid pharmacology. Since 1990 two *cannabinoid receptors CB1* (in CNS) and *CB2* (in peripheral tissues) have been identified and cloned. A host of endogenous ligands for the cannabinoid receptors have also been isolated. *Anandamide*, the ethanolamide of arachidonic acid is the principal endocannabinoid synthesized in the brain. The physiological function subserved by the central and peripheral cannabinoid system is not clearly known. Endocannabinoids are released by macrophages during haemorrhagic shock and cause fall in BP. However, all actions of cannabis are not mimicked by anandamide.

Cannabis produces potent analgesic, antiemetic, antiinflammatory and many other pharmacological actions. The crude herb, its active constituents and some synthetic analogues have been tried in a variety of conditions and many potential clinical applications are proposed.

- To ameliorate muscle spasm and pain in multiple sclerosis, and certain dystonias.
- Cancer chemotherapy induced vomiting. The synthetic cannabinoids nabilone and dronabinol ($^{9}\Delta$ THC) are licenced for this use.
- As a neuronal protective after head injury and cerebral ischaemia.
- To relieve anxiety and migraine.
- To reduce i.o.t. in glaucoma.
- As appetite stimulant.
- As bronchodilator in asthma.

However, the hallucinogenic and psychomotor effects are a limitation; nonhallucinogenic congeners are being investigated.

The hallucinogens, particularly marijuana, produce a dream-like state with disorientation, loss of contact with reality, field of vision may appear to sway and objects distorted like images in a curved mirror, faces may appear grotesque. On closing the eyes an unending series of colourful, very realistic and fantastic images appear to surge; time sense is altered, music appears tangible. Ability to concentrate is impaired, one can read but does not know what he is reading; however, ataxia is not prominent. Many subjects feel relaxed and supremely happy, may laugh uncontrollably (experience a 'high') or may become sad and weep. With higher doses—panic reactions and sinking sensation are common.

Some degree of tolerance occurs, but *reverse tolerance* is not unusual.

All hallucinogens are drugs of abuse. Psychological dependence on hallucinogens may be mild (occasional trips) to marked (compulsive abuse), but physical dependence does not occur.

Hallucinogens have been rarely used in psychiatry to facilitate conversation and for opening up the inner self in case of withdrawn patients.

☞ PROBLEM DIRECTED STUDY

32.1 A 25-year-male was diagnosed as a case of schizophrenia on the basis of disturbed thinking process, inappropriate talking and behaviour, restlessness, bursts of temper, anxiety, poor self-care, disturbed sleep, delusional beliefs and occasional auditory hallucinations. He was treated with tab. haloperidol 5 mg once daily at bed time. The dose was increased to 7.5 mg daily in the 2nd week and to 10 mg daily in the 3rd week. His symptoms gradually subsided and he appeared more calm and organized. However, in the 5th week his family members reported that his restlessness has reappeared, he keeps pacing around in the room, but is not aggressive or combative. On questioning the patient admited an uncontrollable urge to move around and that he feels uncomfortable in remaining still. He is not worried or anxious, but has difficulty in falling asleep.

(a) What could be the reason for the motor restlessness? Should the dose of haloperidol be increased or decreased, or should it be changed to another antipsychotic drug?

(b) Should any other drug be given to relieve the condition?

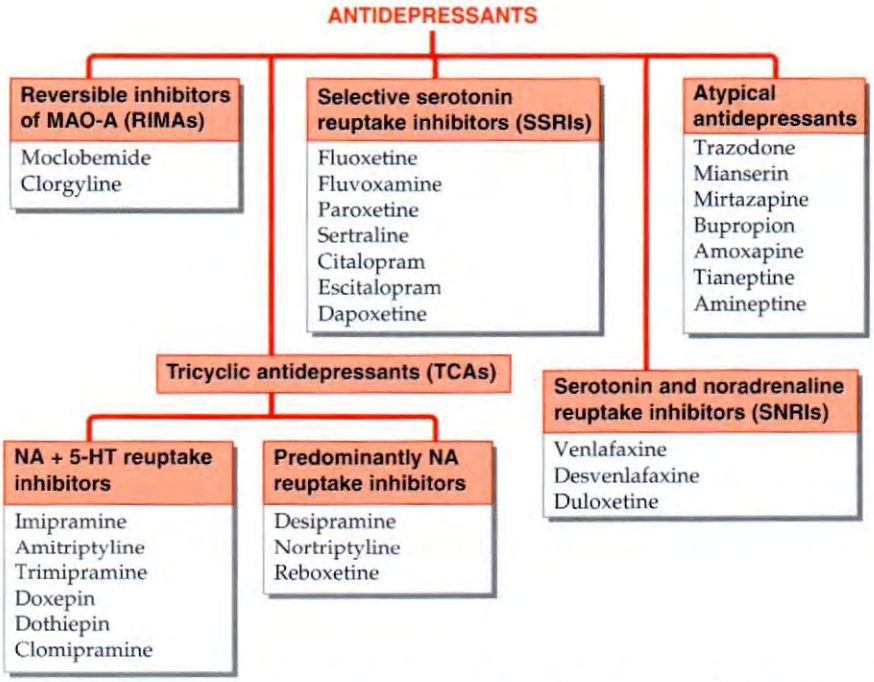
(see Appendix-1 for solution)

Chapter 33 Drugs Used in Mental Illness: Antidepressant and Antianxiety Drugs

Major depression and mania are two extremes of *affective disorders* which refer to a pathological change in the mood state. *Major depression* is characterized by symptoms like sad mood, loss of interest and pleasure, low energy, worthlessness, guilt, psychomotor retardation or agitation, change in appetite and/or sleep, melancholia, suicidal thoughts, etc. It may be a *unipolar* or a *bipolar cyclic disorder* in which cycles of mood swings from mania to depression occur over time. The mood change may have a psychotic basis with delusional thinking or occur in isolation and induce anxiety. On the other hand, pathological anxiety may lead to depression. Anxiety and depression are the leading psychiatric disorders now.

ANTIDEPRESSANTS

These are drugs which can elevate mood in depressive illness. Practically all antidepressants affect monoaminergic transmission in the brain



Many other drugs like Protriptyline, Maprotiline, Nafazodone, etc. are marketed in other countries.

in one way or the other, and many of them have other associated properties. Over the past three decades, a large number of antidepressants with an assortment of effects on reuptake/metabolism of biogenic amines, and on pre/postjunctional aminergic/cholinergic receptors have become available so that a cogent classification is difficult. A working classification has been presented above.

MAO INHIBITORS

MAO is a mitochondrial enzyme involved in the oxidative deamination of biogenic amines (Adr, NA, DA, 5-HT). Two isoenzyme forms of MAO have been identified.

Dopamine is degraded equally by both isoenzymes.

MAO-A: Preferentially deaminates 5-HT and NA, and is inhibited by clorgyline, moclobemide.

MAO-B: Preferentially deaminates phenylethylamine and is inhibited by selegiline.

Distribution of MAO-A and MAO-B also differs. Peripheral adrenergic nerve endings, intestinal mucosa and human placenta contain predominantly MAO-A, while MAO-B predominates in certain areas (mainly serotonergic) of brain and in platelets. Liver contains both isoenzymes.

Two hydrazine drugs—*isoniazid* and *iproniazid* were used for tuberculosis in 1951; the latter was found to cause disproportionate elevation of mood. Its capacity to inhibit degradation of biogenic amines was soon discovered and was believed to be responsible for the mood elevating action. Its less hepatotoxic congeners like *phenelzine* and *isocarboxazid* and some nonhydrazine MAO inhibitors (related to amphetamine) like *tranylcypromine* were used as antidepressants in the 1960s. They inhibited MAO irreversibly and were nonselective for the two isoforms. Because of high toxicity and interaction with foods and other drugs, they have become unpopular.

These MAO inhibitors frequently produce postural hypotension, restlessness, insomnia and interfere with sexual function (impotence, loss of libido, anorgasmia). More importantly they interact with many foods and drugs.

- *Cheese reaction* Certain varieties of cheese, beer, wines, pickled meat and fish, yeast extract contain large quantities of tyramine, dopa, etc. In MAO inhibited patients these indirectly acting sympathomimetic amines escape degradation in the intestinal wall and liver → reaching into systemic circulation they displace and release large amounts of NA from transmitter loaded adrenergic nerve endings → *hypertensive crisis*, cerebrovascular accidents.

Similar reaction can occur with cough and cold remedies which contain ephedrine or similar drugs, as well as with tricyclic antidepressants, SSRIs, SNRIs and levodopa. Hallucinations and atropine poisoning like symptoms occur with anticholinergics. Alcohol, sedative-antihistaminics, barbiturates and opioids are potentiated; they may cause respiratory failure. Pethidine administered to MAO inhibited patients has produced fever, sweating, excitation, delirium, convulsions and respiratory depression. The mechanism of this interaction is:

MAO inhibitors retard hydrolysis of pethidine but not its demethylation. Thus, excess of *norpethidine* (normally a minor metabolite—*see* p. 503) is produced which has excitatory actions.

The selective MAO-A inhibitors possess antidepressant property. Selegiline at low doses (5–10 mg/day) selectively inhibits MAO-B, but these doses are not effective in depression. Selegiline is metabolized to amphetamine and at higher doses it becomes nonselective MAO inhibitor; such doses exhibit antidepressant and excitant properties, therefore not clinically useful.

Reversible inhibitors of MAO-A (RIMAs)

Moclobemide It is a reversible and selective MAO-A inhibitor with short duration of action; full MAO activity is restored within 1–2 days of stopping the drug. Because of competitive enzyme inhibition, tyramine is able to displace it from the enzyme, so that potentiation of pressor response to ingested amines is insignificant, and dietary restrictions are not required. Clinical trials have shown moclobemide to be an efficacious antidepressant, except in severe cases. It lacks the anticholinergic, sedative, cognitive, psychomotor and cardiovascular adverse effects of typical TCAs and is safer in overdose. This makes it an alternative option in elderly patients and in those with heart disease.

Dose: 150 mg BD–TDS (max 600 mg/day)

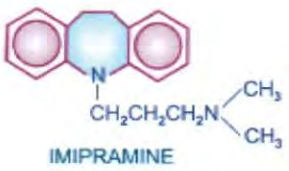
RIMAREX, TRIMA 150, 300 mg tabs.

Adverse effects are nausea, dizziness, headache, insomnia, rarely excitement and liver damage. Chances of interaction with other drugs and alcohol are remote, but caution is advised while coprescribing pethidine, SSRIs and TCAs.

Moclobemide is also useful in social phobia.

TRICYCLIC ANTIDEPRESSANTS (TCAs)

Imipramine, an analogue of chlorpromazine (CPZ) was found during clinical trials (1958) to selectively benefit depressed but not agitated psychotics. In contrast to CPZ, it inhibited NA and 5-HT reuptake into neurones. A large



IMIPRAMINE

number of congeners were soon added and these together are called *tricyclic antidepressants (TCAs)*. In addition to uptake blockade, these early developed compounds have direct effects on adrenergic, cholinergic and histaminergic receptors, and are referred to as '*first generation antidepressants*'.

The subsequently produced *second generation antidepressants* have more selective action on amine uptake; are either *Selective serotonin reuptake inhibitors (SSRIs)*, or *Serotonin and noradrenaline reuptake inhibitors (SNRIs)* with no direct action on cholinergic/adrenergic/histaminergic receptors, or have some *atypical features*. They have a limited spectrum of action resulting in fewer side effects.

PHARMACOLOGICAL ACTIONS

The most prominent action of TCAs is their ability to inhibit norepinephrine transporter (NET) and serotonin transporter (SERT) located at neuronal and platelet membrane. They also interact with a variety of receptors *viz.* muscarinic, α adrenergic, histamine H_1, 5-HT_1, 5-HT_2 and occasionally dopamine D2. However, relative potencies at these sites differ among different compounds. The actions of imipramine are described as prototype.

1. CNS Effects differ in normal individuals and in the depressed.

In normal individuals It induces a peculiar clumsy feeling, tiredness, light-headedness, sleepiness, difficulty in concentrating and thinking, unsteady gait. These effects tend to provoke anxiety. There is no mood elevation or euphoria; effects are rather unpleasant.

In depressed patients Little acute effects are produced, except sedation (in the case of drugs which have sedative property). After 2–3 weeks of continuous treatment, the mood is gradually elevated, patients become more communicative and start taking interest in self and surroundings. Thus, TCAs are not euphorients but only antidepressants. In depressed patients who have preponderance of REM sleep, this phase is suppressed and awakenings during night are reduced. The EEG effects of low doses are similar to hypnotics but high doses cause desynchronization. Sedative property varies among different compounds (*see* Table 33.1). The more sedative ones are suitable for depressed patients showing anxiety and agitation. The less sedative or stimulant ones are better for withdrawn and retarded patients.

The TCAs lower seizure threshold and produce convulsions in overdose. Clomipramine and bupropion have the highest seizure precipitating potential. Respiration is depressed in overdose only.

Mechanism of antidepressant action The TCAs and related drugs inhibit NET and SERT which mediate active reuptake of biogenic amines NA and 5-HT into their respective neurones and thus potentiate them by increasing their availability in the synaptic cleft (*see* Fig. 33.1). Antidepressants, however, differ markedly in their selectivity and potency for different amines, and are classified on this basis. Most of the compounds do not inhibit DA uptake, except bupropion. Moreover, amphetamine and cocaine (which are not antidepressants but CNS stimulants) are strong inhibitors of DA uptake. Tentative conclusions drawn are:

- Inhibition of NA and 5-HT uptake is associated with antidepressant action.
- Inhibition of DA uptake correlates with stimulant action.

Monoaminergic hypothesis of depression This hypothesis supposes that depression is caused by deficient noradrenergic and/or serotonergic transmission in the brain (mainly in cortical and limbic areas). This hypothesis is supported by the observation that reserpine depletes NA and 5-HT from brain and produces depression; and that all classes of antidepressants (TCAs, SNRIs, SSRIs, atypical) enhance

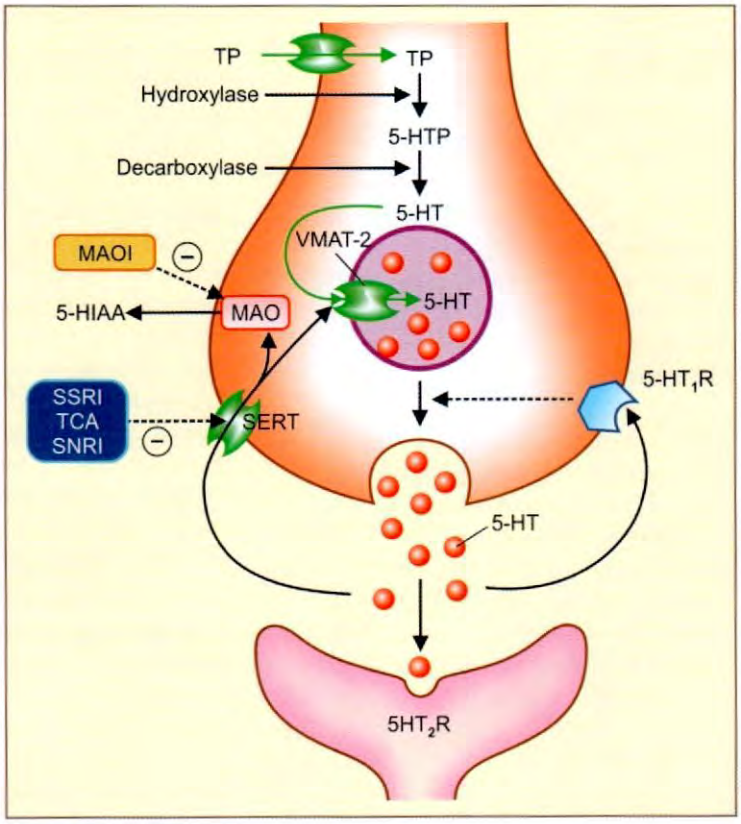


Fig. 33.1: Schematic depiction of cerebral serotonergic synapse and sites of action of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs)
TP—Tryptophan; 5-HTP—5-Hydroxytryptophan; VMAT-2—Vesicular monoamine transporter-2; MAO—Monoamine oxidase; 5-HIAA—5-Hydroxy indole acetic acid; SERT—Serotonin transporter; $5HT_1$-R / $5\text{-}HT_2$-R — $5\text{-}HT_1$ and $5\text{-}HT_2$ receptors.

synaptic availability of NA or 5-HT or both, in one way or the other. However, uptake blockade does not appear to be directly responsible for the antidepressant effect, because uptake blockade occurs quickly, while antidepressant effect develops over several weeks. Explanation offered for this discrepancy is—initially the presynaptic α_2 and $5\text{-}HT_1$ autoreceptors are activated by the increased amount of NA/5-HT in the synaptic cleft resulting in decreased firing of locus coeruleus (noradrenergic) and raphe (serotonergic) neurones. After, long-term administration, antidepressants desensitise the presynaptic α_2, $5\text{-}HT_{1A}$, $5\text{-}HT_{1D}$ autoreceptors and induce other adaptive changes in the number and sensitivity of pre- and postsynaptic NA and/or 5-HT receptors as well as in amine turnover of brain, the net effect of which is enhanced noradrenergic and serotonergic transmission. Thus, uptake blockade appears to initiate a series of time-dependent changes that culminate in antidepressant effect.

Neurotrophic hypothesis of depression This hypothesis proposes that depression is associated with deficiency of brain derived neurotrophic factor (BDNF) and other nerve growth factors (NGFs) in brain areas regulating feelings, emotion, cognition, hedonia, behaviour, etc., and that

antidepressants promote elaboration of NGFs. The NGFs activate receptor tyrosine kinases (RTKs) and enhance axonal/dendritic growth, promote synaptic connection and improve neural plasticity. Reduction of BDNF levels and neural mass in the limbic areas has been demonstrated in depression, while prologed antidressant treatment has been found to elevate BDNF levels as well as enhance neurogenesis and synaptic connections.

The monoaminergic and neurotrophic hypotheses have been reconciled by contending that enhancement of monoaminergic transmission by prolonged antidepressant therapy indirectly promotes neurogenesis in critical brain areas by increasing BDNF production. These growth factors activate RTKs and initiate axonal/dendritic proliferation and formation of synaptic connections. The therapeutic response is delayed due to the time taken for neurogenesis to occur.

2. ANS Most TCAs are potent anticholinergics—cause dry mouth, blurring of vision, constipation and urinary hesitancy as side effect. The anticholinergic potency is graded in Table 33.1.

The TCAs potentiate exogenous and endogenous NA by blocking uptake, but also have weak α_1 adrenergic blocking action. Some, e.g. amitriptyline, doxepin, trimipramine have slight H_1 antihistaminic action as well.

3. CVS Effects on cardiovascular function are prominent, occur at therapeutic concentrations and become dangerous in overdose.

Tachycardia: due to anticholinergic and NA potentiating actions.

Postural hypotension: due to inhibition of cardiovascular reflexes and α_1 blockade.

ECG changes and cardiac arrhythmias: T wave suppression or inversion is the most consistent change in ECG. Arrhythmias occur in overdose mainly due to interference with intraventricular conduction. The NA potentiating + cholinergic blocking actions along with direct myocardial depression compound the proarrhythmic potential. Older patients are more susceptible. The SSRIs, SNRIs and atypical antidepressants are safer in this regard.

Tolerance and dependence

Tolerance to the anticholinergic and hypotensive effects of imipramine-like drugs develops gradually, but antidepressant action is sustained.

Addiction to these drugs is rare, because their acute effects are not pleasant.

There is some evidence of physical dependence occurring when high doses are used for long periods—malaise, chills, muscle pain may occur on discontinuation and have been considered withdrawal phenomena. Gradual withdrawal is recommended, but antidepressants do not carry abuse potential.

PHARMACOKINETICS

The oral absorption of TCAs is good, though often slow. They are highly bound to plasma and tissue proteins, therefore have large volumes of distribution (~20 L/kg). They are extensively metabolized in liver; the major route for imipramine and amitriptyline is demethylation whereby active metabolites—desipramine and nortriptyline respectively are formed. Both these metabolites predominantly block NA reuptake. Few other TCAs also produce active metabolites. Inactivation occurs by oxidation and glucuronide conjugation. Various CYP isoenzymes like CYP2D6, CYP3A4, CYP1A2 and others metabolise tricylic and related antidepressants. Metabolites are excreted in urine over 1–2 weeks. The plasma t½ of amitriptyline, imipramine and doxepin range between 16–24 hours. The t½ is longer for some of their active metabolites. Because of relatively long t½s, once daily dosing (at bed time) is practicable in the maintenance phase.

An unusual *therapeutic window* phenomenon has been observed, i.e. optimal antidepressant effect is exerted at a narrow band of plasma concentrations (between 50–200 ng/ml of imipramine, amitriptyline, nortriptyline).

Wide variation in the plasma concentration attained by different individuals given the same dose has been noted. Thus, doses need to be individualized and titrated with the response, but plasma concentrations are not a reliable guide for adjusting the dose of TCAs.

Table 33.1: Comparative properties of antidepressants

Drug	Sedation	Anti-muscarinic	Hypotension	Cardiac arrhythmia	Seizure precipitation	Daily dose (mg)
Tricyclic antidepressants (TCAs)						
1. Imipramine	+	++	++	+++	++	50–200
2. Amitriptyline	+++	+++	+++	+++	++	50–200
3. Trimipramine	+++	++	++	+++	++	50–150
4. Doxepin	+++	++	++	+++	++	50–150
5. Clomipramine	++	++	+	+++	+++	50–150
6. Dothiepin (Dosulepin)	++	++	++	++	++	50–150
7. Nortriptyline	+	++	+	++	+	50–150
Selective serotonin reuptake inhibitors (SSRIs)						
1. Fluoxetine	±	—	—	—	±	20–40
2. Fluvoxamine	±	—	—	—	—	50–200
3. Paroxetine	+	+	—	—	—	20–50
4. Sertraline	—	—	—	—	—	50–150
5. Citalopram	—	±	—	+	—	20–40
6. Escitalopram	—	±	—	—	—	10–20
Serotonin and noradrenaline reuptake inhibitors (SNRIs)						
1. Venlafaxine	±	—	—	±	—	75–150
2. Duloxetine	+	++	—	—	—	30–80
Atypical antidepressants						
1. Trazodone	+++	—	+	±	—	50–200
2. Mianserin	++	+	++	+	++	30–100
3. Bupropion	—	—	—	—	+++	150–300
4. Amoxapine	+	+	++	++	++	100–300
5. Mirtazapine	+++	+	±	—	—	15–45

+ to +++ indicates increasing intensity of that action; – indicates absence of that action

ADVERSE EFFECTS

Side effects are common with TCAs because of which SSRIs, SNRIs and atypical antidepressants have become the first line drugs.

1. Anticholinergic: dry mouth, bad taste, constipation, epigastric distress, urinary retention (especially in males with enlarged prostate), blurred vision, palpitation.
2. Sedation, mental confusion and weakness, especially with amitriptyline and more sedative congeners.
3. Increased appetite and weight gain is noted with most TCAs and trazodone, but not with SSRIs, SNRIs and bupropion.
4. Some patients receiving any antidepressant may abruptly '*switch over*' to a dysphoric-agitated state or to mania. Probably, these are cases of bipolar depression, the other pole being unmasked by the antidepressant.
5. Sweating (despite antimuscarinic action) and fine tremors are relatively common.

6. Seizure threshold is lowered—fits may be precipitated, especially in children. Bupropion, clomipramine, amoxapine have greater propensity, while desipramine, SSRIs and SNRIs are safer in this regard.
7. Postural hypotension, especially in older patients. It is less severe with desipramine-like drugs and insignificant with SSRIs/SNRIs.
8. Sexual distress: especially delay or interference with erection, ejaculation and occasionally with orgasm.
9. Cardiac arrhythmias, especially in patients with ischaemic heart disease. Arrhythmias may be responsible for sudden death in these patients.
10. Rashes and jaundice due to hypersensitivity are rare. Mianserin is more hepatotoxic.

Acute poisoning Poisoning with TCAs is frequent; usually self-attempted for suicide, and may endanger life. Manifestations are:

Excitement, delirium and other anticholinergic symptoms as seen in atropine poisoning, followed by muscle spasms, convulsions and coma. Respiration is depressed, body temperature may fall, BP is low, tachycardia is prominent. ECG changes and ventricular arrhythmias are common.

Treatment is primarily supportive with gastric lavage, respiratory assistance, fluid infusion, maintenance of BP and body temperature. Acidosis must be corrected by bicarbonate infusion.

Diazepam may be injected i.v. to control convulsions and delirium. Most important is the treatment of cardiac arrhythmias, for which propranolol/lidocaine may be used. The class IA and IC antiarrhythmics and digoxin themselves depress cardiac conduction; are therefore contraindicated.

INTERACTIONS

1. TCAs potentiate directly acting *sympathomimetic amines* (present in cold/asthma remedies). Adrenaline containing local anaesthetic should be avoided.
2. TCAs potentiate *CNS depressants*, including alcohol and antihistaminics.
3. *Phenytoin, phenylbutazone, aspirin and CPZ* can displace TCAs from protein binding sites and cause transient overdose symptoms.
4. *Phenobarbitone* competitively inhibits as well as induces imipramine metabolism. Carbamazepine and other enzyme inducers enhance metabolism of TCAs.
5. SSRIs inhibit metabolism of several drugs (*see* later) including TCAs—dangerous toxicity can occur if the two are given concurrently.
6. By their anticholinergic property, TCAs delay gastric emptying and retard their own as well as other drug's absorption.
7. *MAO inhibitors*—dangerous hypertensive crisis with excitement and hallucinations has occurred when given with TCAs.

Preparations of TCAs

1. Imipramine: DEPSONIL, ANTIDEP 25 mg tab, 75 mg SR cap.
2. Amitriptyline: AMLINE, TRYPTOMER, SAROTENA 10, 25, 75 mg tabs.
3. Trimipramine: SURMONTIL 10, 25 mg tab.
4. Doxepin: SPECTRA, DOXIN, DOXETAR 10, 25, 75 mg tab/cap.
5. Clomipramine: CLOFRANIL 10, 25, 50 mg tab, 75 mg SR tab. CLONIL, ANAFRANIL 10, 25 mg tab
6. Dothiepin (Dosulepin): PROTHIADEN, EXODEP 25, 50, 75 mg tab.
7. Nortriptyline: SENSIVAL, PRIMOX 25 mg tab.
8. Reboxetine: 4 mg BD or 8 mg OD; NAREBOX 4, 8 mg tab.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

The major limitations of TCAs (first generation antidepressants) are:

- Frequent anticholinergic, cardiovascular and neurological side effects.
- Relatively low safety margin. They are hazardous in overdose; fatalities are common.
- Significant number of patients respond incompletely and some do not respond.

To overcome these shortcomings, a large number of newer (second generation) antidepressants have been developed since 1980s. The most significant of these are the SSRIs and SNRIs

which selectively inhibit membrane associated SERT or both SERT and NET. Though, some patients may not respond even to these drugs, the efficacy of second generation antidepressants is rated higher than older TCAs and RIMAs. Some patients not responding to one type of drug may respond to another type. More importantly the newer drugs have improved tolerability at therapeutic doses, as well as safety in overdose. It has been claimed that certain drugs (bupropion, venlafaxine, mirtazapine) have faster onset of antidepressant action, but this has not been unequivocally established.

The relative safety and better acceptability of SSRIs has made them 1st line drugs in depression and allowed their extensive use in anxiety, phobias, panic, OCD and related disorders. The SSRIs produce little or no sedation, do not interfere with cognitive and psychomotor function or produce anticholinergic side effects. They are devoid of α adrenergic blocking action—postural hypotension does not occur, making them suitable for elderly patients. They have practically no seizure precipitating propensity and do not inhibit cardiac conduction—overdose arrhythmias are not a problem. Prominent side effects are gastrointestinal; all SSRIs frequently produce nausea (due to 5-HT_3 receptor stimulation), but tolerance develops over time. Loose motions are due to 5-HT uptake blockade in the gut and activation of 5-HT receptors on enteric plexus neurones. Weight gain is not a problem with SSRIs, but they more commonly interfere with ejaculation or orgasm. A new constellation of mild side effects, *viz.* nervousness, restlessness, insomnia, anorexia, dyskinesia and headache is associated with them, but patient acceptability is good. Increased incidence of epistaxis and ecchymosis has been reported, probably due to impairment of platelet function. Gastric blood loss due to NSAIDs may be increased by SSRIs.

The SSRIs inhibit drug metabolizing isoenzymes CYP2D6 and CYP3A4: elevate plasma levels of TCAs, haloperidol, clozapine, warfarin, β blockers, some BZDs and carbamazepine. '*Serotonin syndrome*' manifesting as agitation, restlessness, rigidity, hyperthermia, delirium, sweating, twitchings followed by convulsions can be precipitated when any serotonergic drug (e.g. MAOIs, tramadol, pethidine) is taken by a patient receiving SSRIs. Some degree of tolerance to the antidepressant action of SSRIs has been noted in few patients after months of use. Discontinuation reaction consisting of paresthesias, bodyache, bowel upset, agitation and sleep disturbances occurs in some patients. However, risk of switching over to hypomania during treatment is less with SSRIs than with TCAs.

Because of freedom from psychomotor and cognitive impairment, SSRIs are preferred over TCAs for prophylaxis of recurrent depression (should be combined with lithium/valproate). Metaanalysis of comparative trials has shown no significant difference in efficacy among individual SSRIs, but there are pharmacokinetic differences and incidence of particular side effects differs somewhat.

Fluoxetine A bicyclic compound, it is the first SSRI to be introduced, and the longest acting. Its plasma t½ is 2 days and that of its active demethylated metabolite is 7–10 days. It has been approved for use in children 7 years or older for depression and OCD on the basis of similar efficacy and side effect profile as in adults, but should be given to children only when psychotherapy fails. Agitation and dermatological reactions are more frequent than with other SSRIs. Because of slower onset of antidepressant effect, it is considered less suitable for patients needing rapid effect, but is more appropriate for poorly compliant patients. Its stimulant effect could worsen patients showing agitation.

FLUDAC 20 mg cap, 20 mg/5 ml susp., FLUNIL, FLUPAR, PRODAC 10, 20 mg cap.

Fluvoxamine It is a shorter-acting SSRI with a t½ of 18 hours and no active metabolite. It has been specifically recommended for generalized anxiety disorder (GAD) and OCD.

Relatively more nausea, dyspepsia, flatulence, nervousness and discontinuation reactions have been reported with fluvoxamine.

FLUVOXIN, SOREST 50, 100 mg tabs.

Paroxetine Another short acting SSRI (t½ 20 hours) which does not produce active metabolite. A higher incidence of g.i. side effects, sexual distress, agitation and discontinuation reaction than with other SSRIs has been noted. Sedation and antimuscarinic effects are mild.

XET, PAXIDEP-CR 10, 20, 30, 40 mg tabs.

Sertraline This SSRI has gained popularity, because in clinical trials fewer patients stopped sertraline due to side effects. Efficacy in juvenile depression has been demonstrated, and it is recommended for anxiety and post-traumatic stress disorder (PTSD) as well. Drug interactions due to inhibition of CYP isoenzymes are less likely to occur with sertraline. Its plasma t½ is 26 hours and it produces a still longer-lasting active metabolite.

SERENETA, SERLIN, SERTIL 50, 100 mg tabs., ZOSERT 25, 50, 100 mg tabs.

Citalopram This SSRI shares with sertraline a lower propensity to cause drug interactions. Its t½ is 33 hours and no active metabolite is known. However, Q-T prolongation and few deaths due to overdose of citalopram are on record, because of which it is to be avoided in patients likely to attempt suicide. Citalopram is the preferred SSRI for mood disorders in premenstrual dysphoric disorder (PMDD).

FELIZ, CITADEP, CELICA 10, 20, 40 mg tabs.

Escitalopram It is the active S(+) enantiomer of citalopram, effective at half the dose, with similar properties, but Q-T prolongation is not reported. Currently, it is a popular SSRI for anxio-depressive disorders. Modest relief from menopausal hot flashes has been obtained in women who cannot take estrogens. Side effects are milder and safety is improved.

ESDEP, FELIZ-S, NEXITO 5, 10, 20 mg tabs.

Dapoxetine This SSRI is being promoted particularly for delaying premature ejaculation, a property common to many SSRIs and some TCAs. Dapoxetine acts rapidly and can be taken 1 hour before sexual intercourse. Combined with behavioural therapies, it has been found to help many sufferers of sexual distress due to early ejaculation. Side effects are nausea, vomiting, loose motions, headache, dizziness and occasionally insomnia.

Dose: 60 mg taken 1 hour before intercourse; older patients 30 mg.

SUSTINEX, DURALAST, KUTUB 30 mg, 60 mg tabs.

Other uses of SSRIs The SSRIs are now 1st choice drugs for OCD, panic disorder, social phobia, eating disorders, PMDD, and PTSD. They are also being increasingly used for anxiety disorders, body dysmorphic disorder, compulsive buying, kleptomania and premature ejaculation. Elevation of mood and increased work capacity has been reported in postmyocardial infarction and other chronic somatic illness patients. Thus, SSRIs are being used to improve outlook on life and to feel good, even in apparently nondepressed patients. Wisdom of such use though is questionable.

SEROTONIN AND NORADRENALINE REUPTAKE INHIBITORS (SNRIs)

1. Venlafaxine A novel antidepressant referred to as SNRI, because it inhibits uptake of both NA and 5-HT but, in contrast to older TCAs, does not interact with cholinergic, adrenergic or histaminergic receptors or have sedative property. Trials have shown it to be as effective antidepressant as TCAs and may work in some resistant cases. A faster onset of action is claimed. Mood changes and hot flashes in menopausal syndrome, social anxiety and eating disorders are also benefited by venlafaxine. It does not produce the usual side effects of TCAs; tends to raise rather than depress BP and is safer in overdose. Prominent side effects are nausea, sweating, anxiety, dizziness, impotence and withdrawal reactions on discontinuation.

VENLOR, SENTOSA 25, 37.5, 75 mg tabs., VENIZ-XR 37.5, 75, 150 mg ER caps.

2. Desvenlafaxine It is desmethylvenlafaxine, an active metabolite of venlafaxine with similar actions, uses, and side effects.

Dose: 50–100 mg/day;

D-VENIZ, NEWVEN, VENZ-OD 50, 100 mg tabs.

3. Duloxetine A newer SNRI similar to venlafaxine. It is mildly sedating with some antimuscarinic effects, but not an antihistaminic or α blocker. Side effects, including g.i. and sexual problems are milder, but agitation, insomnia and rise in BP can occur in few. Antidepressant efficacy is comparable to TCAs. Duloxetine is particularly indicated in diabetic and other types of neuropathic pain, fibromyalgia and stress urinary incontinence in women (because it increases urethral tone). It has also been used for maintenance therapy in panic disorder.

CYMBALTA 20, 30, 60 mg tab, DELOK, DULANE 20, 30, 40 mg caps.

ATYPICAL ANTIDEPRESSANTS

1. Trazodone It is the first atypical antidepressant; less efficiently blocks 5-HT uptake, but has prominent α adrenergic and weak 5-HT_2 antagonistic actions. However, its metabolite is a strong 5-HT_2 blocker. Antidepressant effect is modest. It is sedative but not anticholinergic, causes bradycardia rather than tachycardia, does not interfere with intracardiac conduction, therefore less prone to cause arrhythmia. Nausea is felt, especially in the beginning. Inappropriate, prolonged and painful penile erection (priapism) occurs in few recipients resulting in impotence in a fraction of these. The α_1 adrenergic blocking property has been held responsible for this effect as well as for postural hypotension. Trazodone is infrequently used now in depression; unless associated with insomnia.

TRAZODAC 25, 50 mg tab, TRAZONIL, TRAZALON 25, 50, 100 mg tabs.

2. Mianserin It is unique in not inhibiting either NA or 5-HT uptake; but blocks presynaptic α_2 receptors thereby increasing release and turnover of NA in brain which may be responsible for the antidepressant effect. Antagonistic action at 5-HT_2, 5-HT_{1c} as well as H_1 receptors has also been shown. It is a sedative—relieves associated anxiety and suppresses panic attacks. While anticholinergic and cardiac side effects are less prominent, it has caused seizures in overdose. However, overdose fatality is low. Reports of blood dyscrasias and liver dysfunction have restricted its use.

TETRADEP, SERIDAC 10, 20, 30, mg tabs.

3. Mirtazapine This antidepressant acts by a novel mechanism, *viz.* blocks α_2 auto- (on NA neurones) and hetero- (on 5-HT neurones) receptors enhancing both NA and 5-HT release. The augmented NA further increases firing of serotonergic raphe neurones *via* α_1 receptors. Selective enhancement of antidepressive 5-HT_1 receptor action is achieved by concurrent blockade of 5-HT_2 and 5-HT_3 receptors which are held responsible for some of the adverse effects of high serotonergic tone. Accordingly, it has been labelled as "*noradrenergic and specific serotonergic antidepressant*" (NaSSA). It is a H_1 blocker and moderately strong sedative, but only mildly antimuscarinic and not antidopaminergic. Efficacy in mild as well as severe depression is reported to be comparable to TCAs. Given once daily at bed time, it is particularly suitable for those with insomnia. Increased appetite and weight gain is frequent. Sexual dysfunction is not a problem with mirtazapine.

MIRT 15, 30, 45 mg tabs, MIRTAZ, MATIZ 15, 30 mg tab.

4. Bupropion This inhibitor of DA and NA uptake has excitant rather than sedative property. It is metabolized into an amphetamine-like compound which can cause presynaptic release of DA and NA. A sustained-release formulation is marketed as an aid to smoking cessation. In clinical trials it has been found to yield equivalent smoking abstinence and quitting rates as nicotine replacement, and higher than placebo. Bupropion may be acting by augmenting the dopaminergic reward function. Better results are obtained when it is combined with nicotine patch. The nicotine withdrawal symptoms were less severe in bupropion recipients. However, long-term efficacy is not known, while it can cause insomnia, agitation, dry mouth and nausea, but not sexual side effects. Seizures occur in over dose and in predisposed patients due to lowering of seizure threshold. The dose of 150 mg BD should not be exceeded. It is contraindicated

in eating disorders and in bipolar illness. Bupropion is infrequently used to treat depression except those with atypical features, or it may be added to a SSRI as an augmenting drug. It is not suitable for treatment of anxiety disorders.
SMOQUIT 150 mg tab.

5. Amoxapine This tetracyclic compound is unusual in that it blocks dopamine D2 receptors in addition to inhibiting NA reuptake. It is chemically related to the antipsychotic drug loxapine and has mixed antidepressant + neuroleptic properties; may be used for patients with psychotic depression unresponsive to other antidepressants. Risk of extrapyramidal side effects is also there. Seizures (including status epilepticus) occur in its overdose.
DEMOLOX 50, 100 mg tab.

6. Tianeptine This antidepressant is reported to increase rather than inhibit 5-HT uptake, and is neither sedative nor stimulant. It has shown efficacy in anxiodepressive states, particularly with psychosomatic symptoms, as well as in endogenous depression. Side effects are dry mouth, epigastric pain, flatulence, drowsiness or insomnia, tremor and bodyache.
Dose: 12.5 mg BD–TDS; STABLON 12.5 mg tab.

7. Amineptine Like tianeptine it enhances 5-HT uptake, and has antidepressant property. It produces anticholinergic side effects including tachycardia, confusion and delirium. Postural hypotension, conduction disturbances and arrhythmias can occur, especially in patients with heart disease.
Dose: 100 mg BD at breakfast and lunch.
SURVECTOR 100 mg tabs.

USES

1. *Endogenous (major) depression:* The aim of therapy is to relieve symptoms of depression and restore normal social behaviour. While antidepressants are not the answer to every grief, loss, set-back or other sad events that are part of life, but the less toxic and more patient-friendly SSRIs/SNRIs/atypical antidepressants are now more readily prescribed in depressive illness. Major depression clearly requires antidepressant medication and these drugs are of proven value, but response takes at least 2–3 weeks to appear, full benefits take still longer. Choice of a particular drug for an individual patient depends on the secondary properties (sedative, anticholinergic, hypotensive, cardiotoxic, seizure precipitating, etc.) as described above, and past history of drug response, if available. The SSRIs are currently used as first choice for their better tolerability, safety and may be higher efficacy as well. The SNRIs and newer atypical agents also offer advantages. The only antidepressants clearly shown to be effective in juvenile depression are fluoxetine and sertraline. The TCAs are now used only as alternatives in non-responsive cases or in those not tolerating the second generation antidepressants. Substituting a drug with a different pattern of aminergic action may succeeds in nonresponsive cases. However, few patients fail any single antidepressant. In such cases, augmenting the initially selected drug (usually a SSRI) with an atypical antidepressant like bupropion or with valproate/lithium is an option. Another option is to add a second generation antipsychotic drug in refractory cases.

Psychotic depression needs to be treated with a combination of a SSRI with an atypical antipsychotic like olanzapine, aripiprazole or quetiapine. In case of bipolar depression, it is essential to combine the antidepressant (SSRI/SNRI/TCA/atypical) with valproate or lithium or lamotrigine to avoid the risk of switching over to mania.

After a depressive episode has been controlled, continued treatment at maintenance doses for months is recommended to prevent relapse. Discontinuation of the antidepressant may be attempted after 6–12 months. Long-term therapy may be needed in patients who tend to relapse. ECT may be given in the severely depressed, especially initially while effect of the antidepressant is developing, because no antidepressant has been clearly demonstrated to act fast enough to prevent suicide.

Moclobemide, a reversible inhibitor of MAO-A, is a relatively well tolerated option for mild-to-moderate depression and atypical depression. It is less risky than TCAs for patients with cardiovascular risk factors.

2. *Obsessive-compulsive disorder (OCD):* The SSRIs, particularly fluoxamine, are the drugs of choice due to better patient acceptability. TCAs, especially clomipramine, are also highly effective in OCD. Over 50% patients obtain significant improvement in OCD rating scale, but longer response time of 2–3 months and relatively higher doses are generally needed than for depression. SSRIs and TCAs also reduce compulsive eating in *bulimia*, and help patients with *body dysmorphic disorder, compulsive buying* and *kleptomania,* though these habits may not completely die.

3. *Anxiety disorders:* Antidepressants, especially SSRIs and SNRIs, exert a delayed but sustained beneficial effect in many patients of *social anxiety* and *generalized anxiety disorder.* They may be used along with a short course of BZDs, which act rapidly, to cover exacerbations. They have also proven helpful in *phobic disorders*, long term treatment of *panic attacks* and in *post-traumatic stress disorder (PTSD).* Mood swings and hot flashes in menopausal women may be partly relieved by certain SSRIs when HRT is contraindicated.

4. *Neuropathic pain:* Amitriptyline and other TCAs afford considerable relief in diabetic and some other types of chronic pain. Amitriptyline reduces intensity of post-herpetic neuralgia in ~50% patients. The SSRIs are less effective in these conditions. Duloxetine, a SNRI, is now the first line drug for diabetic neuropathy, fibromyalgia, etc. Other drugs useful in neuropathic pain are pregabalin and gabapentin. Combination of duloxetine + pregabalin may work if monotherapy is not satisfactory.

5. *Attention deficit-hyperactivity disorder (ADHD) in children:* TCAs with less depressant properties like imipramine, nortriptyline and amoxapine are now first line drugs in this disorder, comparable in efficacy to amphetamine-like drugs, with the advantage of less fluctuating action and fewer behavioural side effects. Atomoxetine is a NA reuptake inhibitor unrelated to both TCAs as well as amphetamine, which is used specifically in ADHD.

6. *Premature ejaculation:* It refers to repeated occurrences of ejaculation before or shortly after penetration, or with minimal sexual stimulation. It is a very common sexual complaint, which is often interpreted as sexual weakness; can cause considerable distress and dissatisfaction in the patient as well as in his partner. Sometimes the subject has unreasonable expectations about the optimal/desirable length of intercourse.

Most SSRIs and some TCAs, especially clomipramine have the common property of delaying and in some cases inhibiting ejaculation (this itself can cause sexual distress). The primary treatment of premature ejaculation is counselling and behavioural therapy, but this can be supplemented by drugs. Dapoxetine is a SSRI which has been specifically introduced for this purpose. It acts rapidly; 60 mg taken 1 hour before intercourse has helped many subjects. Clomipramine 10–25 mg three times a day is a slow acting drug which needs to be taken regularly for maximum benefit. For on demand use, 25 mg may be taken 6 hours before sex.

7. *Smoking cessation:* Only bupropion is approved as an aid to smoking cessation, though some TCAs have also been found to reduce craving, albeit inconsistently. In controlled trials, quitting rates were significantly higher in bupropion recipients, than among placebo recipients. Abstinent subjects on bupropion experienced fewer distress symptoms and mood swings. Benefits were comparable to those with nicotine gum, and the two were additive.

8 *Enuresis:* In children above 5 years, imipramine 25 mg at bedtime is effective, but bed wetting may again start when the drug is stopped. Eldery subjects with bed wetting have also benefited.

9. *Migraine:* Amitriptyline has some prophylactic value, especially in patients with mixed headaches.

10. *Pruritus:* Some tricyclics have antipruritic action. Topical doxepin has been used to relieve itching in atopic dermatitis, lichen simplex, etc. NOCTADERM 5% cream.

ANTIANXIETY DRUGS

Anxiety It is an emotional state, unpleasant in nature, associated with uneasiness, discomfort and concern or fear about some defined or undefined future threat. Somatic symptoms like anorexia, breathlessness, palpitation, paresthesias, etc. often accompany. Some degree of anxiety is a part of normal life. Treatment is needed when it is disproportionate to the situation and excessive. Some psychotics and depressed patients also exhibit pathological anxiety.

Cardiac neurosis (unfounded fear of heart disease—palpitation, functional precordial pain); g.i. neurosis (fixation on bowel movement, distention, eructation, reflux, acidity); social anxiety (fear of being observed and evaluated by others); obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD) and various forms of phobias are some specific types of anxiety disorders.

Antianxiety drugs These are an ill-defined group of drugs, mostly mild CNS depressants, which are aimed to control the symptoms of anxiety, produce a restful state of mind without interfering with normal mental or physical functions. The anxiolytic-sedative drugs differ markedly from antipsychotics, and more closely resemble sedative-hypnotics. They:

1. Have no therapeutic effect to control thought disorder of schizophrenia.
2. Do not produce extrapyramidal side effects.
3. Have anticonvulsant property.
4. Produce physical dependence and carry abuse liability.

BENZODIAZEPINES

The pharmacology of benzodiazepines (BZDs) as a class is described in Ch. 29.

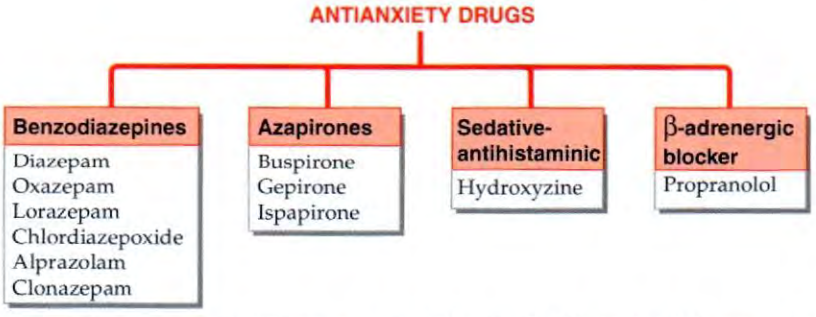
Some members have a slow and prolonged action, relieve anxiety at low doses without producing significant CNS depression. They have a selective taming effect on aggressive animals and suppress induced aggression. They also suppress the performance impairing effect of punishment. In contrast to barbiturates, they are more selective for the limbic system and have proven clinically better in both quality and quantity of improvement in anxiety and stress-related symptoms.

At antianxiety doses, cardiovascular and respiratory depression is minor.

Because anxiety is a common complaint and is a part of most physical and mental illness, and because the BZDs—

- have little effect on other body systems
- have lower dependence producing liability than barbiturates and other sedatives; withdrawal syndrome is milder and delayed due to their long half lives
- are relatively safe even in gross overdosage,

Benzodiazepines are presently one of the most widely used class of drugs. Potent BZDs like lorazepam and clonazepam injected i.m. have adjuvant role in the management of acutely psychotic and manic patients.



In addition to the above drugs, antidepressants, especially the SSRIs and SNRIs are effective in OCD, phobias, panic, PTSD and severe generalized anxiety disorder (GAD).

BZDs act primarily by facilitating inhibitory GABAergic transmission, but other additional mechanisms of action have been suggested. Higher doses induce sleep and impair performance.

Adverse effects of BZDs noted in their use as hypnotics are described in Ch. 29. *Side effects* that occur in their use to relieve anxiety are—sedation, light-headedness, psychomotor and cognitive impairment, confusional state (especially in the elderly), increased appetite and weight gain, alterations in sexual function. Rashes are uncommon. Some women fail to ovulate while on regular BZD medication. The major constraint in their long-term use for anxiety disorders is their potential to impair mental functions and to produce dependence.

Differences between individual BZDs recommended for anxiety are primarily pharmacokinetic: choice of one over the other is largely empirical.

1. Chlordiazepoxide It was the first BZD to be used clinically. Oral absorption is slow. A smooth long lasting effect is produced. It is preferred in chronic anxiety states. Chlordiazepoxide is often combined with other drugs in psychosomatic disorders, and has been the commonest BZD used to cover alcohol withdrawal. Its t½ is 6–12 hours, but active metabolites are produced which extend the duration of action. Its anticonvulsant action is weak.

Daily dose: 25–100 mg; LIBRIUM 10, 25 mg tabs; EQUILIBRIUM 10 mg tab.

2. Diazepam It is quickly absorbed; produces a brief initial phase of strong action followed by prolonged milder effect due to a two phase plasma concentration decay curve (distributive phase t½ 1 hr, elimination phase t½ 20–30 hours). The biological effect t½ is still longer due to production of active metabolites. It is preferred in acute panic states and anxiety associated with organic disease.

Daily dose: 5–20 mg; VALIUM, PLACIDOX 2, 5, 10 mg tabs; CALMPOSE 5, 10 mg tab, 2 mg/5 ml Syr.

3. Oxazepam It is slowly absorbed; being relatively polar, its penetration in brain is also slow. The plasma t½ is about 10 hours. It is metabolized only by glucuronide conjugation, therefore no active metabolite is produced. Duration of action is relatively shorter making it preferable for the elderly and in those with liver disease. It has been used mainly in short lasting anxiety states.

Daily dose: 30–60 mg in 2–3 divided portions; SEREPAX 15, 30 mg tab.

4. Lorazepam Has slow oral absorption. Being less lipid-soluble than diazepam, its rate of entry in brain is slower. The plasma t½ is shorter (10–20 hours); no active metabolite is produced, since it is directly conjugated with glucuronic acid, and is suitable for older patients. However, it is quite sedative and capable of producing marked amnesia when injected i.v. Injection site complications are minor. Therefore, it is the only BZD recommended for i.m. use. Lorazepam has been preferred for short lasting anxiety states, panic, OCD and tension syndromes, as well as for psychosomatic diseases and for i.v. use in status epilepticus.

Daily dose: 1–6 mg; LARPOSE, ATIVAN 1, 2 mg tab. CALMESE 1, 2 mg tabs, 4 mg/2 ml inj.

5. Alprazolam A high potency anxiolytic BZD which in addition has some mood elevating action in mild depression. As such, it is particularly useful in anxiety associated with depression. Good response has been obtained in panic disorders with severe anxiety and autonomic symptoms. Its plasma t½ is about 12 hours, but an active metabolite is produced. Alprazolam is also used as hypnotic. When administered daily as anxiolytic, some patients experience anxiety in between doses, which may be obviated by employing sustained release tablet. Withdrawal symptoms may be more marked on discontinuation than with other BZDs.

Dose: 0.25–1.0 mg TDS; upto 6 mg/day in panic disorder; ALPRAX 0.25, 0.5, 1.0 mg tabs., 0.5, 1.0, 1.5 mg SR tabs; ALZOLAM 0.25, 0.5, 1.0 mg tabs; 1.5 mg SR tab, ALPROCONTIN 0.5, 1.0, 1.5 mg CR tabs. RESTYL 0.25, 0.5, 1.0 mg tabs, RESTYL-SR 0.5, 1.0, 1.5 mg SR tabs.

6. Clonazepam This high potency BZD has prominent anticonvulsant activity and is described in Ch 30. It is also highly effective

for urgent treatment of acute panic attack. In patients with recurrent panic disorder, a SSRI should be started concurrently and continued for sustained benefit while the BZD is gradually withdrawn. Patients with severe GAD may also be treated with clonazepam, but use should be limited to short term, till the maintenance drug (SSRI/SNRI) has taken effect.

Dose: 0.5–1.0 mg OD–TDS;

CLONAPAX, RIVOTRIL, LONAZEP 0.5, 1.0, 2.0 mg tabs.

OTHER ANTIANXIETY DRUGS

Buspirone It is the first azapirone, a class of selective antianxiety drugs, distinctly different from BZDs. Buspirone:

- Does not produce significant sedation or cognitive/functional impairment.
- Does not interact with BZD receptor or modify GABAergic transmission.
- Does not produce tolerance or dependence; no rebound anxiety or withdrawal symptoms on stoppage.
- Does not suppress BZD or barbiturate withdrawal syndrome.
- Has no muscle relaxant or anticonvulsant activity.

Buspirone relieves generalized anxiety of mild-to-moderate intensity, but is ineffective in severe cases and in those showing panic reaction. Buspirone, in relatively higher doses, has also been used to augment the therapeutic effect of SSRIs in OCD. The beneficial effect in anxiety develops slowly; maximum benefit may be delayed up to 2-3 weeks. The mechanism of anxiolytic action is not clearly known, but may be dependent on its selective partial agonistic action on 5-HT_{1A} receptors. By stimulating presynaptic 5-HT_{1A} autoreceptors, it reduces the activity of dorsal raphe serotonergic neurones. Antagonistic action at certain postsynaptic 5-HT_{1A} receptors has also been demonstrated. After chronic treatment, adaptive reduction in cortical 5-HT_2 receptors may occur.

Buspirone is rapidly absorbed; undergoes extensive first pass metabolism; (bioavailability <5%), one metabolite is active and excretion occurs both in urine and faeces; t½ is 2–3.5 hrs. Side effects are minor: dizziness, nausea, abdominal discomfort, headache, light-headedness, rarely excitement. It may cause rise in BP in patients on MAO inhibitors, but does not potentiate CNS depressants. Though most patients on buspirone remain alert, those operating machinery/motor vehicles should be cautioned.

Dose: 5–15 mg OD–TDS:

ANXIPAR, BUSPIN, BUSCALM 5, 10 mg tab.

Hydroxyzine An H_1 antihistaminic with sedative, antiemetic, antimuscarinic and spasmolytic properties. It is claimed to have selective anxiolytic action, but the accompanying sedation is quite marked. Hydroxyzine may be used in reactive anxiety or that associated with marked autonomic symptoms. Due to antihistaminic and sedative property, it is useful in pruritus and urticaria.

Daily dose 50–200 mg;

ATARAX 10, 25 mg tab, 10 mg/5 ml syr, 25 mg/2 ml inj.

β Blockers (*see* Ch. 10)

Many somatic symptoms of anxiety (palpitation, rise in BP, shaking, tremor, gastrointestinal hurrying, etc.) are due to sympathetic overactivity, and these symptoms reinforce anxiety. Propranolol and other nonselective β blockers help anxious patients troubled by these symptoms, by cutting the vicious cycle and provide symptomatic relief. They do not affect the psychological symptoms such as worry, tension and fear, but are valuable in acutely stressful situations (examination fear, unaccustomed public appearance, etc.). They may be used for performance/situational anxiety or as adjuvant to BZDs. The role of β blockers in anxiety disorders is quite limited.

TREATMENT OF ANXIETY

Anxiety is a universal phenomenon, and to experience it in appropriate circumstances is the normal response. It may serve to enhance vigilance and drive. However, if anxiety symptoms are frequent and persist in a severe form, they are a cause of distress/suffering and markedly impair performance. Anxiety should be treated with drugs only when excessive and disabling in its own right.

The established drugs for acute anxiety are BZDs which act quickly, while buspirone and SSRIs/SNRIs act only after chronic treatment. The BZDs should be used in the smallest possible dose. The dose has to be found out for each patient by titration with symptoms of anxiety. Acute anxiety states generally respond better than chronic anxiety. The drug should be withdrawn as soon as it is no longer required. However, when larger doses have been used for longer periods, withdrawal should be gradual. Long-term use of BZDs is of questionable merit due to cognitive impairment and risk of dependence.

The usual practice is to give 1/2 to 2/3 of the daily dose at bed time to ensure good nightly rest; the remaining is divided in 2–3 doses given at day time. Though the t½ of BZDs used in anxiety are longer, divided day time doses or SR tab. are required to avoid high peaks.

Buspirone is a nonsedating alternative to BZDs for chronic treatment of less severe forms of generalized anxiety, but is not suitable for acute cases due to delayed effect. The SSRIs and SNRIs are now extensively used in most forms of chronic anxiety disorders. However, they are not good for acute anxiety. They produce a delayed but often gratifying response and can be combined with BZDs. The SSRIs are now drugs of choice for long term treatment of GAD, social anxiety, OCD, eating disorders and PTSD.

Panic attacks are initially treated with a rapidly acting BZD (e.g. diazepam, alprazolam, or i.m. lorazepam), but BZDs are not suitable for maintenance therapy. SSRIs, venlafaxine and duloxetine are the drugs of choice for maintenance treatment, which in the initial few weeks may be supplemented by continuing the BZD. Valproate is an alternative to SSRIs. Phobic disorders are mostly treated by a SSRI, such as paroxetine, fluvoxamine or sertraline. In situational phobias, propranolol may be added as and when required. Gabapentin has been used as alternative to SSRI.

Patients with hypertension, peptic ulcer, ulcerative colitis, irritable bowel syndrome, gastroesophageal reflux, thyrotoxicosis, angina pectoris are often given low doses of BZD in addition to specific therapy, though anxiety may not be a prominent manifestation.

Fixed dose combination of tranquilizers with vitamins has been banned.

☞ PROBLEM DIRECTED STUDY

33.1 A businessman aged 35 years suffered loss and his employees left. He became very depressed and stopped taking interest in the business. Gradually he stopped going out and withdrew socially. He felt guilty, worthless and tired all the time, lost interest in pleasure and sex, stopped eating properly and had disturbed sleep. When he showed no sign of recovery even after 3 months, the family members consulted a doctor, who diagnosed him to be a case of major depression and prescribed—

Tab Sertraline 50 mg twice a day, and a multivitamin.

The family members brought him back after one week and complained that there was no improvement. On questioning the patient revealed that he felt more restless, had nausea, pain in upper abdomen, headache and no desire to eat.

(a) What could be the reason for no improvement in the depressive symptoms? Is the choice of drug inappropriate? Does the medication needs to be changed, dose increased or decreased? Should another drug be added at this stage?

(see Appendix-1 for solution)

Chapter 34 Opioid Analgesics and Antagonists

Algesia (pain) is an unpleasant bodily sensation perceived as suffering, usually evoked by an external or internal noxious stimulus.

Analgesic A drug that selectively relieves pain by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness.

Pain is a warning signal, primarily protective in nature, but causes discomfort and suffering; may even be unbearable and incapacitating. It is the most important symptom that brings the patient to the physician. Excessive pain may produce other effects—sinking sensation, apprehension, sweating, nausea, palpitation, rise or fall in BP, tachypnoea. Analgesics relieve pain as a symptom, without affecting its cause. They are used when the noxious stimulus (evoking the pain) cannot be removed or as adjuvants to more etiological approach to pain. Analgesics can be divided into three groups, *viz.*

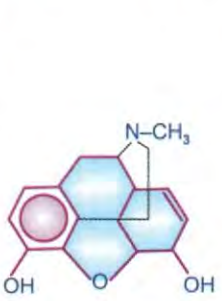
A. Opioid/narcotic/morphine-like analgesics.
B. Nonopioid/non-narcotic/aspirin-like/antipyretic or antiinflammatory analgesics (described in Ch. 14).
C. Adjuvant analgesics: Anticonvulsants, *viz.* gabapentin/pregabalin, carbamazepine, lamotrigine; antidepressants, *viz.* amitryptyline, duloxetine.

OPIOID ANALGESICS

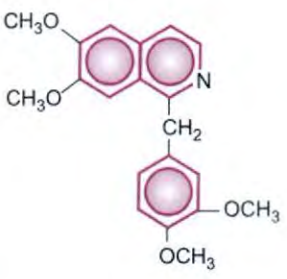
Opium A dark brown, resinous material obtained from poppy (*Papaver somniferum*) capsule. It contains two types of alkaloids.

Phenanthrene derivatives
Morphine (10% in opium)
Codeine (0.5% in opium)
Thebaine (0.2% in opium), (Nonanalgesic)

Benzoisoquinoline derivatives
Papaverine (1%)
Noscapine (6%) } Nonanalgesic



MORPHINE



PAPAVERINE

Opium has been known from the earliest times. It is mentioned in the Eber's papyrus (1500 BC), in the writings of Theophrastus (300 BC) and Galen (2nd century AD). Opium eating became a social custom in China in the 18th century. Serturner, a pharmacist, isolated the active principle of opium in 1806 and named it 'morphine' after the Greek god of dreams Morpheus. In the last century a large number of semisynthetic and synthetic compounds have been developed with morphine-like, antagonistic and mixed agonistic-antagonistic properties.

Compounds that are derived from opium or are chemically related to morphine are called '*opiates*', while all those having morphine-like action, irrespective of chemical nature, are called '*opioids*'. Accordingly, pethidine, endorphins, etc. are opioids, but not opiates.

MORPHINE

Morphine is the principal alkaloid in opium and is widely used till today. Therefore, it is described as prototype.

PHARMACOLOGICAL ACTIONS

1. CNS actions Morphine has site specific depressant and stimulant actions in the CNS by interacting primarily with the μ opioid receptor (for which it has the highest affinity), as a full agonist. The depressant actions are:

(a) Analgesia Morphine is a strong analgesic. Though dull, poorly localized visceral pain is relieved better than sharply defined somatic pain; higher doses can mitigate even severe pain; degree of analgesia increasing with the dose. Nociceptive pain arising from stimulation of peripheral pain receptors is relieved better than neuretic pain (such as trigeminal neuralgia) produced by inflammation of or damage to neural structures. The associated reactions to intense pain (apprehension, fear, autonomic effects) are also dampened. Suppression of pain perception is selective, without affecting other sensations or producing proportionate generalized CNS depression (contrast general anaesthetics).

In contrast to nonopioid analgesics which only relieve pain as a sensation, morphine and other opioids suppress both perception of pain and its emotional component (suffering, distress, anxiety, fear) so that pain is no longer as unpleasant or distressing, i.e. the patient tolerates pain better. The analgesic action of morphine has both spinal and supraspinal components. Intrathecal injection of morphine has been shown to cause segmental analgesia without affecting other modalities. It acts in the substantia gelatinosa of dorsal horn to inhibit release of excitatory transmitters (e.g. glutamate, substance P) from primary afferents carrying pain impulses. The action appears to be exerted through interneurones which are involved in the 'gating' of pain impulses. Release of glutamate from primary pain afferents in the spinal cord and its postsynaptic action on dorsal horn neurones is inhibited by morphine. Action at supraspinal sites in medulla, periaqueductal gray matter, limbic and cortical areas may alter processing and interpretation of pain impulses. In addition, supraspinal action of morphine augments the inhibitory impulses through descending pathways to the spinal cord. Several aminergic (5-HT, NA), GABAergic and other neuronal systems appear to be involved in the action of morphine. Simultaneous action at spinal and supraspinal sites greatly amplifies the analgesia.

A *peripheral action* of opioids on small primary afferent terminals in skin or deeper structures, attenuating their sensitization following tissue injury has also been demonstrated. This may play a role in the analgesic action of morphine in conditions like burns and trauma.

(b) Sedation which is different from that produced by hypnotics is seen. Drowsiness, mental dullness and indifference to surroundings as well as to own body occurs without motor incoordination or ataxia. Higher doses progressively induce sleep and then coma. Morphine has no anticonvulsant action, rather, fits may be precipitated.

(c) Subjective effects and euphoria Morphine has prominent calming effect; there is loss of apprehension, feeling of detachment, lack of initiative, limbs feel heavy and body warm, mental clouding and inability to concentrate occurs. In the absence of pain or apprehension, these effects are generally appreciated as unpleasant by normal people. However, patients in pain or anxiety, and especially addicts, perceive it as pleasurable floating sensation: refer it as 'high'. Rapid i.v. injection by addicts gives them a 'kick' or 'rush' which is intensely pleasurable—akin to orgasm. Thus, one has to learn to perceive the *euphoric* effect of morphine.

The pleasurable and reinforcing effects of μ opioid agonists (morphine-like) appear to involve a separate set of neuronal mechanisms than those involved in analgesia and sedation. The euphoric effects are most likely mediated by DA release in nucleus accumbens, whereas κ agonists (nalorphine like) inhibit DA release and produce aversion. The μ opioid receptors appear to inhibit the inhibitory GABAergic neurones, thereby facilitating DA release in nucleus accumbens. Inhibition of NA release in locus ceruleus by opioids is implicated in their action to allay apprehension and fear.

(d) Respiratory depression Morphine depresses respiratory centre in a dose dependent manner; rate and tidal volume are both decreased. However, analgesic dose in an otherwise healthy individual produces no cognizable respiratory depression, but it may be marked in the presence of other sedatives, as well as in patients of asthma, COPD, corpulmonale, liver and kidney disease. Death in morphine poisoning is due to respiratory failure. Neurogenic, hypercapnoeic and later hypoxic drives to the respiratory centre are suppressed in succession. In addition, there is indifference to breathing: apnoeic patient may breath if commanded.

(e) Cough suppression Cough centre is depressed by morphine, and is more sensitive than respiratory centre.

(f) Temperature regulation Hypothalamic thermostatic centre is depressed; hypothermia occurs in cold surroundings.

(g) Vasomotor centre It is depressed at higher doses and contributes to the fall in BP.

The stimulant central actions of morphine are:

- It sensitises the medullary CTZ to vestibular and other impulses, causing nausea and vomiting as side effect, especially if stomach is full or the patient ambulates. Larger doses depress vomiting centre directly. As such, emetics should not be tried in morphine poisoning.
- It stimulates the Edinger-Westphal nucleus of the IIIrd nerve by inhibiting the GABAergic interneurone which keeps this nucleus tonically inhibited, producing miosis. No miosis occurs on topical application of morphine to the eye. No tolerance develops to this action; addicts have constricted pupils. However, morphine causes mydriasis in some species like cats. Another ocular effect is a decrease in intraocular tension.
- Morphine stimulates the medullary vagal centre producing bradycardia as the usual response.
- Certain cortical areas and hippocampal cells are stimulated. Truncal rigidity and immobility is consistently manifested at high doses (especially on i.v. injection). This may hamper respiratory excursions and cause respiratory complications. This response resembles cataplexy seen in rats and mice. Morphine lowers seizure threshold. Convulsions may occur in morphine poisoning. The proconvulsant action has been ascribed to inhibition of GABA release by hippocampal interneurones. Morphine causes excitation instead of sedation in an occasional individual. Species like cat, lion, horse, sheep and cow are uniformly excited and show hyperthermia.

2. Neuro-endocrine actions Hypothalamic activation by afferent collaterals is dampened. Hypothalamic influence on pituitary is reduced. As a result FSH, LH, ACTH levels are lowered, while prolactin and GH levels are raised (these are under predominant inhibitory control). The sex hormone and cortisol levels are lowered. Heavy opioid abusers often suffer loss of libido, impotence, menstrual irregularities and infertility, but clinical hypocorticism is unusual. Morphine can release ADH and reduce urine volume.

3. Peripheral actions

(a) CVS Morphine causes vasodilatation due to:

- histamine release.
- depression of vasomotor centre.
- direct action decreasing tone of blood vessels.

There is a shift of blood from pulmonary to systemic circuit due to greater vasodilatation in the latter. Therapeutic doses cause little change in the BP of recumbent normovolaemic patient. Postural hypotension and fainting do occur due to venodilatation and impairment of vascular reflexes. Morphine has little direct effect on heart; rate generally decreases due to stimulation of vagal centre, but may increase reflexly if the BP falls. Cardiac work is consistently reduced due to decrease in peripheral resistance, imparting anti-ischaemic property to morphine. Intracranial tension tends to rise as a consequence of CO_2 retention leading to cerebral vasodilatation.

(b) GIT The enteric plexus neurones and g.i. mucosa are rich in opioid receptors. Morphine exerts marked effect on g.i. motility as well as on fluid dynamics across g.i. mucosa. Constipation is a prominent feature of morphine action. Several factors contribute:

- Action on enteric plexus and in the CNS increases tone and segmentation but decreases propulsive movements. Tone of duodenum and colon may be increased to the level of spasm.
- Spasm of pyloric, ileocaecal and anal sphincters.
- Decrease in all gastrointestinal secretions due to reduction in movement of water and electrolytes from mucosa to the lumen. This is mainly a peripheral action through opioid receptors on enteric plexus neurones, but also a central action. Absorption of fluid is increased due to stasis.
- Central action causing inattention to defecation reflex.

  No tolerance develops to this action: addicts remain chronically constipated.

(c) Other smooth muscles

- Morphine causes spasm of sphincter of Oddi → intrabiliary pressure is increased several fold → may cause biliary colic. This action is counteracted by opioid antagonist naloxone and direct smooth muscle relaxants like nitrates.
- Tone of both detrusor and bladder sphincter is increased causing urinary urgency and difficulty in micturition. Contractions of ureter are also enhanced.
- Action on uterine muscle is generally insignificant, but morphine/pethidine may occasionally prolong labour.
- Morphine causes bronchoconstriction by releasing histamine (due to its bulky basic molecule; the mechanism is nonimmunological). This is of no consequence in normal individuals, but can be dangerous in asthmatics.

PHARMACOKINETICS

The oral absorption of morphine is unreliable because of high and variable first pass metabolism; oral bioavailability is nearly 1/4th of parenterally administered drug. About 30% is bound to plasma proteins. Distribution is wide; concentration in liver, spleen and kidney is higher than that in plasma. Only a small fraction enters brain rather slowly. Morphine freely crosses placenta and can affect the foetus more than the mother. It is primarily metabolized in liver by glucuronide conjugation. Morphine-6-glucuronide is an active metabolite (more potent than morphine on μ opioid receptors), which accumulates during chronic dosing and contributes to analgesia, despite its restricted passage across blood-brain barrier. Another metabolite morphine-3-glucuronide has neuroexcitatory property. Glucuronides of morphine are readily excreted by the kidney and to some extent in bile. Plasma t½ of morphine averages 2–3 hours. Effect of a parenteral dose lasts 4–6 hours. Elimination is almost complete in 24 hours and morphine is noncumulative. However, small amounts persist in the body due to enterohepatic circulation.

ADVERSE EFFECTS

1. Side effects Sedation, mental clouding, lethargy and other subjective effects which may even be dysphoric in some subjects; vomiting is occasional in recumbent patient; constipation is common and distressing. Respiratory depression, blurring of vision, urinary retention (especially in elderly male) are other side effects. BP may fall, especially in hypovolaemic patient and if he/she walks about.

2. Idiosyncrasy and allergy Allergic reactions manifesting as urticaria, swelling of lips occur infrequently. Anaphylactoid reaction is rare. A local reaction at injection site and generalized itching may occur due to histamine release. However, itching may also be due to activation of pruritoceptive neurons in the spinal cord, because intrathecal morphine also induces itching.

3. Apnoea of the newborn This may occur when morphine is given to the mother during labour. The blood-brain barrier of the foetus is undeveloped, morphine attains higher concentration in foetal brain than in that of mother. Naloxone 10 μg/kg injected in the umbilical cord is the treatment of choice.

4. Acute morphine poisoning It may be accidental, suicidal or seen in drug abusers. In the nontolerant adult, 50 mg of morphine i.m. produces serious toxicity. The human lethal dose is estimated to be about 250 mg. Manifestations are extensions of the pharmacological action.

Stupor or coma, flaccidity, shallow and occasional breathing, cyanosis, pinpoint pupil, fall in BP and shock; convulsions may be seen in few, pulmonary edema occurs at terminal stages, death is due to respiratory failure.

Treatment: Consists of respiratory support (positive pressure respiration also opposes pulmonary edema formation) and maintenance of BP (i.v. fluids, vasoconstrictors). Gastric lavage should be done with pot. permanganate to remove unabsorbed drug. Lavage is indicated even when morphine has been injected. Being a basic drug it is partitioned to the acid gastric juice, ionizes there and does not diffuse back into blood.

Specific antidote: Naloxone 0.4–0.8 mg i.v. repeated every 2–3 min till respiration picks up, is the specific antagonist of choice because it acts rapidly, does not have any agonistic action and does not *per se* depress respiration (*see* p. 512). Due to short duration of action, naloxone should be repeated every 1–4 hours, according to the response.

5. Tolerance and dependence High degree of tolerance can be developed to morphine and related opioids if the drug is taken repeatedly. It is partly pharmacokinetic (enhanced rate of metabolism), but mainly pharmacodynamic (cellular tolerance). Tolerance is exhibited to most actions, but not to constipating, miotic and proconvulsant actions. Rate of development of tolerance depends on the dose and the interval between doses. Larger doses repeated more quickly induce tolerance more rapidly. Addicts tolerate morphine in grams: lethal dose is markedly increased. Patients in intense pain are relatively tolerant to depressant effects. Cross tolerance among opioids is of high degree. Morphine tolerant subjects are partially cross tolerant to other CNS depressants as well.

Morphine produces pronounced addiction and dependence, its abuse liability is rated high. Recently the NMDA antagonists and nitric oxide synthase inhibitors have been found to block morphine tolerance and dependence in animals. Thus, the analgesic action of morphine can be dissociated from tolerance and dependence which contribute to its abuse. Concern about abuse has been a major limitation in the use of morphine, but appropriate medical use of morphine seldom progresses to dependence and abuse. Morphine abuse is higher among medical and paramedical personnel because they have easier access to the drug. Earlier, morphine addicts tended to be from the middle age group, but now younger individuals are also opting for it. Opium eating has been prevalent among natives in the orient.

Withdrawal of morphine is associated with marked drug-seeking behaviour. Physical manifestations of abstinence are—lacrimation, sweating, yawning, anxiety, fear, restlessness, aggression, gooseflesh, mydriasis, tremor, insomnia, abdominal colic, diarrhoea, dehydration, rise in BP, palpitation and rapid weight loss. Delirium and convulsions are not a characteristic feature (contrast barbiturates) and are seen only occasionally. Cardiovascular collapse and fatality are rare if supportive measures are instituted. Administration of an opioid at this time immediately terminates the withdrawal syndrome.

Opioid antagonists (naloxone, nalorphine) precipitate acute withdrawal syndrome in the dependent subject. In the more severely dependent, even 0.2 mg of naloxone can precipitate marked withdrawal.

Treatment: Consists of withdrawal of morphine and substitution with oral methadone (long-acting, orally effective) followed by gradual withdrawal of methadone (*see* p. 504). However, craving for the opioid may persist for long time, and relapse rate among postaddicts is high. Long-term methadone maintenance and other techniques using agonist-antagonistic drugs are also employed.

PRECAUTIONS AND CONTRAINDICATIONS

Morphine is a drug of emergency, but due care has to be taken in its use.

1. Infants and the elderly are more susceptible to the respiratory depressant action of morphine.
2. It is dangerous in patients with respiratory insufficiency (emphysema, pulmonary fibrosis, cor pulmonale); sudden deaths have occurred. Morphine accentuates sleep apnoea; hypoxic brain damage can occur.
3. Bronchial asthma: Morphine can precipitate an attack by its histamine releasing action. A high potency opioid with lower histamie releasing potential (e.g. fentanyl) should be used, if unavoidable, in an asthmatic.
4. Head injury: Morphine is contraindicated in patients with head injury. Reasons are—
   - By retaining CO_2, it increases intracranial tension which will add to that caused by head injury itself.
   - Even therapeutic doses can cause marked respiratory depression in these patients.
   - Vomiting, miosis and altered mentation produced by morphine interfere with assessment of progress in head injury cases.
5. Hypotensive states and hypovolaemia exaggerate fall in BP due to morphine.
6. Undiagnosed acute abdominal pain: Morphine can aggravate certain conditions, e.g. diverticulitis, biliary colic, pancreatitis. Inflamed appendix may rupture. Morphine can be given after the diagnosis is established. Pentazocine, buprenorphine are less likely to aggravate biliary spasm.
7. Elderly male: Chances of urinary retention are high.
8. Hypothyroidism, liver and kidney disease patients are more sensitive to morphine.
9. Unstable personalities: Are able to continue with its use and become addicted.

Interactions

Phenothiazines, tricyclic antidepressants, MAO inhibitors, amphetamine and neostigmine potentiate morphine and other opioids, either by retarding its metabolism or by a pharmacodynamic interaction at the level of central neurotransmitters. Exaggerated CNS depression can occur if morphine is given with a sedative-hypnotic.

Morphine retards absorption of many orally administered drugs by delaying gastric emptying.

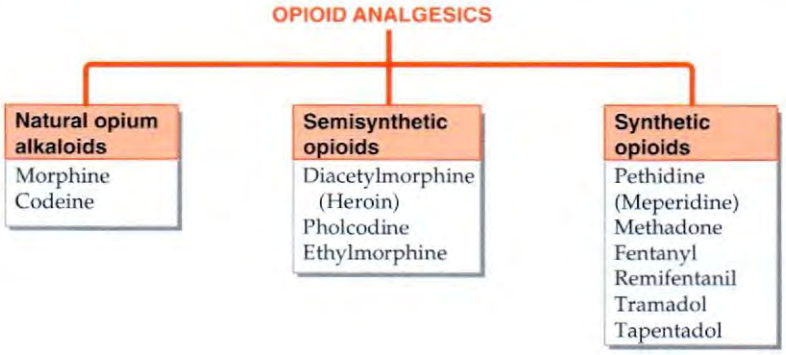
Dose: 10–50 mg oral, 10–15 mg i.m. or s.c. or 2–6 mg i.v.; 2–3 mg epidural/intrathecal; children 0.1–0.2 mg/kg. i.m. or s.c.

MORPHINE SULPHATE 10 mg/ml inj; MORCONTIN 10, 30, 60, 100 mg continuous release tabs; 30–100 mg BD; RILIMORF 10, 20 mg tabs, 60 mg SR tab.

OTHER OPIOIDS

1. Codeine It is methyl-morphine, occurs naturally in opium, and is partly converted in the body to morphine. It is less potent than morphine (1/10th as analgesic), also less efficacious; is a partial agonist at μ opioid receptor with a low ceiling effect. The degree of analgesia is comparable to aspirin (60 mg codeine ~ 600 mg aspirin). Codeine can relieve mild to moderate pain only.

However, codeine is more selective cough suppressant (1/3rd as potent as morphine);



subanalgesic doses (10–30 mg) suppress cough (*see* p. 239). Codeine has very low affinity for opioid receptors. The analgesic action has been ascribed to morphine generated by its demethylation by CYP2D6. Codeine fails to produce analgesia in subjects with polymorphic CYP2D6 who cannot demethylate codeine. However, receptors involved in the antitussive action appear to be distinct, because they bind codeine as well as morphine.

Codeine has good activity by the oral route (oral: parenteral ratio 1:2). A single oral dose acts for 4–6 hours. Constipation is a prominent side effect when it is used as analgesic. Codeine has been used to control diarrhoea (*see* Ch. 48). Other side effects are milder. The abuse liability is low. No parenteral preparation is available.

2. Pholcodine, Ethylmorphine They have codeine like properties and have been used mainly as antitussive (*see* p. 239); claimed to be less constipating.

3. Heroin (Diamorphine, Diacetylmorphine) It is about 3 times more potent than morphine; more lipid soluble, therefore enters the brain more rapidly, acts faster but duration of action is similar. It is considered to be more euphorient (especially on i.v. injection) and highly addicting. Because of its high potency, it has been favoured in illicit drug trafficking. The sedative, emetic and hypotensive actions are said to be less prominent. However, it has no outstanding therapeutic advantage over morphine and has been banned in most countries except U.K.

4. Pethidine (Meperidine)

Pethidine was synthesized as an atropine substitute in 1939, and has some actions like it. Though chemically unrelated to morphine, it interacts with μ opioid receptors and its actions are blocked by naloxone. Important differences in comparison to morphine are:

1. Dose to dose 1/10th in analgesic potency; however, analgesic efficacy approaches near to morphine and is higher than codeine.
2. After i.m. injection, the onset of action is more rapid but duration is shorter (2–4 hours).
3. It does not effectively suppress cough.
4. Spasmogenic action on smooth muscles is less marked—miosis, constipation and urinary retention are less prominent.
5. Tachycardia (due to antimuscarinic action) occurs instead of bradycardia, and cardiac contractility may decrease.

Pethidine is better absorbed than morphine; oral: parenteral activity ratio is higher (1/3 to 1/2). It is nearly completely metabolized in liver. A major part is hydrolysed to *meperidinic acid,* but a small fraction is demethylated to form *norpethidine,* which has excitant effects. The plasma t½ is 2–3 hours.

Apart from usual opioid side effects, pethidine produces some atropinic effects like dry mouth, blurred vision, tachycardia, but constipation, urinary retention and miosis are less prominent.

Overdose of pethidine produces many excitatory effects, *viz.* tremors, mydriasis, hyperreflexia, delirium, myoclonus and convulsions due to accumulation of *norpethidine.* Renal failure patients given repeated doses of pethidine are prone to experience similar effects.

Nonselective MAO inhibitors interfere with hydrolysis but not with demethylation of pethidine—norpethidine is produced in excess and excitement occurs. Pethidine injected in patients receiving a selective serotonin reuptake inhibitor (SSRI) may produce the 'serotonin syndrome' (*see* p. 488) by enhancing 5-HT release.

Clinical use of pethidine as a morphine substitute has very much declined because of these problems. It is occasionally used to control shivering during recovery from anaesthesia and that attending i.v. infusions. Pethidine is not useful in cough and diarrhoea.

Dose: 50–100 mg i.m., s.c. (may cause irritation, local fibrosis on repeated injection). It is occasionally given orally or i.v.

PETHIDINE HCL 50, 100 mg tab. 100 mg/2 ml inj; VERPAT 50 mg/ml inj.

5. Fentanyl A pethidine congener, 80–100 times more potent than morphine, both in analgesia and respiratory depression. In analgesic doses it produces few cardiovascular effects. Cardiac contractility and heart rate are only marginally reduced, and it has lower propensity to release histamine. Because of high lipid solubility, it enters brain rapidly and produces peak analgesia in 5 min after i.v. injection. The duration of action is short: starts wearing off after 30–40 min due to redistribution, while elimination t½ is ~4 hr. In the injectable form it is almost exclusively used in anaesthesia (*see* p. 411-12). Transdermal

fentanyl has become a very frequently used opioid analgesic for cancer/terminal illness pain or other types of chronic pain. Buccal use is possible, but not oral due to high first pass metabolism.

DUROGESIC transdermal patch delivering 12 μg/hr, 25 μg/hr, 50 μg/hr, 75 μg/hr or 100 μg per hour; the patch is changed every 3 days.

6. Remifentanil This faster acting congener of fentanyl has a very brief (10–15 min) duration of action after i.v. injection; Remifentanil is used exclusively in anaesthesia (*see* p. 412).

7. Methadone A synthetic opioid, chemically dissimilar but pharmacologically very similar to morphine. It is a full μ receptor agonist, and has analgesic, respiratory depressant, emetic, antitussive, constipating and biliary actions similar to morphine.

The most important feature of methadone is high oral: parenteral activity ratio (1 : 2) and its firm binding to tissue proteins. In single doses it is only slightly more potent than morphine and has comparable duration of action (4–6 hours on i.m. injection), but it cumulates in tissues on repeated administration—duration of action is progressively lengthened due to gradual release from these sites; plasma t½ on chronic use is 24–48 hours. Plasma protein binding is 90% and it is metabolized in liver, primarily by demethylation and cyclization involving CYP3A4 and CYP2B6. Metabolites are excreted in urine. Rifampin and phenytoin can cause withdrawal symptoms to appear in methadone dependent subjects by inducing its metabolism.

Because of slow and persistent nature of action, sedative and subjective effects are less intense. It is probably incapable of giving a 'kick'. The abuse potential is rated lower than morphine. Tolerance develops more slowly, probably due to progressive filling of tissue stores. Withdrawal syndrome is of gradual onset, taking 1–2 days after discontinuation, is prolonged and less severe.

Methadone has been used primarily as substitution therapy for opioid dependence: 1 mg of oral methadone can be substituted for 4 mg of morphine, 2 mg of heroin and 20 mg of pethidine. After 2–3 days of methadone substitution, it is gradually withdrawn. The resulting withdrawal syndrome is prolonged, but bearable. Another technique is *methadone maintenance* therapy in opioid addicts—sufficient dose of methadone (40–80 mg/day) is given orally over long term to produce high degree of tolerance so that pleasurable effects of i.v. doses of morphine or heroin are not perceived and the subject gives up the habit.

Methadone can also be used as an analgesic for the same conditions as morphine; dose 2.5–10 mg oral or i.m. It is occasionally employed as antitussive.

METHADONE 5 mg/ml and 10 mg/ml syr; 5, 10, 20, 40 mg tabs (for maintenance therapy of opioid dependence).

8. Dextropropoxyphene It is a weak synthetic opioid chemically related to methadone, half as potent analgesic as codeine, which lacks antitussive activity. Perceived to have low/no addicting potential, it was included in many popular over-the-counter analgesic combinations containing paracetamol and other drugs. However, overdose of dextropropoxyphene was found to cause delirium and seizures. Its demethylated metabolite which accumulated on repeated dosing, exhibited cardiotoxicity, and reports of fatalities appeared. Many countries, including UK, Europe, USA withdraw it, and it was banned in India in 2013.

9. Tramadol This centrally acting analgesic is an atypical opioid which relieves pain by opioid as well as additional mechanisms. Its affinity for μ opioid receptor is low, while that for κ and δ is very low. Unlike other opioids, it inhibits reuptake of NA and 5-HT, increases 5-HT release, and thus activates monoaminergic spinal inhibition of pain. Its analgesic action is only partially reversed by the opioid antagonist naloxone.

Injected i.v. 100 mg tramadol is equianalgesic to 10 mg i.m. morphine. Oral bioavailability of tramadol is good (oral: parenteral dose ratio is 1.4). The t½ is 5–6 hours and effects last for 4–6 hrs. Tramadol causes insignificant respiratory depression, sedation, constipation or urinary retention. It is generally well tolerated, but nausea and dizziness may be prominent. Other side effects are sleepiness, dry mouth, sweating and lowering of seizure threshold, therefore contraindicated in epileptics. Haemodynamic effects are minimal. Tramadol should not be

given to patients taking SSRI therapy because of risk of 'serotonin syndrome' (*see* p. 488).

Tramadol is indicated for mild-to-moderate short-lasting pain due to diagnostic procedures, injury, surgery, etc, as well as for chronic pain including cancer pain, but is not effective in severe pain. Little tendency to dose escalation by chronic users is seen and abuse potential is low.

Dose: 50–100 mg oral/i.m./slow i.v. infusion (children 1–2 mg/kg) 4–6 hourly.

CONTRAMAL, DOMADOL, TRAMAZAC 50 mg cap, 100 mg SR tab; 50 mg/ml inj in 1 and 2 ml amps.

ULTRACET, URGENDOL: tramadol 75 mg + paracetamol 325 mg tab.

10. Tapentadol This newer atypical opioid is similar to tramadol in structure and mechanism of action: binding to μ opioid receptor is weak, and it acts mainly *via* monoaminergic pain mechanisms. Compared to tramadol, inhibition of NET is more marked than that of SERT; thus, it primarily activates central noradrenergic pathways to elicit analgesia.

Tapentadol is well absorbed orally, largely glucuronide conjugated, and the metabolite is excreted in urine. It is useful in the treatment of moderately severe pain conditions, and appears to be at least as effective as tramadol, but head-to-head comparative data is inadequate to establish relative efficacy.

Side effects are similar to tramadol, but nausea and vomiting appears to be less troublesome. However, it can trigger 'serotonin syndrome' in patients treated with SSRIs, and carries risk of precipitating seizures in predisposed patients. Thus, tapentadol is a useful alternative to tramadol for acute as well as chronic pain of moderate severity.

Dose: 50–100 mg 2–4 times/day.

TAPOSER, DUOVOLT, TAPCYNTA 50, 75, 100 mg tab; TAPOSER-P: Tapentadol 50 mg + paracetamol 325 mg tab.

USES (Of morphine and its congeners)

1. *As analgesic* Opioid analgesics are indicated in severe pain of any type. However, they only provide symptomatic relief without affecting the cause. Pain may be valuable for diagnosis; should not be relieved by a potent analgesic unless proper assessment of the patient has been done. Indiscriminate use of opioids can be hazardous. On the other hand, inadequate dose or reluctance to use an opioid for a patient in distress is equally deplorable.

Important features of opioid analgesics with agonist, partial agonist and agonist-antagonist action on opioid receptors are compared in Table 34.1.

Morphine (or one of its parenteral congeners) is indicated especially in traumatic, visceral, ischaemic (myocardial infarction), postoperative, burn, cancer pain, renal colic and the like. It should be given promptly in myocardial infarction to allay apprehension and reflex sympathetic stimulation. Opioids, especially pethidine, have been extensively used for obstetric analgesia, but one must be prepared to deal with the foetal and maternal complications.

Adequate use of morphine (even i.v.) is indicated in an emergency. It may prevent neurogenic shock and other autonomic effects of excruciating pain such as that of crush injuries. Patients in severe pain require higher doses of opioids and tolerate them without manifesting toxicity. There is considerable individual variability in the response to opioids. Opioids should not be restricted in case of pain of terminal illness (e.g. cancer pain), but for other chronic conditions, due consideration must be given to their addicting liabilities. Neuropathic pain responds less predictably to opioid analgesics, while pregabalin, amitriptyline, duloxetine are the major drugs for such pain.

Epidural (2–3 mg) or intrathecal (0.2 mg) injection of morphine produces segmental analgesia lasting ~12 hour without affecting other sensory, motor or autonomic modalities. It is being used for surgical analgesia in abdominal, lower limb and pelvic operations as well as for labour, postoperative, cancer and other intractable pain. Respiratory depression occurs after a delay due to ascent of the opioid through the subarachnoid space to the respiratory centre. Use of fentanyl in place of morphine produces faster analgesia and reduces the risk of respiratory depression because of greater uptake of fentanyl by nerves at the site of injection.

Patient controlled analgesia (PCA) is an attractive technique of postoperative pain control in which the patient himself regulates the rate of i.v. fentanyl infusion according to intensity of pain felt.

Table 34.1: Comparative features of opioid analgesics, partial agonist analgesics and agonist-antagonist analgesics

Drug	*Nature of analgesia*	*Ceiling efficacy*	*Oral: parenteral ratio*	*Equivalent analgesic dose*	*Duration of analgesia*
1. Morphine	μ agonist	++++	Low	10 mg	4–6 hr
2. Codeine	Partial μ agonist	+	High	60 mg	4–6 hr
3. Pethidine	μ agonist	++++	Medium	60–100 mg	2–4 hr
4. Methadone	μ agonist	++++	High	6–10 mg	4–6 hr $
5. Fentanyl	μ agonist	++++	Low	0.1 mg	1–1.5 hr
6. Tramadol	μ agonist (low affinity)	++	High	50–100 mg	4–6 hr
7. Pentazocine	κ agonist	++	Medium	30–60 mg	3–5 hr
8. Butorphanol	κ agonist	+++	— #	2.0 mg	4–6 hr
9. Nalbuphine	κ agonist	+++	— #	10 mg	3–6 hr
10. Buprenorphine	Partial μ agonist	+++	Low	0.3 mg	6–8 hr

+ to ++++ Low to high (full) analgesic efficacy.
# Parenteral use only; no oral preparation.
$ Duration of action increases after repeated dosing.

Chronic terminal illness pain, including cancer pain, needs to be treated aggressively without regard to the risk of dependence. Oral morphine in continuous release formulation is often used, but increasing doses are required as tolerance develops. Substituting oral methadon for morphine or rotating the two opioids may some times help. Transdermal fentanyl is a suitable option that is now frequently used. The patch produces analgesia after ~12 hr, but then blood levels of fentanyl and intensity of analgesia remain fairly uniform if the patch is changed every 3 days. For severe chronic pain continuous opioid analgesia with a long-acting preparation works better than a short-acting opioid given intermittently. Rescue short-acting opioid is to be added to the continuous analgesia for 'breakthrough pain'. Buprenorphine (a strong agonist-antagonist) as sublingual tablet or transdermal patch is another opioid used for chronic cancer pain.

For milder pain, e.g. toothache, headache, arthralgia, etc. aspirin-like analgesics are preferred. When they are not effective—codeine/ tramadol/ tapentadol may be used orally, either alone or in combination with paracetamol. The combination enhances the ceiling analgesia. For majority of painful conditions, especially more severe and longerlasting pain, a NSAID may be combined with the opioid. This serves to enhance analgesia while keeping the opioid dose low.

2. *Preanaesthetic medication* Morphine and pethidine are used in few selected patients (*see* p. 413).

3. *Balanced anaesthesia and surgical analgesia* Fentanyl, remifentanil or morphine are an important component of intraoperative anaesthetic techniques (*see* p. 411-12).

4. *Relief of anxiety and apprehension* Especially in myocardial infarction, internal bleeding (haematemesis, threatened abortion, etc.) morphine has been employed. It may prevent worsening of the condition by suppressing reflex overactivity. However, opioids should not be used as anxiolytics or to induce sleep.

5. *Acute left ventricular failure/acute pulmonary edema* Morphine injected i.v. affords dramatic relief by—

(a) Reducing preload on heart due to vasodilatation and peripheral pooling of blood.
(b) Tending to shift blood from pulmonary to systemic circuit; relieves pulmonary congestion and edema.

(c) Allaying air hunger and dyspnoea by depressing respiratory centre.
(d) Cutting down sympathetic stimulation by calming the patient, thereby reduces cardiac work.

Morphine is also indicated to relieve pulmonary edema due to infarction of lung, but not due to irritant gases. It is contraindicated in bronchial asthma.

6. *Cough* Codeine or more commonly its substitutes are widely used for suppressing dry, irritating cough (*see* Ch. 16).

7. *Diarrhoea* The constipating action of codeine has been used to check diarrhoea and to improve the consistency of stools in colostomy. Loperamide and diphenoxylate are synthetic opioids used exclusively as antidiarrhoeals. The risk and benefits of their use are detailed in Ch. 49.

OPIOID RECEPTORS

Morphine and other opioids exert their actions by interacting with specific receptors present on neurones in the CNS and in peripheral tissues. Chemical modification of morphine structure has yielded a number of compounds which have a complex pattern of morphine-like and other agonistic and antagonistic actions that cannot be explained on the basis of a single opioid receptor. Radioligand binding studies divided the opioid receptors into three types (μ, κ, δ); which have been cloned, mapped and studied with modern techniques. Each has a specific pharmacological profile and pattern of anatomical distribution in the brain, spinal cord and peripheral tissues (mainly gut, blood vessels, heart, lungs and immune cells). Subtypes of μ and κ receptor have been identified. Actions mediated by the 3 types of opioid receptors are listed in Table 34.2.

Opioid ligands can interact with different opioid receptors as agonists, partial agonists or competitive antagonists. The overall pattern of effect of a particular agent depends not only on the nature of its interaction with different opioid receptors, but also on its relative affinity for these, e.g. morphine is an agonist on μ, κ and δ receptors, but its affinity for μ receptors is much higher than that for the other two. The effects, therefore, are primarily the result of μ receptor activation.

The nature and intensity of action of complex action opioids and antagonists are summarized in Table 34.3.

μ receptor The μ receptor is characterized by its high affinity for morphine. It is the major receptor mediating actions of morphine and its congeners. Endogenous ligands for μ receptor are peptides called *Endomorphins 1 and 2*, which have been found in mammalian brain. These pepticles produce biological effects ascribed to μ receptor. Other opioid peptides *viz*. β-endorphin, enkephalins and dynorphins bind to μ receptor with lower affinity. High density of μ receptors has been detected in periaqueductal gray, thalamus, nucleus tractus solitarious, nucleus ambiguus and area postrema.

Table 34.2: Actions ascribed to the three types of opioid receptors

μ (mu)	*κ (kappa)*	*δ (delta)*
Analgesia (supraspinal μ_1 + spinal μ_2)	Analgesia (spinal κ_1) (supraspinal-κ_3)	Analgesia (spinal + affective component of supraspinal)
Respiratory depression (μ_2)	Respiratory depression (lower ceiling)	Respiratory depression
Sedation	Dysphoria, psychotomimetic	Affective behaviour
Euphoria	Miosis (lower ceiling)	Reinforcing actions
Miosis	Sedation	Reduced g.i. motility
Muscular rigidity	Dependence (nalorphine type)	Proconvulsant
Reduced g.i. motility (μ_2)	Reduced g.i. motility	
Dependence (morphine type)		

Table 34.3: Nature of interaction of opioid ligands with the three major types of opioid receptors

Ligand	μ (mu)	κ (kappa)	δ (delta)
1. Morphine	Ago. (Strong)	Ago. (Weak)	Ago. (Weak)
2. Nalorphine	Anta. (Strong)	Ago. (Medium)	—
3. Pentazocine	P.Ago, Anta. (Weak)	Ago. (Medium)	—
4. Butorphanol	P.Ago (Weak)	Ago. (Strong)	—
5. Nalbuphine	Anta. (Weak)	Ago. (Strong)	—
6. Buprenorphine	P.Ago	Anta. (Medium)	—
7. Naloxone	Anta. (Strong)	Anta. (Medium)	Anta. (Weak)
8. Naltrexone	Anta. (Strong)	Anta. (Strong)	Anta. (Weak)
9. Met/Leu enkephalin	Ago. (Medium)	—	Ago. (Strong)
10. β-Endorphin	Ago. (Strong)	—	Ago. (Strong)
11. Dynorphin A, B	Ago. (Weak)	Ago. (Strong)	Ago. (Weak)

Ago.—Agonist; Anta.—Antagonist
P. Ago—Partial agonist: have lower efficacy, though affinity (potency) may be high.

Two subtypes of μ receptor have been proposed:

μ_1: Has higher affinity for morphine, mediates supraspinal analgesia and is selectively blocked by naloxonazine.

μ_2: Has lower affinity for morphine, mediates spinal analgesia, respiratory depression and constipating action.

κ receptor This receptor is defined by its high affinity for ketocyclazocine and dynorphin A; the latter is considered to be its endogenous ligand. *Norbinaltorphimine* is a selective κ antagonist. Two subtypes of κ receptor κ_1 and κ_3 are functionally important. Analgesia caused by κ agonists is primarily spinal (through κ_1 receptor). However, κ_3 receptors mediate lower ceiling supraspinal analgesia. Other κ actions are listed in Table 34.2.

δ receptor This receptor has high affinity for leu/met enkephalins which are its endogenous ligands. The δ mediated analgesia is again mainly spinal (δ receptors are present in dorsal horn of spinal cord). The limbic areas are rich in δ receptors, suggesting role of these receptors in the affective component of supraspinal analgesia, reinforcing actions and dependence. The proconvulsant action is more prominent in δ agonists. Myenteric plexus neurones express high density of δ receptors, which mediate reduced g.i. motility. *Naltrindole* is a selective δ antagonist.

It thus appears that μ and δ receptor responses are quite similar, but those exerted through κ receptor are distinct. In certain areas κ actions are antagonistic to μ actions.

The σ (sigma) receptor is no longer considered an opioid receptor, because it is neither activated by morphine nor blocked by naloxone. However, certain opioids, e.g. pentazocine, butorphanol and many unrelated compounds (including the hallucinogens phencyclidine) bind to σ receptors. Certain naloxone insensitive effects of pentazocine like drugs, e.g. dysphoria, psychotomimetic action, tachycardia, mydriasis are believed to be mediated by σ receptors.

Opioid receptor transducer mechanisms

All 3 types of opioid receptors (μ, κ, δ) have been cloned; all are GPCRs located mostly on prejunctional neurones. They generally exercise inhibitory modulation by decreasing release of the junctional transmitter (Fig. 34.1). As such, various monoaminergic (NA, DA, 5-HT), GABA, glutamate (NMDA/AMPA) pathways are intricately involved in opioid actions.

Opioid receptor activation reduces intracellular cAMP formation and opens K^+ channels (mainly through μ and δ receptors) or closes voltage gated N type Ca^{2+} channels (mainly κ receptor). These actions result in neuronal hyperpolarization and reduced availability of

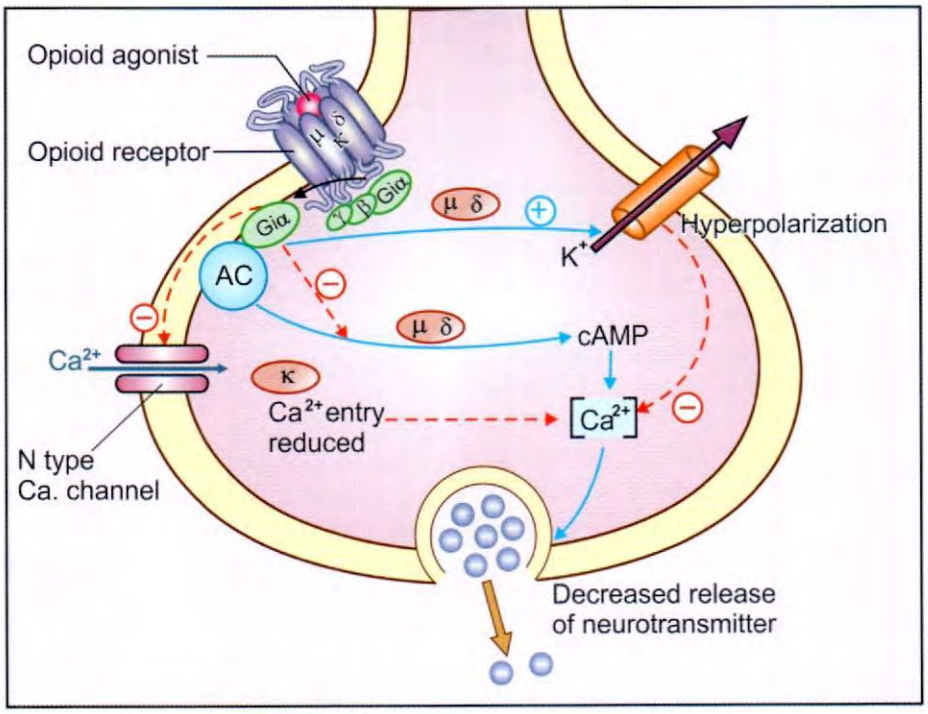


Fig. 34.1: Opioid receptor transducer mechanisms
AC-Adenylyl cyclase; Gi-coupling protein; cAMP-Cyclic AMP

intracellular Ca^{2+} → decreased neurotransmitter release by cerebral, spinal, and myenteric neurones (e.g. glutamate and neuropeptides from primary nociceptive afferents). Opioid receptors are also expressed on postjunctional neurones. Activation of these receptors results in K^+ channel opening, hyperpolarization and neuronal inhibition. However, other mechanisms and second messengers may also be involved, particularly in the long-term.

COMPLEX ACTION OPIOIDS

Clinically, the agonist-antagonist (agonist at one opioid receptor, antagonist at another) and partial/weak agonist (low intrinsic activity) opioids are analgesics of limited efficacy equivalent to lower doses of morphine. They cause submaximal (low ceiling) respiratory depression and are less addicting. However, in only few situations they have proven to be advantageous over the full μ receptor agonists. None of these drugs should be administered to a subject who has received μ opioid agonist, or who is likely to be dependent on such a drug, because analgesia may be reduced or a severe withdrawal reaction may be precipitated.

COMPLEX ACTION OPIOIDS

Agonist-antagonists (κ analgesics)	Partial μ agonist + κ antagonist
Nalorphine	Buprenorphine
Pentazocine	
Butorphanol	
Nalbuphine	

1. Nalorphine It is N-allyl-normorphine, and was the first opioid antagonist introduced in 1951 which could reverse morphine action. Later it was found to have agonistic action on κ receptor as well, producing lower ceiling analgesia. It is not used clinically because of dysphoric and psychotomimetic effects.

2. Pentazocine It is the first agonist-antagonist to be used as an analgesic. Along with being a weak μ antagonist, it has more marked κ agonistic actions. Distinctive features of pentazocine are:

(a) Analgesia caused by pentazocine has a lower ceiling and is primarily spinal (κ_1). It has a different character than that caused by morphine.

(b) Sedation and respiratory depression is 1/3 to 1/2 of morphine at lower doses, and has a lower ceiling, does not increase much beyond 60 mg dose.

(c) Tachycardia and rise in BP are produced at higher doses due to sympathetic stimulation. This may increase cardiac work. Pentazocine is better avoided in coronary ischaemia and myocardial infarction.

(d) Biliary spasm and constipation are less marked.

(e) Vomiting is less frequent. Other side effects are sweating and lightheadedness.

(f) Subjective effects are pleasurable (morphine-like) at lower doses. These are recognised by post-addicts to be opiate. However, as dose is increased, effects become unpleasant (nalorphine-like at > 60 mg i.m.) and psychotomimetic effects (κ, σ mediated) appear.

Tolerance and dependence to pentazocine develops on repeated use. Withdrawal syndrome has features of both morphine and nalorphine abstinence, but is milder in intensity. 'Drug seeking' is less intense.

Injected in morphine dependent subjects, it precipitates withdrawal. In pentazocine dependent subjects, naloxone precipitates withdrawal, but at higher doses.

Pentazocine is effective orally. Though considerable first pass metabolism occurs; oral: parenteral ratio is 1 : 3. It is oxidized and glucuronide conjugated in liver and excreted in urine. Plasma t½ is 3–4 hours, duration of action of a single dose is 3–5 hours.

Oral dose: 50–100 mg.

Parenteral dose: 30–60 mg i.m., s.c., may cause local fibrosis on repeated injection due to irritant property.

FORTWIN 25 mg tab., 30 mg/ml inj., FORTSTAR, SUSEVIN 30 mg/ml inj; FORTAGESIC pentazocine 15 mg+paracetamol 500 mg tab.

Pentazocine is not a favoured analgesic now, but may be used for postoperative and moderately severe pain in burns, trauma, fracture, cancer, etc. Frequent side effects and potential for dysphoric/psychotomimetic effect limits its utility in chronic (cancer) pain.

3. Butorphanol It is a κ analgesic, similar to but stronger and more potent than pentazocine (butorphanol 2 mg = pentazocine 30 mg). Likewise, analgesia and respiratory depression have a lower ceiling than morphine. Sedation is more prominent, but nausea, cardiac stimulation and other side effects are similar to pentazocine. Subjective effects are less dysphoric. Psychotomimetic effects are occasional (it is a weaker σ agonist at higher doses). BP is not raised.

Postaddicts recognize butorphanol as a barbiturate rather than an opiate and mostly dislike it. However, it produces dependence, and withdrawal can be precipitated by high dose of naloxone, but the syndrome is mild. The abuse potential of butorphanol is low. The most outstanding feature is that butorphanol can neither substitute for, nor antagonize morphine. This shows its very weak interaction with μ receptors.

Butorphanol has been used in a dose of 1–4 mg i.m. or i.v. for postoperative and other short-lasting (e.g. renal colic) painful conditions, but should be avoided in patients with cardiac ischaemia. The t½ and duration of action is similar to morphine.

BUTRUM 1 mg/ml, 2 mg/ml inj.

4. Nalbuphine A structural analogue of naloxone, this is another strong κ agonist with weak μ receptor antagonistic property. Nalbuphine is a more potent analgesic than pentazocine, and produces few dysphoric or psychotominetic effects at recommended doses (10–20 mg). Much higher doses, however, do produce weird thoughts, hallucinations and dysphoria. Ceiling effect is exhibited; no further

analgesia or respiratory depression is produced above 30 mg i.m. dose. Unlike pentazocine it dose not cause sympathetic stimulation. There are no cardiovascular effects, and it is considered safe for use in M.I.

Nalbuphine is extensively metabolized with a plasma t½ of 2–3 hours. Dependence, withdrawal symptoms and abuse potential is low and similar to pentazocine. Drug seeking is minimal. Nalbuphine can precipitate morphine withdrawal in dependent subjects, reflecting its weak μ antagonistic property. It is indicated in postoperative and other moderately severe pain requiring a parenteral opioid. Cardiac ischaemia is no restriction to its use.

Dose: 10 mg i.m., s.c. or i.v. every 4–6 hours; increase dose to 20 mg, if needed.

NALFY, RUFFY 10 mg in 1 ml and 20 mg in 1 ml inj.

5. Buprenorphine It is a synthetic thebaine congener, highly lipid-soluble μ analgesic that is 25 times more potent than morphine but with lower intrinsic activity and ceiling effect. The onset of action is slower and duration longer. After a single dose, analgesia lasts for 6–8 hours; but with repeated dosing, duration of action increases to ~24 hours due to accumulation in tissues. Certain other effects last still longer.

Sedation, vomiting, miosis, subjective and cardiovascular effects are similar to morphine, but constipation is less marked. Postural hypotension is prominent. Respiratory depression (and analgesia) exhibit ceiling effect. Buprenorphine substitutes for morphine at low levels of morphine dependence, but precipitates withdrawal in highly morphine dependent subjects, reflecting its partial agonistic action at μ receptors. Antagonistic action on κ receptor has also been detected.

Lower degree of tolerance, dependence and addiction develops with buprenorphine. Its withdrawal syndrome resembles that of morphine, but is delayed for several days, is milder and longer lasting. 'Drug seeking' is present. Abuse liability is rated lower than morphine.

Naloxone (high dose) can prevent buprenorphine effect, but only partially reverses it when given afterwards. Naloxone does not precipitate buprenorphine withdrawal; probably because of more tight binding of buprenorphine to opioid receptors.

Buprenorphine has good efficacy by sublingual route, is highly plasma protein bound and remains in tissues for several days; terminal t½ is 40 hours. It is mostly excreted unchanged in bile and finds its way out of the body in faeces.

Dose: 0.3–0.6 mg i.m., s.c. or slow i.v., also sublingual 0.2–0.4 mg 6–8 hourly.

NORPHIN, TIDIGESIC 0.3 mg/ml inj. 1 and 2 ml amps. 0.2 mg sublingual tab; BUPRIGESIC, PENTOREL, BUPRINOR 0.3 mg/ml inj in 1, 2 ml amp.

Use: Buprenorphine is indicated for long-lasting painful conditions requiring an opioid analgesic, e.g. cancer pain. It has also been recommended for premedication, postoperative pain, in myocardial infarction and in the treatment of morphine dependence as an alternative to methadone.

Buprenorphine is not suitable for use during labour, because if respiratory depression occurs in the neonate, it cannot be effectively reversed by naloxone.

Meptazinol and *Dezocine* are other agonist-antagonist opioids introduced in some countries.

PURE OPIOID ANTAGONISTS

Three opioid antagonists are in use:

Naloxone
Naltrexone
Nalmefene

1. Naloxone It is N-alylnor-oxymorphone and a competitive antagonist on all types of opioid receptors. However, it blocks μ receptors at much lower doses than those needed to block κ or δ receptors. It is devoid of any kind of agonistic activity even at high doses (20 times μ blocking dose). No subjective or autonomic effects are produced in individuals who have not received an opioid. No addiction, dependence or abstinence syndrome has been observed.

Injected intravenously (0.4–0.8 mg) it promptly antagonizes all actions of morphine: analgesia

is gone, respiration is not only normalized but stimulated—probably due to sudden sensitization of respiratory centre to the retained CO_2, or it may be a manifestation of acute withdrawal; pupils dilate. However, sedation is less completely reversed.

At 4–10 mg dose it also antagonizes the agonistic actions of nalorphine, pentazocine, etc., but the dysphoric and psychotomimetic effects of some of them are incompletely suppressed. The naloxone insensitive component is believed to be mediated through σ receptors.

Actions of buprenorphine are prevented but not effectively reversed by naloxone, because it fails to displace buprenorphine that has already bound to the opioid receptors.

Naloxone 0.4 mg i.v. precipitates morphine withdrawal in dependent subjects: the syndrome lasts for 2–3 hours; 5 mg or more is required to precipitate nalorphine and pentazocine withdrawal.

Naloxone also blocks the actions of endogenous opioid peptides (*see* below). These peptides have been implicated in a variety of physiological functions; it is surprising that naloxone does not produce hyperalgesia or other effects in normal individuals. However, it has been found to render those individuals more susceptible to pain who normally have high tolerance. It blocks *placebo, acupuncture* and *stress-induced analgesia,* showing involvement of endogenous opioid peptides in these responses. Naloxone partly antagonizes respiratory depression produced by certain nonopioids, e.g. N_2O, diazepam as well.

Naloxone is inactive orally because of high first pass metabolism in liver. Injected i.v. it acts in 2–3 min. The primary pathway of metabolism is glucuronidation. Plasma t½ is 1 hour in adults and 3 hours in newborns. Duration of action is 1–3 hr.

Adverse effects of naloxone are uncommon; may include rise in BP and pulmonary edema.

NARCOTAN 0.4 mg in 1 ml (adult) and 0.04 mg in 2 ml (infant) amps; NALOX, NEX 0.4 mg inj.

Use Naloxone is the drug of choice for morphine poisoning (0.4–0.8 mg i.v. every 2–3 min: max 10 mg) and for reversing neonatal asphyxia due to opioid use during labour (10 μg/kg in the cord). It is also used to treat overdose with other opioids and agonist-antagonists (except buprenorphine). Repeated doses of naloxone are needed because of its short duration of action.

Other possible clinical applications of naloxone are:

- To reverse respiratory depression due to intraoperative use of opioids: 0.1–0.2 mg i.v. (this dose usually preserves analgesia in the postoperative period).
- It has also been tried as an adjunct to intraspinal opioid analgesia: reverses respiratory depression without abolishing pain relief.
- Diagnosis of opioid dependence—precipitates withdrawal in dependent subjects.
- It also partially reverses alcohol intoxication.
- Naloxone has been found to elevate BP in endotoxic or hypovolaemic shock, stroke and spinal injury. In these conditions injection of morphine worsens cardiovascular status. Opioid peptides are believed to be involved in the pathogenesis. However, the value of naloxone compared to conventional therapy is uncertain.

2. Naltrexone It is chemically related to naloxone and is another pure opioid antagonist, that is devoid of subjective and other agonistic effects, but very high doses have caused unpleasant feelings in some individuals. It is more potent than naloxone. Naltrexone differs from naloxone in being orally active and having a long duration of action (1–2 days) which makes it suitable for 'opioid blockade' therapy of postaddicts: 50 mg/day is given orally so that if the subject takes his/her usual shot of the opioid, no subjective effects are produced and the craving subsides. Alcohol craving is also reduced by naltrexone, and it is approved for prevention of relapse of heavy drinking (*see* p. 421). Nausea is a common side effect; another is headache. High doses can cause hepatotoxicity.

NALTIMA 50 mg tab.

3. Nalmefene This pure opioid antagonist lacks hepatotoxicity of naltrexone, has higher oral bioavailability and is longer acting.

Methyl naltrexone This derivative of naltrexone does not penetrate the blood-brain barrier, but effectively blocks peripheral action of μ opioids. It is being used to reverse constipation

in cancer patients receiving chronic opioid analgesia and in those taking methadone maintenance therapy.

Alvimopan is another peripheral μ receptor antagonist which has limited absorption from the gut and penetration into the brain. It is approved for the treatment of postoperative ileus following gut resection surgery.

ENDOGENOUS OPIOID PEPTIDES

In the mid 1970s, with herculean efforts, a number of peptides having morphine-like actions were isolated from mammalian brain, pituitary, spinal cord and g.i.t. These peptides are active in very small amounts, their actions are blocked by naloxone, and they bind with high affinity to the opioid receptors. There are 3 major families of opioid peptides. Each is derived from a specific large precursor polypeptide.

1. Endorphins β-endorphin (β-END), having 31 amino acids, is the most important of the endorphins. It is derived from Pro-opiomelanocortin (POMC) which also gives rise to γ-MSH, ACTH and two lipotropins. β-END is primarily μ agonist, but also has δ action.

2. Enkephalins Methionine-enkephalin (met-ENK) and leucine-enkephalin (leu-ENK) are the most important. Both are pentapeptides. The large precursor peptide *proenkephalin* has 4 met-ENK and 1 leu-ENK residues. The two ENKs have a slightly different spectrum of activity; while met-ENK has equal affinity for μ and δ sites, leu-ENK prefers δ receptors.

3. Dynorphins Dynorphin A and B (DYN-A, DYN-B) are 8–17 amino acid peptides derived from *prodynorphin* which contains 3 leu-ENK residues also. DYNs are more potent on κ receptors, but also activate μ and δ receptors.

Distribution of the 3 families of peptides is summarized below:

1. *POMC* (limited distribution)
   - Arcuate nucleus which sends projections to limbic areas and medulla.
   - Anterior pituitary (modulates hormone release).
   - Pancreatic islets (modulates insulin, glucagon release).
2. *Proenkephalin* (wide distribution)
   - Pain areas in spinal cord, trigeminal nucleus, periaqueductal grey matter.
   - Affective areas in limbic system, locus coeruleus and cortex.
   - Medulla (autonomic functions).
   - Median eminence of hypothalamus (neuro-endocrine control).
   - Adrenal medulla, gastric and intestinal glands.
3. *Prodynorphin*
   - Wide distribution roughly parallel to proenkephalin, but in distinct neurones of the same area.

Receptor selectivity of the 3 major opioid peptide families may be graded as:

Opioid peptide	*Relative receptor selectivity*
β-Endorphin	$\mu > \delta >> \kappa$
Enkephalin (Met/Leu)	$\delta \geq \mu >> \kappa$
Dynorphin A,B	$\kappa >> \mu = \delta$

The opioid peptides constitute an endogenous opioid system which normally modulates pain perception, mood, hedonic (pertaining to pleasure) and motor behaviour, emesis, pituitary hormone release and g.i.t. motility, etc.

β-END injected directly into the brain is 20–40 times more potent analgesic than morphine. Its primary localization in hypothalamus and pituitary and its long t½ prompts that it has a *neurohormone* function which modulates the release of other hormones. β-END decreases LH, FSH release and increases GH, prolactin release. Naloxone has opposite effects on the levels of these hormones—suggesting that the system is constitutively active.

The wide distribution of ENKs and DYNs along with their short t½ suggests that they function as *neuromodulator* or *neurotransmitter*. They appear to regulate pain responsiveness at spinal and supraspinal levels. Naloxone blocks placebo, acupuncture and stress-induced analgesia, suggesting the involvement of opioid peptides in these responses. Opioid peptides also appear to participate in regulation of affective behaviour and autonomic function.

A novel opioid peptide Nociceptin/orphanin FQ (N/OFQ) has been isolated from mammalian brain. It is localized in cortex, hippocampus, spinal cord and certain sensory

sites. N/OFQ is believed to play a role in stress response, reward and reinforcing actions, learning and memory. The N/OFQ receptor, is now called *Nociceptin opioid peptide (NOP)* receptor. At certain sites, N/OFQ can act as an 'antiopioid' through the NOP receptor. In the pain control mechanisms, N/OFQ appears to play both opioid-like as well as antagonistic roles, depending on the site and the basal state of pain.

Morphine and other opioids act as exogenous agonists on some of the receptors for these peptides. This has given an explanation for the existence of specific receptors in the body for exogenous substances like morphine. Morphine itself has now been detected in mammalian brain.

☞ PROBLEM DIRECTED STUDY

34.1 A boy aged 14 years is brought to the hospital emergency with crush injury of both lower legs. An eye witness who brought the boy told that a bus had run over his legs about 20 min. ago. The legs were crushed but he had not bled much. He also told that initially the boy was shrieking in pain, but had fainted on way to the hospital. Preliminary examination reveals that the patient is in a semiconscious state, looks pale, the pulse is fast, low volume and collapsing. Both legs have sustained multiple fractures, the skin and soft tissues have lacerated from which blood is oozing, but there is no active bleeding. There is no apparent head injury.

(a) Should any medicine be administered immediately, before even completing a thorough physical examination? If so, which drug, by what route, and why?

(see Appendix-1 for solution)

Chapter 35 CNS Stimulants and Cognition Enhancers

CNS STIMULANTS

These are drugs whose primary action is to stimulate the CNS globally or to improve specific brain functions.

I. CONVULSANTS

1. Strychnine It is an alkaloid from the seeds of *Strychnos nux-vomica,* that is a potent convulsant. The convulsions are reflex, tonic-clonic and symmetrical. Strychnine acts by blocking *post-synaptic* inhibition produced by the inhibitory transmitter glycine. One of the sites that has been clearly demonstrated is the Renshaw cell-motoneurone junction in the spinal cord through which inhibition of antagonistic muscles is achieved.

Accidental strychnine poisoning may occur, especially in children. Treatment of poisoning is similar to that of status epilepticus (*see* Ch. 30).

2. Picrotoxin It is obtained from 'fish berries' of East Indies *Anamirta cocculus.* Picrotoxin is a potent convulsant—convulsions are clonic, spontaneous and asymmetrical. The convulsions are accompanied by vomiting, respiratory and vasomotor stimulation.

Picrotoxin acts by blocking *presynaptic* inhibition mediated through GABA. However, it is not a competitive antagonist; does not act on GABA receptor itself, but on an allosteric site and prevents Cl^- channel opening (*see* p. 429). Diazepam, which facilitates GABAergic transmission, is the drug of choice to treat picrotoxin poisoning.

3. Bicuculline This synthetic convulsant has picrotoxin-like actions. It is a competitive $GABA_A$ receptor (intrinsic Cl^- channel receptor) antagonist. It is only a research tool.

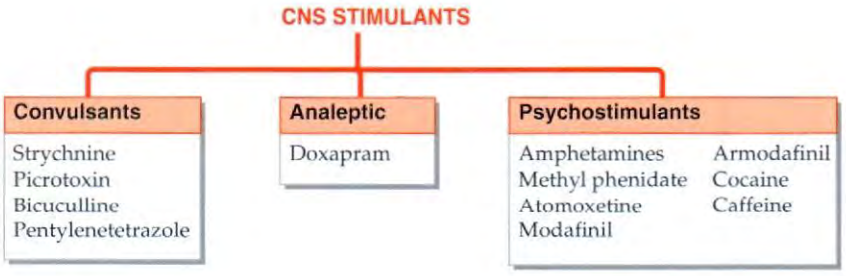
4. Pentylenetetrazol (PTZ) It is a powerful CNS stimulant, believed to be acting by direct depolarization of central neurones. However, it has also been shown to interfere with GABAergic inhibition—may be acting in a manner analogous to picrotoxin.

Low doses cause excitation, larger doses produce convulsions which are similar in pattern to those caused by picrotoxin. Antagonism of PTZ induced convulsions is an established method of testing anticonvulsant drugs in laboratory animals (*see* Ch. 30).

II. ANALEPTICS (Respiratory stimulants)

These are drugs which stimulate respiration and were believed to have resuscitative value in coma or fainting. They do stimulate respiration in subconvulsive doses, but margin of safety is narrow.

Doxapram and some other analeptics injected i.v. were used in the past as an expedient measure in fainting, barbiturate poisoning, suffocation, drowning, ventilatory failure in COPD, but are outmoded now.



III. PSYCHOSTIMULANTS

These drugs have predominant cortical action; their psychic effects are more prominent than those on medullary vital centres.

1. Amphetamines Amphetamine (racemic), dexamphetamine (d-isomer) and methamphetamine are synthetic sympathomimetic compounds with predominant central actions. The latter two have higher central: peripheral activity ratio than amphetamine. All three stimulate mental rather than motor activity; convulsive doses are much higher. Their pharmacology and uses are described in Ch. 9.

2. Methylphenidate It is chemically and pharmacologically similar to amphetamine. Both act primarily by releasing NA and DA in the brain. Both produce increase in mental activity at doses which have little action on other central and peripheral functions. Methylphenidate is considered superior to amphetamine for attention deficit hyperkinetic disorder (ADHD) in children (*see* p. 151), because it causes lesser tachycardia and growth retardation. Behaviour and learning ability are improved in 3 out of 4 treated children. Methylphenidate can also be used for concentration and attention defect in adults, and for narcolepsy, but should not be employed to treat depression, dementia, obesity or to keep awake.

Methylphenidate is well absorbed orally, metabolized and excreted in urine, plasma t½ is 4–6 hours, but central effects last much longer. Twice daily dosing (morning and afternoon) is enough.

Side effects are anorexia, insomnia, growth retardation, abdominal discomfort and bowel upset.

Dose: Adults 5–10 mg BD; children 0.25 mg/kg/day initially, increased up to 1 mg/kg/day if needed.

RETALIN 5, 10, 20, 30 mg tab.

3. Atomoxetine This is a selective NA reuptake inhibitor, unrelated to amphetamine as well as to imipramine, which does not enhance DA release in the brain, and is neither a CNS stimulant nor an antidepressant. However, it has been found to improve attention span and behaviour in ADHD. It is indicated in children >6 years and in adults with concentration and attention problems.

Atomoxetine is absorbed orally, hydroxylated by CYP2D6 and excreted in urine, mainly as glucuronide. While majority of individuals are extensive metabolizers (EM), few are poor metabolizers (PM) due to polymorphism of CYP2D6. Inhibitors of CYP2D6 like fluoxetine, paroxetine, quinidine increase concentration and toxicity of atomoxetine. It should not be given with MAO inhibitors and is contraindicated in glaucoma.

Dose: 0.5 mg/kg/day in the morning, may be increased upto 1.2 mg/kg/day and split into morning and afternoon doses. Adults 40 mg OD, max 100 mg/day.

ATTENTROL 10, 18, 25, 40 mg caps, AXEPTA 18, 25 mg caps.

Atomoxetine is relatively well tolerated. Common side effects are dyspepsia, anorexia and other abdominal symptoms. Others are sleep disturbances, mood swings, emotional lability, rarely suicidal thoughts and hepatotoxicity. Growth retardation is possible in children.

4. Modafinil This newer psychostimulant is popular with night-shift (call centre) workers and other professionals who want to improve alertness and keep awake. It is claimed to increase attention span and improve accuracy that has been compromized by fatigue and sleepiness. Although, modafinil has been shown to inhibit NA and DA uptake as well as alter junctional concentration of glutamate and GABA, its actual mechanism of action is not known. The approved indications are day-time sleepiness due to narcolepsy, sleep-apnoea syndrome and shift-work disorder (SWD). It has also been found to reduce euphoria produced by cocaine and to suppress cocaine withdrawal symptoms. Modafinil is being evaluated as a drug to prevent relapse of cocaine dependence.

The most common side effects are insomnia and headache. Others are nausea, dyspepsia, dizziness, confusion, amnesia, personality disorders, tremors and hypertension. Dependence is a possibility on long-term use.

Modafinil is absorbed within 2–4 hours of oral administration, and is eliminated with a t½ of 15 hours.

Dose: 100–200 mg morning and afternoon for day-time sleepiness due to narcolepsy or sleep-apnoea syndrome; or 200 mg 1 hour before starting night-shift work.
MODALERT, PROVAKE 100, 200 mg tabs.

Armodafinil A congener of modafinil which has been recently approved for improving wakefulness in patients with obstructive sleep apnoea (OSA), SWD and narcolepsy.

5. Cocaine (*see* Ch. 26)

6. Caffeine Out of the three naturally occurring methylxanthines, only caffeine is used as a CNS stimulant. Its pharmacological actions are described in Ch. 16 along with those of theophylline.

Pharmacokinetics Caffeine has poor water solubility; is rapidly but inconsistently absorbed after oral administration. It is < 50% bound to plasma proteins, distributed all over the body, and nearly completely metabolized in liver by demethylation and oxidation. Metabolites are excreted in urine; plasma t½ is 3–6 hours in adults.

Adverse effects Toxic effects of caffeine are extensions of its pharmacological actions. Caffeine poisoning is rare, and it is less toxic than theophylline.
Gastric irritation, nausea and vomiting may occur as side effects.
Excitatory and motor effects such as nervousness, insomnia, agitation, muscular twitching, rigidity, rise in body temperature, delirium and convulsions are produced at toxic doses.
Tachycardia, occasionally extrasystoles occur at high doses.
Caffeine is to be avoided in peptic ulcer patients.

Uses

1. In analgesic mixture: caffeine benefits headache probably by allaying fatigue and boredom. It has no analgesic action of its own.
2. Migraine: Caffeine is used in combination with ergotamine for treatment of migraine attack. It appears to benefit by augmenting constriction of cranial vessels and by enhancing absorption of ergotamine from the g.i.t.
3. Apnoea in premature infants: as alternative to theophylline (*see* Ch. 16).

Caffeine is available only in combined formulations with ergotamine or analgesics in tablets.
CAFERGOT: Caffeine 100 mg + ergotamine 1 mg tab.
MICROPYRIN: Caffeine 20 mg + aspirin 350 mg tab.
DOLOPAR: Paracetamol 500 mg + caffeine 25 mg tab.

Tonics containing caffeine are banned in India.

COGNITION ENHANCERS (Cerebroactive drugs)

These are a heterogenous group of drugs developed for use in dementia and other cerebral disorders. They do elicit pharmacological effects, but widely different mechanisms of action are claimed. Therapeutic benefits are limited, and at the best, short-lasting.

Dementia Refers to acquired global impairment of intellect, memory, ability to comprehend and recognize people, loss of orientation and other cognitive functions, in the absence of gross clouding of consciousness or motor dysfunction. Memory, capacity to solve problems of day to day living, performance of learned motor skills, social skills and control of emotions are primarily affected.

Alzheimer's disease (AD) A progressive neurodegenerative disorder which affects older individuals and is the most common cause of dementia. It may progress to a totally vegitative state. Atrophy of cortical and subcortical areas is associated with deposition of *β-amyloid protein* in the form of extracellular senile (amyloid) plaques and formation of intracellular neurofibrillary tangles made up of 'tau' protein. These abnormal proteins accumulate mostly due to reduced clearance, but in some cases, due to overproduction, and cause neuronal damage followed by neuron loss. There is marked cholinergic deficiency in the brain, though other neurotransmitter systems, especially glutamate and neuropeptide, are also affected.

The indications of cognition enhancers include:
1. Alzheimer's disease (AD) and multi-infarct dementia (MID).
2. Mild cognitive impairment (MCI) or 'common symptoms' of the elderly; dizziness and episodic memory lapses.
3. Mental retardation in children, learning defects, attention deficit disorder.
4. Transient ischaemic attacks (TIAs), cerebrovascular accidents, stroke.
5. Organic psychosyndromes and sequelae of head injury, ECT, brain surgery.

Apart from some cholinergic activators and glutamate antagonist introduced over the past

2–3 decades, the above therapeutic field is barren and commercially highly profitable. A variety of drugs have been briskly promoted by manufacturers and wishfully prescribed by physicians. The mechanism by which they are believed to act are:

- Increasing global/regional cerebral blood flow (CBF)
- Direct support of neuronal metabolism.
- Enhancement of neurotransmission.
- Improvement of descrete cerebral functions, e.g. memory.

All cerebroactive drugs are tested for their vasodilator activity. The basic assumption has been that selective improvement in cerebral circulation is possible, real and therapeutically useful. However, precise measurements have shown that in many cases such claims are merely expectations. A global vasodilator effect may even be harmful in stroke by worsening cerebral edema and inducing 'steal' phenomenon, i.e. diversion of blood flow to non-ischaemic areas to the detriment of ischaemic area. No doubt, cerebral blood flow is reduced in AD, but this is probably a consequence of loss of neurones and not its cause.

1. Cholinergic activators Since brain ACh and choline acetyl transferase levels are markedly reduced and cholinergic neurotransmission is the major sufferer in AD, various approaches to augment brain ACh have been tried. Precursor loading with choline or lecithin have failed because there is no shortage of these substrates in the brain. Cholinergic agonists (arecoline, bethanechol, oxotremorine) and conventional anticholinesterases (anti-ChEs) like physostigmine produce symptom improvement, but at the cost of marked peripheral side effects. Over the past two decades 4 cerebroselective antiChEs have been introduced and 3 are widely used in AD.

Tacrine It was the first centrally acting anti-ChE to be introduced for AD, but has gone out of use due to hepatotoxicity.

Rivastigmine This carbamate derivative of physostigmine inhibits both AChE and BuChE, but is more selective for the G1 isoform of AChE that predominates in certain areas of the brain. Rivastigmine is highly lipid-soluble—enters brain easily. Greater augmentation of cholinergic transmission in the brain is obtained with mild peripheral effect. The carbamyl residue introduced by rivastigmine into AChE molecule dissociates slowly resulting in inhibition of cerebral AChE for upto 10 hours despite the 2 hr plasma t½ of the drug.

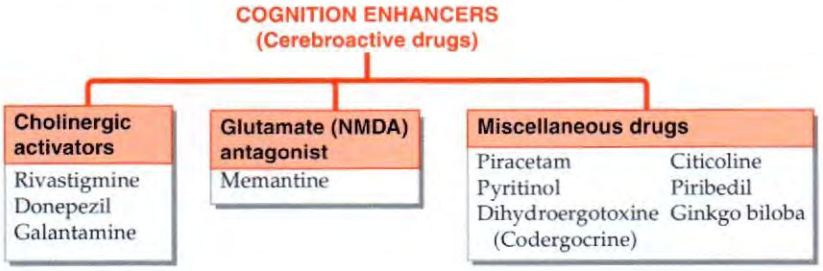
In clinical trials an average of 3.8 point improvement in Alzheimer's Disease Assessment Scale (ADAS-cog) has been obtained compared to placebo. Other symptoms like apathy, delusions, hallucinations and agitation also improve, but to a lesser extent. Disease progression is not affected. Peripheral cholinergic side effects are mild. It has not produced liver damage. Rivastigmine is indicated in mild-to-moderate cases of AD, but not in advanced disease.

Dose: Initially 1.5 mg BD, increase every 2 weeks by 1.5 mg/day upto 6 mg/BD.

EXELON, RIVAMER 1.5, 3, 4.5, 6.0 mg caps.

Transdermal patches delivering 4.6 mg, 9.5 mg or 13.3 mg rivastigmine per 24 hours have also been produced.

Donepezil This cerebroselective and reversible anti-AChE produces measurable improvement in several cognitive as well as non-cognitive (activities of daily living) scores in AD, which is maintained upto 2 years. The benefit is



ascribed to elevation of ACh level in the cortex, especially in the surviving neurones that project from basal forebrain to cerebral cortex and hippocampus. Therapeutic doses produce only weak peripheral AChE inhibition: cholinergic side effects are mild. Because of long t½ (~70 hr), donepezil is administered once daily at bed time; a distinct advantage over rivastigmine and galantamine which need twice daily dosing. Moreover, it can be used even in relatively severe case of AD. Donepezil is generally well tolerated and is not hepatotoxic.
Dose: 5 mg OD HS (max 10 mg OD);
DONECEPT, DOPEZIL, DORENT 5, 10 mg tabs.

Galantamine It is a natural alkaloid which selectively inhibits cerebral AChE and has some direct agonistic action on nicotinic receptors as well. Galantamine has produced cognitive and behavioural benefits in AD which are comparable to rivastigmine and donepezil. It is well tolerated, but needs twice daily dosing.
Dose: 4 mg BD (max 12 mg BD)
GALAMER 4, 8, 12 mg tabs.

There is now firm evidence that rivastigmine, donepezil and galantamine afford similar, but modest symptomatic benefit in at least 50% patients of mild to moderate AD. Cognitive decline is slowed or halted for a short time, but not prevented. These anti-ChEs should be stopped in patients who do not benefit by 3 month therapy. Their side effects, mostly diarrhoea, anorexia, nausea, muscle pain and weird dreams, fatigue, hallucinations, insomnia are also comparable among the three. There is now some, but not conclusive evidence to support their use in MCI and non-Alzheimer dementia as well.

2. Memantine This newer NMDA receptor antagonist, related to amantadine (that is also a NMDA antagonist), has been found to slow the functional decline in moderate-to-severe AD, but benefit in milder disease is unclear. Symptom relief is similar to or lesser than anti-AChEs. It appears to block excitotoxicity of the transmitter glutamate in a noncompetitive and use-dependent manner. Beneficial effects have also been noted in parkinsonism.

Memantine is better tolerated than anti-AChEs used in AD. Side effects are constipation, tiredness, headache, dizziness, and drowsiness. It is indicated in moderate-to-severe AD, either to replace anti-AChEs or to supplement them. Memantine can be used for other types of dementia as well.
Dose: Initially 5 mg OD, increase gradually upto 10 mg BD; stop if no clinical benefit in 6 months.
ADMENTA, MENTADEM 5, 10 mg tabs, ALMANTIN 5 mg tab.

3. Piracetam This cyclic GABA derivative has no GABA-like activity and has been called 'nootropic' meaning a drug that selectively improves efficiency of higher telencephalic integrative activities.

Piracetam is not a vasodilator, does not affect total/regional CBF, but may reduce blood viscosity. In India and some other countries it has long been promoted for cognitive impairment and dementia in the elderly as well as for mental retardation in children. However, a Cochrane Database review (2004) has concluded that published data does not support such use. In the UK, it is approved for adjunctive treatment of cortical myoclonus, but it is not approved in the USA.

Side effects are minor: gastric discomfort, nervousness, excitement, insomnia, dizziness and skin rash.
Dose: 0.8–1.6 g TDS oral; children 20 mg/kg BD–TDS; 1–3 g i.m. 6 hourly in stroke/head injury; 7.2 g/day in divided doses for myoclonus.
NORMABRAIN, NEUROCETAM, NOOTROPIL 0.4 g, 0.8 g, 1.2 g. caps, 500 mg/5 ml syr., 300 mg/ml inj.

4. Pyritinol (Pyrithioxine) Pyritinol consists of two pyridoxine molecules joined through a disulfide bridge, but has no vit B_6 activity. It is claimed to activate cerebral metabolism by selectively increasing glucose transport across blood-brain barrier and improving regional blood flow in ischaemic brain areas. It has been promoted for:

- Sequelae of cerebrovascular accidents, head injury, prolonged anaesthesia.
- Infants and children with developmental disorders of CNS, delayed milestones.
- Concentration and memory defects, senility, organic brain syndromes.

However, therapeutic benefit, if any, is uncertain.

ENCEPHABOL 100, 200 mg tab. 100 mg/5 ml suspension; 200 mg dry powder with 2 ml solvent for i.v. infusion.
Dose: 100–200 mg TDS, children 50–100 mg TDS orally; 200–400 mg every 4–6 hours (max. 1 g/day) i.v.
Pyritinol has been withdrawn in some countries due to risk of reactions.

5. Dihydroergotoxine (Codergocrine): It is a semi-synthetic ergot alkaloid having α adrenergic blocking property; claimed to increase cerebral blood flow selectively. It is believed to act by protecting altered brain metabolism. In a dose of 1.0–1.5 mg TDS oral/sublingual or 0.3 mg i.m. OD, it has been recommended for MCI and dementia, but therapeutic valve is not established.

HYDERGINE 1 mg tab, 0.3 mg/ml inj. CERELOID 1 mg tab.

Side effects: flushing, headache, nasal congestion, postural hypotension, g.i. disturbances and rashes.

6. Piribedil: It is a dopaminergic agonist claimed to improve memory, concentration, vigilance and to suppress giddiness, tinnitus in the elderly caused by cerebral circulatory insufficiency, but benefit is unsubstantiated. Minor symptomatic relief in parkinsonism has also been reported. Side effects are mild g.i. complaints.

Dose: 50 mg OD, BD; TRIVASTAL LA 50 mg tab.

7. Citicoline It is a compound derived from choline and cytidine, that is involved in biosynthesis of lecithin. Citicoline is believed to improve cerebral function by increasing blood flow to the brain and enhancing cerebral metabolism. Some studies have demonstrated short-term improvement in memory and behaviour in cerebrovascular disorders, but there is little convincing evidence. In the absence of effective medicines and under promotional pressure, citicoline is being prescribed for impaired brain function due to ischaemic stroke, parkinsonism, head injury, etc.

Dose: 0.5–1 g/day i.m. or i.v. inj, 200–600 mg/day oral in divided doses.

CITILIN, CITINOVA 500 mg tab, 500 mg/2 ml inj, STROLIN 500 mg tab.

8. Ginkgo biloba The dried extract of this Chinese plant contains a mixture of ginkgoflavon glycosides (e.g. ginkgolide B) which have PAF antagonistic action. Since PAF has been implicated in cerebral thrombosis and infarcts, it is professed that *G. biloba* will prevent cerebral impairment in cerebrovascular insufficiency. Ginkgo biloba has been promoted for a variety of cognitive and behavioural disorders in the elderly, but a Cochrane metaanalysis (2007) concluded that *G. biloba* produced minor overall improvement in cognitive performance. However, most trials were small and results were inconsistent.

Side effects are mild upper g.i.t. symptoms, and increased risk of bleeding.

Dose: 40–80 mg TDS for a minimum period of 4 weeks; GINKOCER, BILOVAS, GINKOBA 40 mg tab.

SECTION 7

☞ PROBLEM DIRECTED STUDY

35.1 A 75-year-old man was brought with a history of progressive functional decline, so much so that he now needs to be looked-after all the time. He misplaces his daily need articles, forgets what he said few minutes ago, is unable to perform simple calculations, mixes up what happened today and what happened yesterday, has poor control of emotions, but vision, hearing and other sensations are well preserved, and there is no gross ataxia. He was diagnosed to be having moderately advanced Alzheimer's disease and was prescribed Tab Donepezil 5 mg at bed time daily. After one week, his son reported that while his mental and functional state is unchanged, he has developed pain in abdomen, muscle ache, loud eructations, loose motion and is refusing to take the medicine.

(a) What could be the reason for no improvement in the mental and functional state of the patient? Are the new symptoms due to the medication? Should the drug be stopped, changed or another one added at this stage? What alternative drug could be used?

(see Appendix-1 for solution)

CARDIOVASCULAR DRUGS

Cardiac Electrophysiological Considerations

Drugs having their major action on heart or blood vessels, or those used primarily for cardiovascular disorders are designated cardiovascular drugs. They can act directly on the cardiovascular structures or through autonomic or central nervous system, kidney, autacoids or hormones which regulate cardiovascular function.

CARDIAC ELECTROPHYSIOLOGY

The properties which are especially important for understanding drug action on heart are:

1. Impulse generation Electrophysiologically, two types of myocardial fibres can be distinguished (Fig. VIII.1).

(a) *Nonautomatic fibres* These are the ordinary working myocardial fibres. They cannot generate an impulse of their own. During diastole, the resting membrane potential remains stable (approximately 90 mv negative inside). When stimulated, they depolarize very rapidly (fast 0 phase) with considerable overshoot (+ 30 mv) → rapid return to near isoelectric level (phase-1) → maintenance of membrane potential at this level for a considerable period (phase-2, plateau phase) during which Ca^{2+} ions flow in and bring about contraction → relatively rapid repolarization (phase-3) during which the Na^+ and Ca^{2+} channels remain closed and the repolarizing K^+ current (I_K) develops slowly. The membrane Na^+K^+ pump gets activated and tends to restore ionic distribution to the resting pattern. Resting membrane potential, once attained, does not decay (stable phase-4).

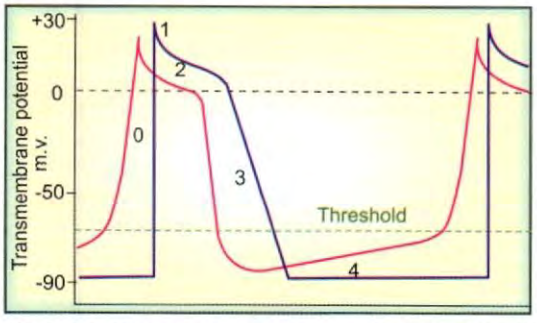


Fig. VIII.1: Transmembrane potential of automatic (red) and nonautomatic (purple) myocardial fibres recorded through intracellular electrodes

(b) *Automatic fibres* These are present in the sinoatrial (SA) and atrioventricular (A-V) nodes, and in the His-Purkinje system, i.e. especialized conducting tissue. In addition, patches of automatic tissue are present in the interatrial septum, A-V ring and around openings of the great veins. The most characteristic feature of these fibres is *phase*-4 or *slow diastolic depolarization*, i.e. after repolarizing to the maximum value, the membrane potential decays spontaneously. When it reaches a critical threshold value—sudden depolarization occurs automatically. Thus, they are capable of generating their own impulse. The rate of impulse generation by a particular fibre depends on the value of maximal diastolic potential, the slope of phase-4 depolarization and the value of threshold potential.

Normally, the SA node has the steepest phase-4 depolarization, undergoes self-excitation

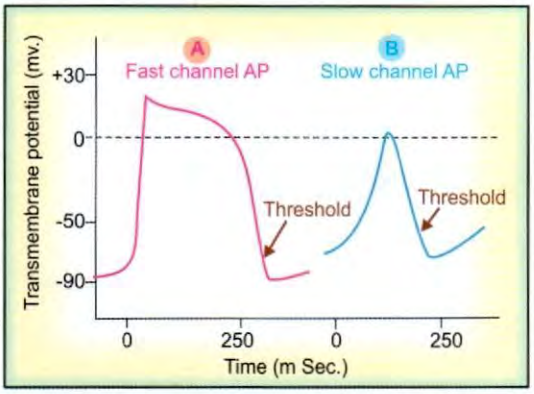


Fig. VIII.2: (A) Fast channel action potential (AP) in a Purkinje fibre, (B) Slow channel action potential in a SA node fibre

and propagates the impulse to rest of the heart. In other words, it acts as the *pacemaker*. Other automatic fibres which are also undergoing phase-4 depolarization, but at a slower rate, receive the propagated impulse before reaching threshold value and remain as *latent pacemakers*.

Two types of action potential (AP) are possible. These are depicted in Fig. VIII.2. Their characteristics are given in Table VIII.1.

The slow channel AP is characterised by:

(a) Initiation at a higher threshold (less negative level).
(b) Slower depolarization during 0 phase.
(c) Less overshoot, low amplitude.
(d) Very slow propagation, decremental conduction and a low safety factor for conduction.
(e) Can arise and propagate in fibres too depolarized to support fast channel responses.

Slow channel AP in SA node, A-V node, etc. has a shorter duration and phases 1–3 are not clearly demarkated. Slow channel AP can occur in Purkinje fibres (PF) also, but this has a much longer duration with a prominent plateau phase.

2. Conduction The rate of conduction through a fibre is a function of its *membrane responsiveness*, which is defined by rate of rise of AP (dv/dt) as a function of membrane potential at which activation occurs (Fig. VIII.3); a more completely polarized membrane depolarizes faster because more Na^+ channels have recovered (voltage- dependent reactivation). This type of relationship is seen in atrial, ventricular and Purkinje fibres (fast channel fibres which depolarize by Na^+ current), but not in SA and A-V nodal cells which remain refractory for some time even after attainment of maximal resting potential (Ca^{2+} channel reactivation is time-dependent).

The Na^+ channels get progressively inactivated as the resting membrane potential (RMP) drops over the –80 to –60 mV range. Consequently, less negative the RMP at which activation occurs, fewer are the Na^+ channels available for activation—slope of '0' phase depolarization, AP amplitude and conduction velocity are reduced.

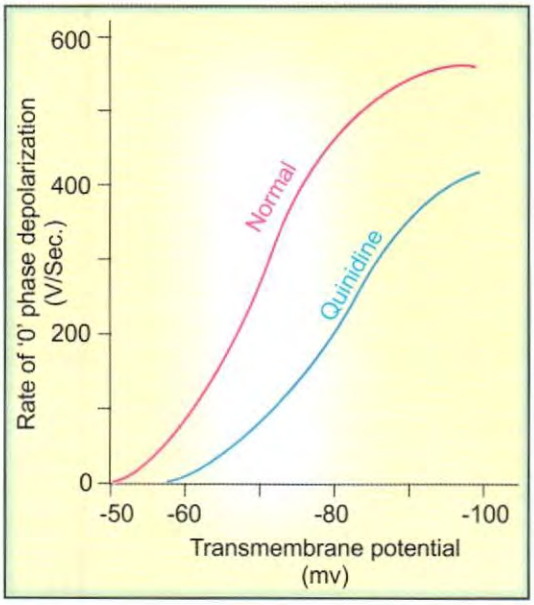
A drug which reduces the slope of 0 phase (at any given resting membrane potential) will shift the membrane responsiveness curve to the right and impede conduction. The reverse occurs with a drug that shifts the curve to the left. Membrane responsiveness curve can also be altered by disease.

Small cells at the upper margin of A-V node have very low conduction velocity (20 mm/sec).

Table VIII.1: Characteristics of fast channel and slow channel action potentials

	Fast channel AP	*Slow channel AP*
1. Sites of occurrence	Atria, ventricles, Purkinje fibres	SA and A-V nodes, round A-V ring, coronary sinus opening
2. Predominant ion moving in 0 phase	Na^+	Ca^{2+}
3. Activation-inactivation kinetics	Fast	Slow
4. Channel reactivation	Voltage-dependent	Time-dependent
5. Activation potential (threshold voltage)	–60 to –70 mv	–45 to –55 mv
6. Conduction velocity	0.5–5 m/sec	0.01–0.1 m/sec
7. ERP–APD* relationship	ERP < APD	ERP > APD
8. Selective channel blocker	Tetrodotoxin, Local anaesthetics	Verapamil, Diltiazem, Mn^{2+}

*ERP—Effective refractory period; APD—Action potential duration.



VIII.3: Membrane responsiveness curve of a myocardial fibre showing the relationship between membrane polarization and dv/dt of 0 phase. Note the depressant action of quinidine

Normally Purkinje fibres (PFs) have the highest conduction velocity (4000 mm/sec) except near their junction with the ventricular fibres 'gate region', or if they change over from fast channel to slow channel response.

3. Excitability This property of a fibre is defined by the strength of stimulus required to elicit a response or to produce an AP. Hyperpolarization decreases excitability while small reductions in resting membrane potential increase excitability by respectively increasing and decreasing the gap between it and the threshold potential. Thus, in fast channel fibres excitability is generally super-normal during the end of phase-3. However, when the resting membrane potential is reduced to a value below –55 mV, the fibre becomes inexcitable, since all Na^+ channels are inactivated.

4. Refractory period Pharmacologically, the effective refractory period (ERP) which is the minimum interval between two propagating APs, is the most important. It is closely related to the AP duration (APD). An AP can be evoked in fast channel fibres even before complete repolarization, because Na^+ channels recover in a voltage-dependent manner above the threshold potential. As such ERP/APD is <1. Another implication of voltage dependent recovery of Na^+ channel is that partially depolarized fibres recover more slowly, and ERP is prolonged. By contrast, the Ca^{2+} channels recover in a time-dependent manner progressively after the fibre has fully repolarized. Thus, in slow channel fibres ERP/APD is > 1. Most antiarrhythmic drugs increase ERP/APD ratio.

Autonomic influences on cardiac electrophysiology and contractility

It would be profitable to recapitulate the influence of sympathetic and parasympathetic stimulation on variables of cardiac function, because many cardiovascular drugs have indirect/secondary autonomic effects (Table VIII.2).

Table VIII.2: Autonomic influences on cardiac electrophysiology and contractility

Parameter	*Effect of stimulation*	
	Parasympathetic (ACh)	*Sympathetic (Adr)*
1. Automaticity		
SA node	Bradycardia	Tachycardia
Ectopic ventricular	—	Enhanced
2. Refractory period		
Atria	Shortened (inhomogeneous)	Shortened
Conducting tissue	Prolonged	Shortened
3. Conductivity	Depressed	Enhanced
4. Contractility	Decreased (little effect on ventricle)	Increased

Chapter 36 Drugs Affecting Renin-Angiotensin System

RENIN-ANGIOTENSIN SYSTEM

Angiotensin-II (Ang II) is an octapeptide generated in the plasma from a precursor plasma α_2 globulin called *angiotensinogen*, and is involved in electrolyte, blood volume and pressure homeostasis. Pressor action of kidney extracts was known since the turn of the 19th century. The active material was termed '*Renin*'. In the 1940s renin was shown to be a protease enzyme which acted indirectly by producing a pressor principle from plasma protein. Subsequently, it became clear that the product of renin action was an inactive decapeptide *angiotensin-I* (Ang I) which was converted to the active octapeptide Ang II by an *angiotensin converting enzyme (ACE)*. The renin-angiotensin system (RAS) has attracted considerable attention over the past 30 years, particularly after the development of ACE inhibitor *captopril*.

Circulating renin-angiotensin system The generation and metabolism of Ang II in circulation is depicted in Fig. 36.1. Normally, the amount of renin in plasma secreted by the juxtaglomerular cells in the kidney acts as the limiting factor for Ang II generation. The plasma t½ of renin is 15 min. The biological potency of Ang I is only 1/100 that of Ang II, but it is rapidly converted into the latter by ACE which is a *dipeptidyl carboxypeptidase*, an ectoenzyme located primarily on the luminal surface of vascular endothelial cells (especially in lungs). Circulating Ang II also has a very short t½ (1 min). The first degradation product produced by the action of an aminopeptidase is the heptapeptide termed *Angiotensin-III* (Ang III). It is 2–10 times less potent than Ang II, except in stimulating aldosterone secretion, in which it is equipotent. Ang III is again attacked by another aminopeptidase, and the resulting hexapeptide (3-8) is called Ang IV which has very different central (and some peripheral) actions elicited through a specific AT_4 receptor. Both Ang III and Ang IV are broken into inactive fragments by nonspecific peptidases termed *angiotensinases*.

Tissue (local) renin-angiotensin systems

Extrinsic local RAS Apart from Ang II generated in circulation as described above, blood vessels capture circulating angiotensinogen and renin to produce Ang II at the surface of their intima. This Ang II diffuses to act locally on the angiotensin receptors producing localized responses.

Intrinsic local RAS Many tissues, especially heart, blood vessels, brain, kidneys, adrenals possess the capacity to synthesize all components of RAS within their cells. They generate Ang II and III intracellularly as per physiological need and pathological status. These signal molecules are instrumental in regulating organ function, cell growth (hypertrophy), cell death (apoptosis), remodeling and fibrosis.

The local RAS operate in several organs in addition to the liver and kidney dependent circulating RAS.

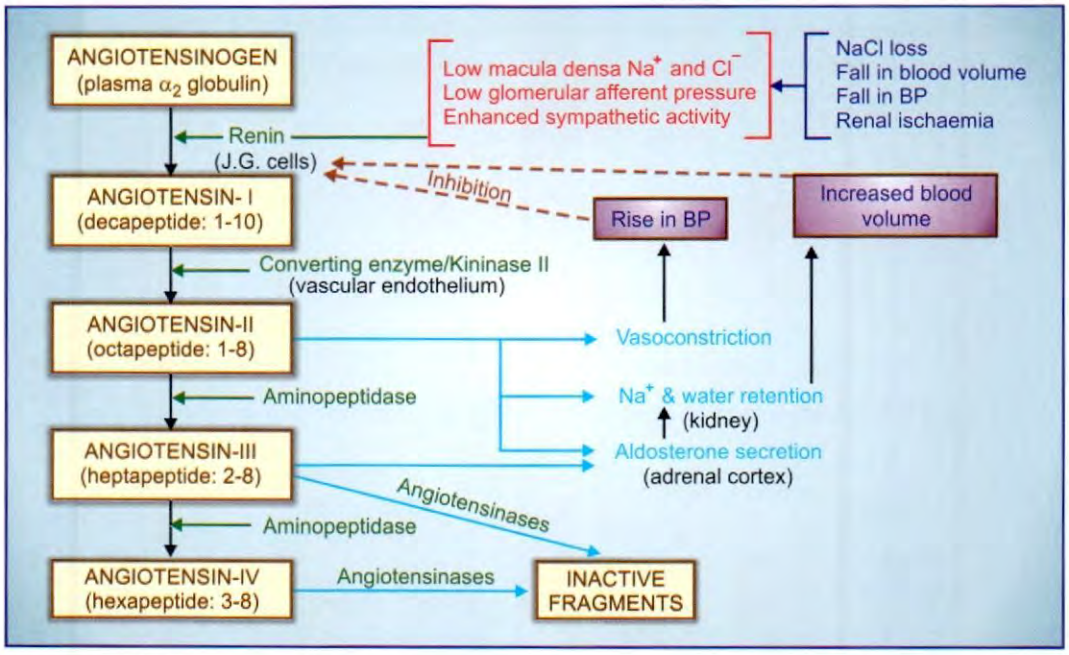


Fig. 36.1: Physiological regulation of electrolyte balance, plasma volume and blood pressure by the renin-angiotensin system
J.G. cells—Juxtaglomerular cells

Prorenin and (Pro) renin receptor (PRR)

Renin is synthesized in the juxtaglomerular (JG) cells of kidney and in tissues expressing local RAS as a larger peptide *pre-prorenin*. In response to appropriate stimuli both prorenin and renin are secreted; the former in much larger quantities. The concentration of prorenin in circulation is 5–10 fold higher than that of renin. Till recently, prorenin was considered to be only the inactive precursor of renin, but now it is recognized to be active in its own right.

Prorenin is activated both enzymatically and non-enzymatically (Fig. 36.2). The enzymatic activation is carried out by proteases like proconvertase-1 or Cathepsin B, which cleave off the hindering 'propeptide' to produce renin with exposed catalytic domain. This activation is irreversible. Nonenzymatic and reversible activation occurs by binding of prorenin to another transmembrane protein called *(Pro) renin receptor (PRR)*, so named because it binds renin as well. The PRR is richly expressed in heart, blood vessels, kidney, brain, eye and liver. Binding of prorenin to PRR brings about a conformational change, the 'propeptide' segment unfolds and the catalytic domain is exposed. When renin binds to PRR, its catalytic activity is augmented several fold. However, prorenin/renin can dissociate from PRR to return to their original state, and the nonenzymatic activation/augmentation is reversible. Nonenzymatic activation of prorenin plays a major role in local RAS, where prorenin exerts effects *via* Ang II dependent and Ang II independent pathways (Fig. 36.3).

(a) *Ang II dependent pathway*: Activation of prorenin/renin generates Ang I which is converted to Ang II by ACE. Ang II acts on AT receptors on the tissue cells to produce effects on cell growth, inflammation, apoptosis, etc.

(b) *Ang II independent pathway*: Binding of prorenin/renin to PRR on cell surface directly triggers intracellular signalling *via* activation of MAP kinase, plasminogen activator-inhibitor-1

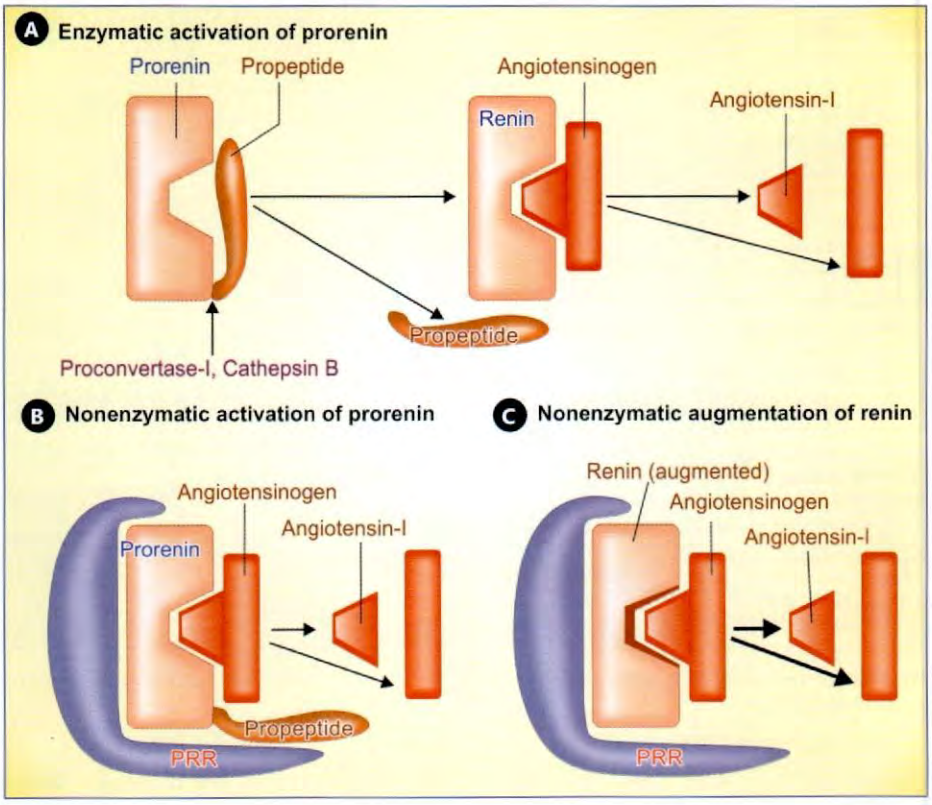


Fig. 36.2: Schematic depiction of enzymatic (A) and nonenzymatic activation of prorenin (B) and nonenzymatic augmentation of renin (C) in the tissue (local) renin-angiotensin system
PRR—(Pro) renin receptor; Ang I—Angiotensin I.

(PAI-1), JAK-STAT pathway, transcription factors, protooncogenes, etc. to regulate cell growth, collagen deposition, fibrosis and apoptosis. Overactivity of RAS *via* such signalling abundantly contributes to pathological changes and end-organ damage in many conditions like hypertensive vascular and ventricular hypertrophy, post-infarction myocardial fibrosis and remodeling, congestive heart failure, nephropathy, retinopathy, etc. The ratio of circulating prorenin to renin is markedly elevated in diabetes, which may be causative in nephropathy and retinopathy.

Alternative (ACE-independent) pathway of Ang II production

In addition to the primary pathway described above, small quantities of Ang I and Ang II can be produced from angiotensinogen by the action of other proteases like cathepsin. Moreover, chymase can convert (although at a much slower rate) Ang I to Ang II, particularly in heart and kidney.

Other angiotensin peptides

In addition to Ang II and Ang III some other biologically active angiotensin peptides are produced in small quantities whose physio-pathological role is not well understood.

Angiotensin IV (Ang IV) It is a hexapeptide (Ang 3-8) produced by removal of arginine from aminoterminal of

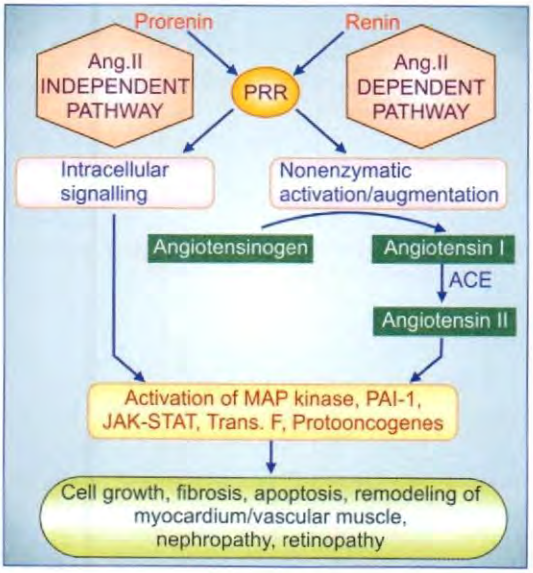


Fig. 36.3: (Pro) renin receptor (PRR) mediated action of tissue prorenin/renin through angiotensin II (Ang II) dependent and Ang II independent pathways.
PAI-1—Plasminogen activator inhibitor-1;
Trans. F—Transcription factors

Ang III by an aminopeptidase. Ang IV inhibits an insulin regulated aminopeptidase (IRAP) which is considered to be its specific receptor and is labelled *AT_4 receptor*. Binding of Ang IV to IRAP prevents degradation of neuropeptides involved in cognitive function and memory in animals. Thus Ang IV improves memory. Some vascular, renal and other peripheral effects of Ang IV have also been described.

Angiotensin (1-7) This heptapeptide can be produced from Ang I or Ang II by the action of another carboxypeptidase labelled ACE 2. In animals, Ang (1-7) produces effects which are in general opposite to those of Ang II, including vasodilatation (NO dependent), antithrombotic, anti-ischaemic and antiproliferative effects by binding to a protooncogene receptor. The clinically used ACE inhibitors do not inhibit ACE 2. Rather, when these drugs are given levels of Ang (1-7) are increased due to diversion of Ang I from ACE and inhibition of degradation of Ang (1-7).

Attempts are being made to therapeutically exploit the Ang II related peptides.

ACTIONS

1. CVS The most prominent action of Ang II is vasoconstriction, which is produced directly as well as by enhancing Adr/NA release from adrenal medulla/adrenergic nerve endings and by increasing central sympathetic outflow. In addition, Ang II inhibits reuptake of NA and augments responsiveness of vascular smooth muscle to it. The vasoconstriction involves arterioles and venules and occurs in all vascular beds. However, it is less marked in cerebral, skeletal muscle, pulmonary and coronary vessels. Ang II induced vasoconstriction promotes movement of fluid from vascular to extravascular compartment. Injected i.v. Ang II is much more potent than NA as a pressor agent. No tachyphylaxis is seen in the pressor action of Ang II; rather long-term infusion of low concentration of Ang II produces progressive and sustained rise in BP by its renal effects promoting salt and water reabsorption, as well as by enhancing endothelin generation.

Ang II increases force of myocardial contraction by promoting Ca^{2+} influx. It can increase heart rate by enhancing sympathetic activity, but this is opposed by the reflex effect of rise in BP. Cardiac output is often reduced and cardiac work is increased (due to rise in peripheral resistance). In contrast to NA, Ang II does not activate latent pacemakers. As such, it has little arrhythmogenic propensity.

Ang II acting on a chronic basis induces hypertrophy, hyperplasia and increased intercellular matrix production in the myocardium as well as vascular smooth muscle by direct cellular effects involving expression of protooncogenes and transcription of several growth factors. Indirectly, volume overload and increased t.p.r. caused by Ang II contributes to the hypertrophy and remodeling (abnormal redistribution of muscle mass) in heart and blood vessels. Long standing hypertension increases vessel wall as well as intimal thickness and causes ventricular hypertrophy. Fibrosis and dilatation of infarcted area with hypertrophy of the noninfarcted ventricular wall is seen after myocardial infarction. Progressive cardiac myocyte death and fibrotic transformation occurs in CHF. These changes are important risk factors for cardiovascular morbidity and mortality. ACE inhibitor therapy retards/reverses many

of these changes imparting a pivotal role to Ang II in vascular and ventricular hypertrophy, apoptosis and remodeling. As described above, the local RAS and prorenin-PRR systems are crucial in these responses.

2. Adrenal cortex Ang II and Ang III are trophic to the zona glomerulosa of adrenal cortex. They enhance synthesis and release of aldosterone which acts on distal tubule in kidney to promote Na^+ reabsorption and K^+/H^+ excretion. These effects are exerted at concentrations lower than those required to cause vasoconstriction.

3. Kidney In addition to exerting indirect effect on kidney through aldosterone, Ang II promotes Na^+/H^+ exchange in proximal tubule $\rightarrow$ increased Na^+, Cl^- and HCO_3^- reabsorption. Further, Ang II reduces renal blood flow and GFR, and produces intrarenal haemodynamic effects which normally result in Na^+ and water retention. However, an opposite effect has been observed in cirrhotics and renovascular disease patients in whom Ang II increases GFR by strongly constricting glomerular efferent vessels.

4. CNS It has been noted that systemically administered Ang II can gain access to certain periventricular areas of the brain to induce drinking behaviour and ADH release—both of which would be conducive to plasma volume expansion. Ang II also increases central sympathetic outflow, which contributes to the pressor response.

5. Peripheral sympathetic structures Ang II enhances sympathetic activity by peripheral action as well. It releases Adr from adrenal medulla, stimulates autonomic ganglia and increases the output of NA from adrenergic nerve endings.

Angiotensin receptors and transducer mechanisms Specific Ang II receptors are expressed on the surface of target cells. Two subtypes (AT_1 and AT_2) have been differentiated pharmacologically: *Losartan* is a selective AT_1 antagonist, while PD 123177 is a selective AT_2 antagonist. Both subtypes are GPCRs. However, all major effects of Ang II are mediated by AT_1 receptor. Ang III also activates AT_1 and AT_2 receptors, but is a much weaker agonist at most sites, except on adrenal cortex causing aldosterone release.

The AT_2 receptor is abundantly expressed in foetal tissues. In adults, it has been demonstrated in vascular endothelium, adrenal medulla, kidney and some brain areas. The functional role of AT_2 receptor is not well delineated, but is generally opposite to that of AT_1 receptor. Activation of AT_2 receptor causes NO-dependent vasodilatation, promotes apoptosis, inhibits cell proliferation and may lower BP.

Other angiotensin peptides like Ang IV and Ang (1-7) act on their own (AT_4 and *Mas* respectively) receptors.

The AT_1 GPCR utilizes different transducer mechanisms in different tissues. By coupling with Gq protein the phospholipase C–IP_3/DAG–intracellular Ca^{2+} release mechanism underlies vascular and visceral smooth muscle contraction by activating myosin light chain kinase (MLCK). In addition, membrane Ca^{2+} channels are activated. Enhanced Ca^{2+} movement also induces aldosterone synthesis/release, cardiac inotropy, depolarization of adrenal medullary and autonomic ganglionic cells, resulting in CA release or sympathetic discharge. DAG activates protein kinase C (PKC) which phosphorylates several intracellular proteins and augments the above responses as well as participates in promotion of cell growth. In liver and kidney, Ang II inhibits adenylyl cyclase by AT_1 receptor coupled to Gi protein. The intrarenal homeostatic action involves phospholipase A_2 activation and PG/LT production.

In many tissues, especially myocardium, vascular smooth muscle and fibroblasts, AT_1 receptor also mediates long-term effects of Ang II on cell growth. Ang II activates MAP kinase, TAK2 tyrosine protein kinase, PKC and utilizes the JAK-STAT pathway which together enhance expression of proto-oncogenes, transcription factors and growth factors. As a result, cell growth is promoted and more intercellular matrix is synthesized.

PATHOPHYSIOLOGICAL ROLES

1. *Mineralocorticoid secretion* There is no doubt that Ang II (also Ang III) is the physiological stimulus for aldosterone secretion from

adrenal cortex. It also exerts trophic influence on the glomerulosa cells so that effects are augmented under conditions which persistently raise Ang II levels.

2. *Electrolyte, blood volume and pressure homeostasis* The RAS plays an important role in maintaining electrolyte composition and volume of extracellular fluid (*see* Fig. 36.1). Changes that lower blood volume or blood pressure, or decrease Na^+ content induce renin release by three mechanisms.

- *Intrarenal baroreceptor pathway:* By decreasing tension in the afferent glomerular arterioles, it operates partly through increased production of prostaglandins (PGE_2), nitric oxide, etc, and partly *via* stretch sensitive ion channels.
- *Macula densa pathway:* Low Na^+ and Cl^- concentration in the tubular fluid sensed by macula densa cells triggers this pathway. It has been found that COX-2 and neuronal nitric oxide synthase (nNOS) are induced in macula densa cells by Na^+ depletion → release of PGE_2 and PGI_2 is enhanced both due to increased amount of COX-2 as well as its activation by NO. The locally released PGs act on juxtaglomerular cells to promote renin secretion.
- *β adrenoceptor pathway*: Baroreceptor and other reflexes which increase sympathetic impulses to JG cells activate β_1 adrenoceptors expressed on their surface → increased intracellular cAMP triggers renin release.

Increased renin is translated into increased plasma Ang II which produces acute rise in BP by vasoconstriction, and more long-lasting effects by directly as well as indirectly increasing Na^+ and water reabsorption in the kidney. Rise in BP in turn inhibits renin release : the *long-loop negative feedback mechanism.* It has been shown that Ang II can be formed within the kidney and exerts important local regulatory effects. A *short-loop negative feedback mechanism* operates within the kidney : activation of AT_1 receptors on JG cells inhibits renin release directly. Long-term stabilization of BP despite varying salt and water intake appears to be achieved through these mechanisms.

The mechanisms of regulation of renin release have important pharmacological implications:

- ACE inhibitors and AT_1 antagonists enhance renin release by interfering with both the short-loop and long-loop negative feedback mechanisms.
- Vasodilators and diuretics stimulate renin release by lowering BP.
- Loop diuretics increase renin production by reducing entry of Na^+ and Cl^- into macula densa cells.
- Central sympatholytics and β blockers decrease renin release by interfering with the β adrenoceptor pathway.
- NSAIDs, including selective COX-2 inhibitors, and nNOS inhibitors decrease renin release by inhibiting PG production → cause Na^+ and water retention.

3. *Development of hypertension* The RAS is directly involved in renovascular hypertension: plasma renin activity (PRA) is raised in most patients. In essential hypertension also it appears to have a permissive role, though PRA may be either raised or low. Since ACE inhibitors consistently lower BP in hypertensives, the involvement of this system appears to be more widespread. A positive correlation between circulating angiotensinogen levels and essential hypertension has also been found. Several evidences point to causation of pregnancy-induced hypertension (preeclampsia) by production of autoantibodies which activate AT_1 receptor. The role of Ang II in hypertrophy/remodeling of heart and blood vessels is now well recognized (*see* above).

4. *Secondary hyperaldosteronism* The RAS is instrumental in the development of secondary hyperaldosteronism.

5. *CNS* Ang II can be formed locally in the brain and may function as transmitter or modulator. Regulation of thirst, hormone release and sympathetic outflow may be the responses mediated.

Ang II is not available commercially, and not used clinically.

Inhibition of renin-angiotensin system

This can be achieved by:

1. Sympathetic blockers (β blockers, adrenergic neurone blockers, central sympatholytics)—decrease renin release.
2. Direct renin inhibitors (DRIs, e.g. aliskiren): block renin action—interfere with generation of Ang I from angiotensinogen (rate limiting step).
3. Angiotensin converting enzyme (ACE) inhibitors (e.g. captopril)—prevent generation of the active principle Ang II.
4. Angiotensin receptor blockers (ARBs, e.g. losartan)—antagonise the action of Ang II on target cells.
5. Aldosterone antagonists (e.g. spironolactone)—block mineralocorticoid receptors.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Captopril, a dipeptide analogue, is the first orally active ACE inhibitor which was introduced in 1977 and quickly gained wide usage. A multitude of other ACE inhibitors have since been added, of which—*enalapril, lisinopril, benazepril, ramipril, fosinopril, quinapril, trandolapril, imidapril* and *perindopril* are available in India. Many others are marketed elsewhere.The pharmacology of captopril is described as prototype, since most of its effects are class effects common to all ACE inhibitors.

Captopril

It is a sulfhydryl containing dipeptide surrogate of proline which abolishes the pressor action of Ang I but not that of Ang II: It does not block AT_1 or AT_2 receptors.

ACE is a relatively nonspecific enzyme; splits off a dipeptidyl segment from several peptides including bradykinin, substance P, a natural stem cell regulating peptide, enkephalins, etc. in addition to Ang I. As such, captopril increases plasma kinin levels and potentiates the hypotensive action of exogenously administered bradykinin. Pretreatment with B_2 kinin receptor antagonist has shown that kinins do contribute to the acute vasodepressor action of ACE inhibitors, but they appear to have little role in the long-term hypotensive effect, probably because, firstly kinins play only a minor role, if at all, in BP regulation, and, secondly another enzyme 'Kininase I' (which also degrades bradykinin) is not inhibited by captopril. Nevertheless, elevated kinins (and PGs whose synthesis is enhanced by kinins) may be responsible for cough and angioedema induced by ACE inhibitors in susceptible individuals. ACE inhibitors interfere with degradation of substance P also. Rise in the level of stem cell regulator peptide caused by ACE inhibitors could, in part, be responsible for their cardioprotective effect in CHF.

Captopril lowers BP, but in the short-term, magnitude of response is dependent on the Na^+ status and the level of RAS activity. In normotensive Na^+ replete individuals, the fall in BP attending initial few doses of ACE inhibitors is modest. Fall in BP is more marked when Na^+ has been depleted by dietary restriction or diuretics, because renin level is high. In CHF also, the renin level is raised and antihypertensive doses of captopril initially cause marked fall in BP. ACE inhibitor therapy in these situations has to be initiated at much lower doses. A greater fall in BP also occurs in renovascular, accelerated and malignant hypertension. In essential hypertension it has been found that RAS is overactive in 20%, normal in 60% and hypoactive in the rest. Thus, this system contributes to maintenance of vascular tone in over 80% cases and its inhibition results in lowering of BP. Treatment with ACE inhibitors causes feedback increase in renin release resulting in overproduction of Ang I. Since its conversion to Ang II is blocked, Ang I is diverted to produce more Ang (1-7) which has vasodilator property, and could contribute to the BP lowering action of ACE inhibitors. In the long-term however, no correlation has been observed between plasma renin activity (PRA) and magnitude of fall in BP due to captopril.

Captopril induced hypotension is a result of decrease in total peripheral resistance. The arterioles dilate and compliance of larger arteries is increased. Both systolic and diastolic BP fall. Cardiac output is not affected. Cardiovascular reflexes are not interfered with and there is little dilatation of capacitance vessels. As such, postural hypotension is not a problem. Reflex sympathetic stimulation does not occur despite vasodilatation, and ACE inhibitors can be safely used in patients with ischaemic heart disease. The renal blood flow is not compromized even when BP falls substantially. This is due to greater dilatation of renal vessels (Ang II markedly constricts them). Cerebral and coronary blood flow are also not compromized.

Reflex (postural) changes in plasma aldosterone are abolished and basal levels are somewhat decreased as a consequence of loss of its regulation by Ang II. However, physiologically sufficient mineralocorticoid is still secreted under the influence of ACTH and plasma K^+. Levels of plasma renin and Ang I are increased as a compensatory measure, but the physiological significance of this appears to be minor (most actions are exerted through generation of Ang II).

Pharmacokinetics About 70% of orally administered captopril is absorbed. Presence of food in stomach reduces its bioavailability. Penetration in brain is poor. It is partly metabolized and partly excreted unchanged in urine. The plasma t½ is ~2 hours, but actions last for 6–12 hours.

Adverse effects The adverse effect profile of all ACE inhibitors is similar. Captopril is well tolerated by most patients, especially if daily dose is kept below 150 mg.

- *Hypotension:* An initial sharp fall in BP occurs especially in diuretic treated and CHF patients; persistent hypotension may be troublesome in MI patients.
- *Hyperkalaemia:* This is likely in patients with impaired renal function and in those taking K^+ sparing diuretics, NSAIDs or β blockers. In others significant rise in plasma K^+ is rare.
- *Cough:* A persistent brassy cough occurs in 10–16% patients within 1–8 weeks, often requires discontinuation of the drug—subsides 4–6 days thereafter. It is not dose related and appears to be caused by inhibition of bradykinin/substance P breakdown in the lungs of susceptible individuals.
- *Rashes, urticaria:* Occur in 1–4% recipients; but do not usually warrant drug discontinuation. *Angioedema* is rare.
- *Dysgeusia:* Reversible loss or alteration of taste sensation due to captopril occurs in few patients, rarely with other ACE inhibitors.
- *Foetopathic:* Foetal growth retardation, hypoplasia of organs and foetal death may occur if ACE inhibitors are given during later half of pregnancy. A recent report indicates 2.7-fold higher malformation rate in foetuses exposed to ACE inhibitors in the first trimester. ACE inhibitors must be stopped when the woman conceives.
- *Headache, dizziness, nausea and bowel upset:* Each of these is reported in 1–4% patients.
- *Granulocytopenia and proteinuria:* These are rare, but warrant withdrawal. Renal disease predisposes to these adverse effects. However, ACE inhibitors retard diabetic nephropathy, reduce attendant proteinuria, and are renoprotective.
- *Acute renal failure:* It may be precipitated by ACE inhibitors in patients with bilateral renal artery stenosis due to fall in glomerular filtration pressure.

Interactions

- Diuretics synergise with the hypotensive action of ACE inhibitors by depleting Na^+ and raising renin levels. In diuretic treated patients, the starting dose of ACE inhibitors should be low.
- Indomethacin (and other NSAIDs) attenuate the hypotensive action by retaining salt and water. Incidents of renal failure have been reported when a NSAID was given to

patients (especially elderly) receiving ACE inhibitor + diuretic.
- Hyperkalaemia can occur if K^+ supplements/ K^+ sparing diuretics are given with any ACE inhibitor.
- Antacids reduce bioavailability of captopril.
- ACE inhibitors reduce Li^+ clearance and predispose to its toxicity.

Dose: 25 mg BD, increased gradually upto 50 mg TDS according to response. In patients on diuretics and in CHF patients it is wise to start with 6.25 mg BD to avoid marked fall in BP initially. Tablets should be taken 1 hr before or 2 hr after a meal.

Captopril has become less popular due to need for twice/thrice daily dosing and possibly higher incidence of side effects compared to other ACE inhibitors.

ANGIOPRIL 25 mg tab, ACETEN 12.5, 25 mg tab.

OTHER ACE INHIBITORS

All ACE inhibitors have the same pharmacological actions, therapeutic uses and spectrum of adverse effects, drug interactions and contraindications. Differences among them are primarily pharmacokinetic, reflected in time course of action. Their important features are compared in Table 36.1. No single drug is superior to others.

Enalapril This is the second ACE inhibitor to be introduced. It is a prodrug, deesterified in the liver to *enalaprilat* (a tripeptide analogue), which is not used as such orally because of poor absorption, but is marketed as injectable preparation in some countries. Enalapril may offer certain advantages over captopril:

1. More potent, effective dose 5–20 mg OD or BD.
2. Its absorption is not affected by food.
3. Onset of action is slower (due to need for conversion to active metabolite), less liable to cause abrupt first dose hypotension.
4. Has a longer duration of action: most hypertensives can be treated with single daily dose.
5. Rashes and loss of taste are probably less frequent.

ENAPRIL, ENVAS, ENAM 2.5, 5, 10, 20 mg tab.

Lisinopril It is the lysine derivative of enalaprilat; does not require hydrolysis to become active ACE inhibitor. Its oral absorption is slow (making first dose hypotension less likely) and incomplete, but unaffected by food. The duration of action is considerably longer, permitting single daily dose and ensuring uniform hypotensive action round the clock.

LINVAS, LISTRIL, LIPRIL 2.5, 5, 10 mg tab, LISORIL 2.5, 5, 10, 20 mg tab.

Perindopril Another long-acting ACE inhibitor with a slow onset of action: less chance of first dose hypotension. Though 66–95% of orally administered perindopril is absorbed, only about 20% is converted to the active metabolite *perindoprilat*. Extensive metabolism

Table 36.1: Comparative features of some ACE inhibitors

	Captopril	*Enalapril*	*Lisinopril*	*Fosinopril*	*Perindopril*	*Ramipril*
1. Chemical nature	Sulfhydryl	Carboxyl	Carboxyl	Phosphinate	Carboxyl	Carboxyl
2. Activity status	Active	Prodrug	Active	Prodrug	Prodrug	Prodrug
3. Bioavailability (as active form)	70%	50%	25%	30%	30–50%	60%
4. Time to peak action	1 hr	4–6 hr	6–8 hr	3–5 hr	6 hr	3–6 hr
5. Elimination t½*	2 hr	11 hr	12 hr	12 hr	25–30 hr	8–18 hr
6. Mode of excretion	Renal	Renal	Renal	Renal/ hepatic	Renal	Renal
7. Duration of action	6–12 hr	24 hr	≥ 24 hr	24 hr	> 24 hr	>24 hr
8. Daily dose (mg)	25–150	2.5–40	5–40	10–40	2–8	1.25–10

* t½ including that of active metabolite

to other inactive products occurs. Efficacy and tolerance of perindopril are similar to other ACE inhibitors.
COVERSYL 2, 4 mg tab.

Fosinopril This ACE inhibitor is unique in being a phosphinate compound that is glucuronide conjugated and eliminated both by liver and kidney. The t½ is not altered by renal impairment and the dose remains the same. However, like most others, it is a prodrug suitable for once daily administration. First dose hypotension is more likely.
Dose: Initially 10 mg (elderly 5 mg) OD; maximum 40 mg/day.
FOSINACE, FOVAS 10, 20 mg tabs.

Ramipril The distinctive feature of this long-acting ACE inhibitor is its extensive tissue distribution. Greater inhibition of local RAS has been claimed. However, whether this confers any therapeutic advantage is not known. The plasma t½ of its active metabolite ramiprilat is 8–18 hours, but terminal t½ is longer due to slow release of tissue bound drug.
CARDACE, RAMIRIL, CORPRIL, R.PRIL 1.25, 2.5, 5 mg caps.

Quinapril A prodrug carboxyl ACE inhibitor that is rapidly and completely converted in the liver to the active form Quinaprilat. Like ramiprilat, it is highly bound to the tissue ACE and exhibits a biphasic plasma t½ of 2 hours and 24 hours. Elimination occurs in urine and bile in a ratio of 2:1.
Dose: 10–40 mg/day
ACCUPRIL-H: Quinapril 20 mg + hydrochlorothiazide 12.5 mg tab.

Trandolapril It is a carboxyl prodrug that is 40–60% bioavailable in the active form. Absorption is delayed but not decreased by food. The peak effect occurs at 4–6 hours. It is partly metabolized and eliminated both in urine and faeces. The plasma t½ of active metabolite is biphasic 10–24 hours, suitable for once daily dosing.
Dose: 2–4 mg (max 8 mg) OD; ZETPRIL 1, 2 mg tabs.

Imidapril The oral bioavailability of this long-acting prodrug ACE inhibitor is 40%, which is reduced by taking the drug with meals. The peak effect occurs at 6–8 hours and plasma t½ is >24 hours.
Dose: Initially 5 mg OD taken 1 hour before food; usual maintenance dose 10 mg OD.
TANATRIL 5, 10 mg tabs.

Benazepril Another nonsulfhydryl prodrug ACE inhibitor; has a bioavailability of 37% and is excreted by kidney with a t½ of 10–12 hr.
Dose: 10 mg initially, max 20–40 mg/day;
BENACE 5, 10, 20 mg tab.

USES

1. Hypertension The ACE inhibitors are first line drugs in all grades of hypertension, but the angiotensin receptor blockers (ARBs) have now surpassed them in popularity. About 50% patients of essential hypertension respond to monotherapy with ACE inhibitors and many of the rest to their combination with diuretics or β blockers. The antihypertensive effect of lower doses develops gradually over 2–3 weeks. They offer the following advantages:

- Free of postural hypotension, electrolyte disturbances, feeling of weakness and CNS effects.
- Can be used in asthmatics, diabetics and peripheral vascular disease patients.
- Long-term ACE inhibitor therapy has the potential to reduce incidence of type 2 diabetes in high risk subjects.
- Secondary hyperaldosteronism and K^+ loss due to diuretics is prevented.
- Renal blood flow is well maintained.
- Left ventricular hypertrophy and increased wall-to-lumen ratio of blood vessels that occurs in hypertensive patients is reversed.
- No hyperuricaemia, no deleterious effect on plasma lipid profile.
- No rebound hypertension on withdrawal.
- Minimum worsening of quality of life parameters like general wellbeing, work performance, sleep, sexual performance, etc.

Large multicentric trials have confirmed that ACE inhibitors reduce cardiovascular morbidity and increase life expectancy of hypertensive

patients. It appears that by their specific effect on myocardial and vascular cell growth/remodeling, they have greater protective potential than other classes of antihypertensive drugs.

ACE inhibitors are effective and first choice drugs in renovascular and resistant hypertension. They are particularly suitable for diabetic hypertensives in whom they reduce cardiovascular complications more than other antihypertensive drugs, probably by improving endothelial function.

2. CHF ACE inhibitors cause both arteriolar and venodilatation in CHF patients; reduce afterload as well as preload on heart and improve all haemodynamic parameters. Though they have no direct action on myocardium, stroke volume and cardiac output are increased, while heart rate is reduced. Diuresis occurs initially and the accumulated salt and water are lost due to improved renal perfusion and abolition of mineralocorticoid mediated Na^+ retention. Cardiac work as measured by heart rate × pressure product is reduced; thereby, exercise capacity of CHF patients is enhanced. Beneficial effects are well sustained with chronic therapy and the NYHA functional class of most patients is improved.

Robust multicentric trials have shown that ACE inhibitors retard the progression of left ventricular systolic dysfunction and prolong survival of CHF patients of all grades (I to IV). Mortality is reduced by ~ 20% in symptomatic CHF patients. Unless contraindicated, ACE inhibitors are now advocated by several professional bodies, including American Heart Association and American College of Cardiology, as first line drugs in all patients with symptomatic as well as asymptomatic left ventricular inadequacy because even in asymptomatic cases, they prevent progression to overt heart failure. A diuretic, β blocker with or without digitalis may be added according to need. ACE inhibitors reduce episodes of decompensation, myocardial infarction and sudden death. In addition to improved haemodynamics, long-term benefits of ACE inhibitors accrue from withdrawal of Ang II mediated ventricular hypertrophy, remodeling, accelerated myocyte apoptosis and fibrosis. Indirect benefits occur due to reduction in sympathetic activation and aldosterone levels.

The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial on 3164 heart failure patients (NYHA class II to IV) has shown that high dose lisinopril (32.5–35 mg/day) given for 39–58 months was more effective in reducing all cause mortality, hospitalization for heart failure and risk of MI than lower dose (2.5–5 mg/day). To afford maximum protection against progression of heart failure, the dose of ACE inhibitors needs to be titrated to nearly the upper limit of recommended dose range, as shown in other mega trials like GISSI-3, SOLVD, AIRE, etc. as well. ACE inhibitors are effective in reducing development of ventricular dysfunction, heart failure and related mortality in post-MI patients also (SAVE, TRACE, AIRE trials).

3. Myocardial infarction (MI) Several mega-trials have established that oral ACE inhibitors administered while MI is evolving (within 24 hr of an attack) and continued for 6 weeks reduce early as well as long-term mortality, irrespective of presence or absence of systolic dysfunction, provided hypotension is avoided. In high risk patients and those with latent or overt ventricular dysfunction (CHF) extension of therapy continues to afford survival benefit over years. In unstable angina/non-ST segment elevation MI (NSTEMI), long-term ACE inhibitor therapy reduces recurrent MI and need for coronary angioplasty (SAVE and SOLVD trials), though no benefit was apparent in the short-term (ISIS-4 study). Current evidence shows that if there are no contraindications, all MI patients stand to gain from ACE inhibitor therapy, though magnitude of benefit is greatest in those having associated hypertension and/or diabetes.

4. Prophylaxis in high cardiovascular risk subjects The results of Heart Outcomes Prevention Evaluation (HOPE) study in 9297 post-MI and other high risk subjects, but having no left ventricular dysfunction or heart failure have shown that ramipril reduced cardiac death and MI or stroke by 22% over a period of 4.5 years. Risk of developing heart failure or diabetes was also reduced. These results were

confirmed by the EUROPA trial and appear to hold true even for patients who have undergone coronary revascularization (APRES trial). Thus, ACE inhibitors are protective in high cardiovascular risk subjects even when there is no associated hypertension or left ventricular dysfunction. Protective effect is exerted both on myocardium as well as vasculature; may involve improved endothelial function, and is independent of hypotensive action.

5. Diabetic nephropathy Prolonged ACE inhibitor therapy has been found to prevent or delay end-stage renal disease in type I as well as type II diabetics. Albuminuria (an index of glomerulopathy) remains stable in those treated with ACE inhibitor, but aggravates in untreated diabetics. Treated patients have higher creatinine clearance, require less dialysis and have longer life expectancy. Benefits appear to be due to haemodynamic (systemic and intrarenal) as well as abnormal mesangial cell growth attenuating effects of ACE inhibitors. They reduce intraglomerular pressure and hyperfiltration. ACE inhibitors arrest/partly reverse any degree of albuminuria, but benefits in type 2 diabetics are rather limited once macroalbuminuria has set in. The RAS seems to accentuate micro- and macrovascular complications in diabetics, and ACE inhibitors have specific organ protective effect by attenuating the same. All patients with diabetic nephropathy, whether hypertensive or normotensive, deserve ACE inhibitor therapy. Deterioration of retinopathy in diabetics also appears to be retarded by ACE inhibitors.

Nondiabetic nephropathy There is evidence now that chronic renal failure due to nondiabetic causes may also be improved by ACE inhibitors. These drugs reduce proteinuria by decreasing the pressure gradient across glomerular capillaries as well as by altering membrane permeability. This retards disease progression. Among hypertensive nephropathy patients the incidence of doubling of serum creatinine or end stage renal failure is significantly lower in those treated with ACE inhibitors than those treated with other antihypertensive drugs.

6. Scleroderma crisis The marked rise in BP and deterioration of renal function in scleroderma crisis is mediated by Ang II. ACE inhibitors produce dramatic improvement and are life saving in this condition.

Captopril test This test has been devised to obviate the need for renal angiography for diagnosis of renovascular hypertension. The basis of the test is—acute blockade of Ang II formation by captopril results in a reactive increase in PRA which is much higher in renovascular compared to essential hypertension. However, this test is only of adjunctive value.

ANGIOTENSIN ANTAGONISTS (Angiotensin receptor blockers or ARBs)

Over the past 25 years, several nonpeptide orally active AT_1 receptor blockers (ARBs) have been developed as alternatives to ACE inhibitors. These include *losartan, candesartan, valsartan, telmisartan, olmesartan* and *irbesartan*. Selective antagonists of AT_2 receptors as well as combined $AT_1 + AT_2$ antagonists have also been produced, but are not used clinically.

Losartan It is a competitive antagonist and inverse agonist, 10,000 times more selective for AT_1 than for AT_2 receptor; does not block any other receptor or ion channel, except thromboxane A_2 receptor (has some platelet antiaggregatory property). All overt actions of Ang II, *viz.* vasoconstriction, central and peripheral sympathetic stimulation, release of aldosterone and Adr from adrenals, renal actions promoting salt and water reabsorption, central actions like thirst, vasopressin release and growth-promoting actions on heart and blood vessels are blocked. No inhibition of ACE has been noted.

Pharmacologically, ARBs differ from ACE inhibitors in the following ways:

- They do not interfere with degradation of bradykinin and other ACE substrates: no rise in level or potentiation of bradykinin, substance P occurs. Consequently, ACE inhibitor related cough is rare.
- They result in more complete inhibition of AT_1 receptor activation, because responses to Ang II generated *via* alternative pathways

and consequent AT_1 receptor activation (which remain intact with ACE inhibitors) are also blocked.

- They result in indirect AT_2 receptor activation. Due to blockade of AT_1 receptor mediated feedback inhibition—more Ang II is produced which acts on AT_2 receptors that remain unblocked.
- ARBs cause little increase in the level of Ang (1-7) which is raised by ACE inhibitors, since Ang (1-7) is also partly degraded by ACE.

The impact of these differences on clinical efficacy and therapeutic value of the two classes of RAS inhibitors is not known.

Losartan causes fall in BP in hypertensive patients which lasts for 24 hours, while HR remains unchanged and cardiovascular reflexes are not interfered. No significant effect on plasma lipid profile, carbohydrate tolerance or insulin sensitivity has been noted. A mild probenecid-like uricosuric action is produced.

Pharmacokinetics Oral absorption of losartan is not affected by food, but bioavailability is only 33% due to first pass metabolism. It is partially carboxylated in liver to an active metabolite (E3174) which is a 10–30 times more potent noncompetitive AT_1 receptor antagonist. After oral ingestion peak plasma levels are attained at 1 hr for losartan and at 3–4 hours for E3174. Both compounds are 98% plasma protein bound, do not enter brain and are excreted by the kidney. The plasma t½ of losartan is 2 hr, but that of E3174 is 6–9 hr. No dose adjustment is required in renal insufficiency, but dose should be reduced in presence of hepatic dysfunction.

Adverse effects Losartan is well tolerated; has side effect profile similar to placebo. Like ACE inhibitors it can cause hypotension and hyperkalemia, but first dose hypotension is uncommon. Though, a few reports of dry cough have appeared, losartan is considered to be free of cough and dysgeusia inducing potential. Patients with a history of ACE inhibitor related cough have taken losartan without recurrence. Angioedema is reported in fewer cases. Headache, dizziness, weakness and upper g.i. side effects are mild and occasional. However, losartan has fetopathic potential like ACE inhibitors; it should not be administered during pregnancy.

Dose: 50 mg OD, rarely BD; in liver disease or volume depleted patients 25 mg OD; addition of hydrochlorothiazide 12.5–25 mg enhances its effectiveness.

LOSACAR, LOSAR, TOZAAR, ALSARTAN 25, 50 mg tabs.

Candesartan It has the highest affinity for the AT_1 receptor and produces largely unsurmountable antagonism, probably due to slow dissociation from the receptors or receptor desensitization. Elimination occurs by both hepatic metabolism and renal excretion with a t½ of 8–12 hours: action lasts 24 hours.

Dose: 8 mg OD (max 8 mg BD), liver/kidney impairment 4 mg OD.

CANDESAR 4, 8, 10 mg tab., CANDILONG, CANDESTAN 4, 8 mg tabs.

Irbesartan The oral bioavailability of this ARB is relatively high. It is partly metabolized and excreted mainly in bile. The t½ is ~12 hours.

Dose: 150–300 mg OD.

IROVEL, IRBEST 150, 300 mg tabs.

Valsartan The AT_1 receptor affinity of valsartan is similar to that of losartan. Its oral bioavailability averages 23% and food interferes with its absorption. Elimination occurs mainly by the liver in unchanged form with a t½ of 6–9 hours; action lasts 24 hours.

Dose: 80–160 mg OD 1 hour before meal (initial dose in liver disease 40 mg).

DIOVAN, STARVAL, VALZAAR 40, 80, 160 mg tabs.

Olmesartan Another potent ARB with high affinity for AT_1 receptor. It is available as an ester prodrug which is completely hydrolysed during absorption from the gut. It is eliminated in urine as well as in bile with a t½ of ~12 hours. No dose adjustment is needed in liver or kidney disease, unless it is severe. Abdominal pain and sprue-like symptoms have been reported in few recipients.

Dose: 20–40 mg OD; OLMAT, OLSAR 20, 40 mg tabs.

Telmisartan The AT_1 receptor blocking action of telmisartan is similar to losartan, but it does not produce any active metabolite. After an oral dose, peak action occurs in 3 hours and

action lasts > 24 hours. It is largely excreted unchanged in bile; dose reduction is needed in liver disease.

Dose: 20–80 mg OD.

TELMA, TELSAR, TELVAS 20, 40, 80 mg tabs.

Eprosartan It is a newer AT_1 receptor antagonist which is believed to lower BP by blocking vasoconstrictor AT_1 receptors as well as by reducing NA release. Though, blockade of prejunctional AT_1 receptors on sympathetic neurones and resultant decrease in sympathetic outflow is a class effect of ARBs, this action is claimed to be more prominent in eprosartan, so as to be clinically meaningful. Oral bioavailability of eprosartan is low (~13%) and it is mainly excreted unchanged in faeces. Renal excretion is about 10% and the terminal elimination t½ is 20 hours.

Dose: 600 mg OD (range 400–800 mg OD).

TEVETEN, EPROZAR 600 mg tab.

Uses of ARBs

The ARBs have the same overall range of clinical utility as ACE inhibitors, but the suitability and efficacy of one over the other is not clearly defined; may depend on the condition being treated and/or specific features of the patient.

Hypertension Losartan and other ARBs are now first line drugs, comparable in efficacy and desirable features to ACE inhibitors, with the advantage of not inducing cough and a lower incidence of angioedema, rashes and dysgeusia. As such, they are more commonly prescribed now than ACE inhibitors, though superiority of one over the other is not established. Like ACE inhibitors, the maximum antihypertensive effect is reached in 2–4 weeks and ventricular/vascular hypertrophy/remodeling is arrested/reversed similarly. No additional benefit has been obtained by combining an ACE inhibitor with an ARB in the treatment of hypertension.

The Losartan intervention for endpoint reduction in hypertension (LIFE, 2002) study has found losartan to be more effective than β-blockers in reducing stroke among > 9000 hypertensive patients with left ventricular hypertrophy, and is approved for stroke prevention. In cirrhotics, losartan has been found to control portal hypertension.

CHF The ARBs afford clear-cut symptomatic relief as well as survival benefit in CHF. However, their relative value compared to ACE inhibitors, especially in long-term morbidity and mortality reduction, is still uncertain.

A number of large randomized endpoint trials like Evaluation of losartan in the elderly (ELITE, 1997), ELITE-II (2000), OPTIMAAL (2002), Valsartan in acute MI (VALIANT, 2003) have produced inconsistent results. This may be due to within group differences among specific ARBs. Valsartan and candesartan have produced superior benefits than losartan and irbesartan. Thus, for CHF, it may be prudent to use ACE inhibitors as the first choice drugs and to reserve specific ARBs for those who fail to respond well or who develop cough/angioedema/other intolerance to ACE inhibitors.

Myocardial infarction The evidence so far indicates that utility of ARBs in MI, including long-term survival, is comparable to ACE inhibitors. However, the latter are generally used first, since there is greater experience with them.

Diabetic nephropathy Several studies have confirmed that ARBs are renoprotective in type 2 diabetes mellitus, independent of BP lowering. The magnitude of benefit is comparable to ACE inhibitors, but because of better tolerability profile, many consider ARBs to be the first choice now.

Combination of ACE inhibitors with ARBs There are theoretical reasons to combine an ACE inhibitor with an ARB to obtain more complete suppression of RAS and achieve added cardioprotection in CHF or renoprotection in diabetic nephropathy. These are:

- Ang II is generated in several tissues (especially heart and kidney) by non-ACE mechanisms, whose effect can be blocked by ARBs.
- ACE inhibitors produce bradykinin and Ang (1-7) related vasodilatation and other effects that are not produced by ARBs.
- ARBs cause compensatory increase in Ang II production that can be checked by ACE inhibitors.

Additional haemodynamic and symptomatic improvement over short-term has been obtained in CHF with addition of an ARB to existing ACE inhibitor therapy. However, risk of hyperkalemia, hypotension and renal impairment is also increased. Several large randomized trials

including Randomized evaluation of strategies for left ventricular dysfunction (RESOLVD, 1999), Valsartan heart failure trial (VAL-He FT, 2001), CHARM-additive trial (2003), VALIANT (2003) trial, Ongoing Telmisartan alone and in combination with ramipril global endpoint trial (ON TARGET, 2008) of combinations of ARBs and ACE inhibitors *Vs* their monotherapy in affording mortality and other endpoint benefits in CHF have yielded discordant results. Thus, it is not certain that long-term use of ARB + ACE inhibitor combination is uniformly beneficial. However, selected cases, not optimally benefited by monotherapy, may be offered combined therapy, especially by including candesartan or valsartan as the ARB.

In non-diabetic renal disease, the Combination treatment of ARB and ACE inhibitor randomized trial (COOPERATE, 2003) has concluded that ARB + ACE inhibitor combination therapy retards progression of non-diabetic renal disease to a greater extent compared with their monotherapy.

DIRECT RENIN INHIBITOR

Aliskiren

Direct renin inhibitors (DRIs) are the latest class of RAS inhibitory drugs, of which only one member *Aliskiren* has become available for the treatment of cardiovascular and renal diseases in which ACE inhibitors and ARBs are currently used. Aliskiren is a nonpeptide which binds selectively to the catalytic site of renin and competitively blocks the access of angiotensinogen to this site. As a result Ang I is not produced and the effector chain of RAS is interrupted. While the concentration of renin in plasma is increased by feed back, the plasma renin activity (PRA) is decreased. Ang I and Ang II levels fall in a dose-dependent manner.

Aliskiren causes dose related fall in BP which is more marked in the Na^+ depleted subjects with high basal PRA. Similar to ACE inhibitors, plasma aldosterone levels are lowered accompanied by mild natriuresis and a tendency to K^+ retention. The antihypertensive efficacy of aliskiren is nearly equivalent to that of ACE inhibitors or ARBs. Combination of these drugs with aliskiren produces greater fall in BP, at least in the short term. This is due to blockade of rise in PRA caused by ACE inhibitors/ARBs. The pattern of haemodynamic effect of aliskiren resembles ACE inhibitors; postural hypotension is not a problem.

Trials so far have shown that aliskiren reduces hypertensive left ventricular hypertrophy and benefits CHF patients, but its value compared to ACE inhibitors/ARBs as monotherapy and as additional drug remains to be established on the basis of outcome data. Aliskiren reduces albuminuria and has renoprotective effect in hypertension and diabetes mellitus.

At present, aliskiren is recommended as an alternative antihypertensive drug (for those who do not respond or do not tolerate 1st line drugs) and in combination with ACE inhibitor/ARB to achieve more complete RAS blockade and greater BP lowering/cardioprotection. However, addition of aliskiren to ACE inhibitor/ARB in type 2 diabetics has not produced any beneficial effect; may even worsen outcome and is not advised.

Pharmacokinetics Aliskiren is administered orally, but bioavailability is very low due to active extrusion of the absorbed drug by P-glycoprotein. The drug is mainly eliminated in faeces; small amount in urine. The plasma $t_{1/2}$ is > 24 hours, and its BP lowering effect persists for days after regular intake.

Adverse effects Aliskiren produces few and mild side effects—mainly dyspepsia, abdominal pain, loose motions, headache and dizziness. Acute hypotension, hyperkalemia, cough, angioedema and rashes are less frequent than with ACE inhibitors. Aliskiren is contraindicated during pregnancy.

Dose: 150–300 mg OD; RASILEZ 150 mg tab; RASILEZ-HC: along with hydrochlorothiazide.

PROBLEM DIRECTED STUDY

36.1 A 65-year-male was diagnosed to be suffering from congestive heart failure (CHF). He had pitting edema of feet, dyspnoea and cough on mild exertion, fatigue, engorged neck veins, soft enlargement of liver, pulmonary congestion and mild cardiac dilatation. The pulse was 100/min, respiration 20/min and BP 130/86 mm of Hg. He was prescribed—

Tab furosemide 40 mg once daily in the morning.

Tab captopril 25 mg twice daily, morning and evening.

After 2 hours of taking the medicines, he started passing increased quantity of urine and in the next few hours he gradually started feeling weakness, nausea, sweating and fainted while walking to the toilet. The pulse was recorded as 110/min and BP 80/40 mm Hg.

(a) What could be the cause of sudden onset symptoms and the marked fall in BP?

(b) Is the choice of drugs incorrect?

(c) How could such adverse event be prevented?

(d) What immediate management is required?

(see Appendix-1 for solution)

Chapter 37 Nitric Oxide and Vasoactive Peptide Signal Molecules

NITRIC OXIDE

It is one of the oxides of nitrogen with molecular formula NO$^{\bullet}$ indicating that it is a free radical with an unpaired electron. Nitric oxide is the smallest endogenous signal molecule and the only one which is a gas at normal temperature. Since its discovery as a biological mediator in 1980, it is now known to perform a wide array of functions.

Furchgott and Zwadzki (1980) demonstrated that ACh caused vascular smooth muscle relaxation only when the endothelial lining was intact, but not when it was denuded by rubbing. They proposed that on activation by ACh, the endothelial cells released a soluble 'endothelium derived relaxing factor' (EDRF) which diffused to the underlying smooth muscle cell causing relaxation. A little earlier Farid Murad (1977) had already shown that GTN caused vasodilatation by releasing NO. Ignarro in 1987 confirmed that EDRF infact was NO. All three, Furchgott, Murad and Ignarro received Nobel Prize in 1998 for these discoveries. Soon a number of other vasorelaxants (histamine, 5-HT, bradykinin, etc.) were also shown to act through EDRF release. It is now established that NO is a key messenger in the cardiovascular and nervous systems, as well as in inflammatory and some other types of cells.

Generation and fate of NO: Nitric oxide is produced in the cells from the amino acid L-argenine by the enzyme nitric oxide synthase (NOS) using molecular oxygen and NADPH (Fig. 37.1); flavin mononucleotide (FMN), flavin adenine dinucleotide (FAD), haeme and tetrahydrobiopterin (H_4B) act as coenzyme to NOS. The rate of NO production depends on the activity of NOS, because the substrate is normally present in excess.

Three isoforms of NOS, *viz.* neuronal NOS (nNOS or NOS-1), inducible NOS (iNOS or NOS-2) and endothelial NOS (eNOS or NOS-3) have been characterized. Though all

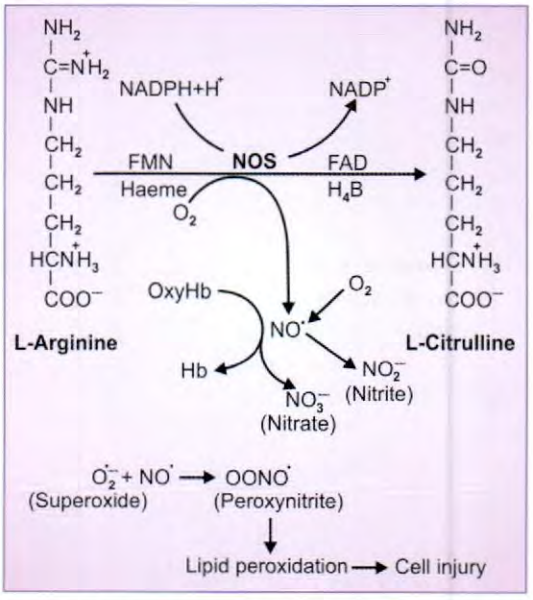


Fig. 37.1: Generation and metabolism of nitric oxide (NO) FMN—Flavin mononucleotide; FAD—Flavin adenine dinucleotide; NADP—Nicotinamide adenine dinucleotide phosphate; NADPH—Reduced form of NADP; H_4B—Tetrahydrobiopterin; NOS—Nitric oxide synthase

3 isoforms are expressed by several types of cells, they are designated on the basis of their primary localization. While eNOS and nNOS are constitutive enzymes, i.e. are synthesized at uniform rate, which is relatively low; the iNOS found in macrophages, monocytes, neutrophils, hepatocytes, etc. is induced by bacterial endotoxins, cytokines and TNFα, etc. Inflammation induces production of large quantities of iNOS in macrophages and other cells. This results in generation of huge amount of NO which can continue over hours or even days. Activation of eNOS and nNOS is Ca^{2+}-calmodulin dependent. Agents and mediators activate eNOS/nNOS by raising cytosolic Ca^{2+}. In contrast, iNOS is active as such, and not Ca^{2+} dependent. After induction by inflammation, macrophages and other cells start generating NO without needing any iNOS activator.

After generation, NO exists in tissues only for 4–10 seconds due to its rapid reaction with O_2 to form nitrites (NO_2), and with metalloproteins, especially with Hb, to produce nitrates (NO_3), both of which are excreted in urine. Exposed to reactive oxygen species superoxide, NO reacts very avidly to form peroxynitrite, a highly reactive oxidant. Produced in excess, peroxynitrite leads to lipid peroxidation, DNA damage and other cytotoxic effects. Superoxide dismutase, a superoxide scavenger, enhances and prolongs NO action.

Actions and roles of NO

1. *Vascular system:* Nitric oxide is a potent vasodilator and serves to regulate vascular tone. Produced in the endothelium it freely diffuses to the nearby smooth muscle cell and activates a soluble guanylyl cyclase (sGC) raising cytosolic cGMP concentration (Fig. 37.2). This in turn activates a cGMP-dependent protein kinase (PKG) which dephosphorylates the myosin light chain kinase (MLCK) → reduced availability of phosphorylated (active) MLCK so that actin-myosin interaction is interfered resulting in muscle relaxation. The PKG also phosphorylates membrane Ca^{2+} channels reducing influx of Ca^{2+}→ decreased availability of Ca^{2+}-calmodulin complex further interferes with MLCK-mediated actin–myosin interaction, promoting muscle relaxation.

As already described, NO mediates the vasodilator action of endogenous vasodilators like ACh, bradykinin, etc. There is some evidence that deficient NO production plays a role in the development of hypertension. Bronchial, gastrointestinal and other visceral smooth muscles are also relaxed by NO, but the effect is less marked than in blood vessels.

2. *Platelets:* Just as in smooth muscle, NO activates the cGMP pathway in platelets to inhibit aggregation and thrombus formation. Defective endothelial and platelet NOS-NO function increases the risk of thrombosis. NO also has antiatherogenic property. Adhesion of leucocytes to the endothelium and cellular proliferation/migration are suppressed by NO, conferring it a protective effect on plaque formation. Defective NO generation is implicated in the development of atherosclerosis.

3. *Infection, inflammation and immune function:* Normally the iNOS activity in macrophages, etc. is very low. Bacterial endotoxins, TNFα, interferon and interleukins induce iNOS in macrophages and other inflammatory cells which then generate large quantities of NO. Activated macrophages also produce superoxides that combine with NO to form peroxynitrite which decomposes to release free redicals that have broad antimicrobial action on bacteria, viruses, fungi and protozoa. Thus, NO helps in combating infection. NO has many proinflammatory actions, *viz.* vasodilatation, increased vascular permeability and enhanced PG production. On the other hand, excess and prolonged NO production has detrimental consequences by promoting tissue injury. Raised iNOS and NO levels have been found in bronchial epithelium of asthma patients, in mucosal lesions of inflammatory

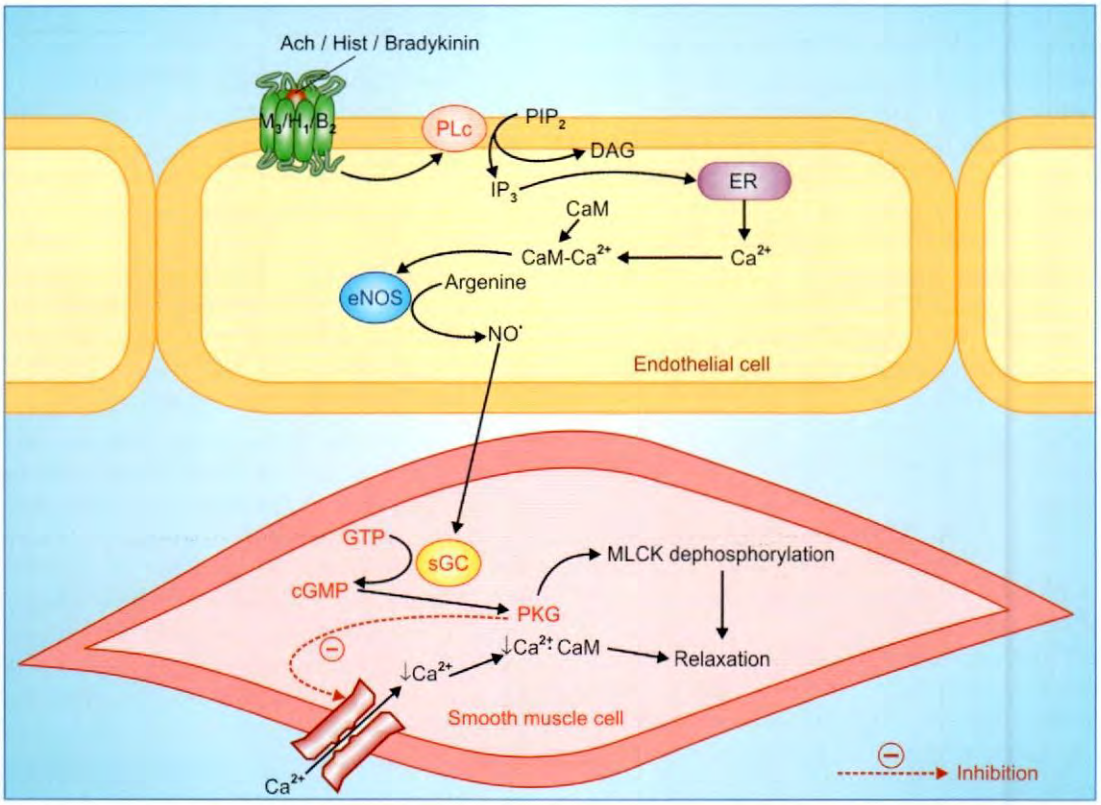


Fig. 37.2: Schematic depiction of major steps in endothelium-dependent vasodilatation and role of nitric oxide (NO) GPCR—G-protein coupled receptor ($M_3/H_1/B_2$); PLC—Phospholipase C; PIP_2—Phosphatidyl inositol bisphosphate; DAG—Diacylglycerol; IP_3—Inositol trisphosphate; eNOS—endothelial nitric oxide synthase; sGC—soluble guanylyl cyclase; PKG—Protein kinase G; MLCK—Myosin light chain kinase.

bowel disease (IBD) and in many other chronic inflammatory conditions.

Excessive production of NO has been implicated in causing severe hypotension attending septic shock. Sepsis induces iNOS in inflammatory cells as well as in many other types of cells which produce massive amount of NO over long periods, contributing to the sustained and refractory fall in BP (*see* box). However, use of drugs which check NO production has not yet yielded survival benefit in septic shock.

Major actions of Nitric Oxide

- Relaxes vascular and visceral smooth muscle
- Prevents platelet aggregation
- Serves as neurotransmitter in brain and periphery
- Mediates microbicidal action of macrophages
- Plays a role in inflammatory diseases, septic shock, pulmonary arterial hypertension, etc.

4. *Nervous system:* Nitric oxide serves as neurotransmitter/neuromodulator in central as well as in peripheral nervous system. Both nNOS and eNOS are expressed in the central neurones, but unlike other transmitters, there are no preformed stores of NO. It is synthesized on demand and released by diffusion (not exocytosis). NO is released

at many neuronal sites in the brain, the most prominent of which is the excitatory glutamate neurones. Activation of NMDA glutamate receptors causes long-lasting Ca^{2+} influx triggering NO release. Several functions are ascribed to NO in the brain, *viz.* nociception, increased cerebral blood flow, learning and memory. NO is believed to mediate 'synaptic plasticity' a process by which junctional transmission is strengthened in a use dependent manner. This is achieved by retrograde diffusion of post-junctional NO to enhance prejunctional transmitter release. Excessive production of NO has been implicated in promoting 'excitotoxicity' due to over- stimulation of glutamate neurones. Aberrant NO generation has been ascribed a causative role in degenerative neurological diseases like Huntington's disease, Parkinsońs disease, amyotrophic lateral sclerosis, etc.

In the genitalia and g.i. tract, certain nonadrenergic noncholinergic (NANC) neurones function by releasing NO. It is now established that pelvic nerve stimulation causes penile erection by releasing NO from NANC neurones in the corpora cavernosa. NO relaxes cavernosal smooth muscle, filling the sinusoids with blood and causing penile tumescence (*see* p. 327). Accordingly, sildenafil and other PDE-5 inhibitors are effective in the treatment of erectile dysfunction, because they inhibit degradation of cGMP which mediates NO action. NO appears to play a role in relaxing pyloric sphincter and facilitating gastric emptying. Defective NO signaling is believed to be involved in pyloric stenosis and gastric dilatation.

5. *Lungs:* NO appears to play a prominent role in the regulation of pulmonary vascular resistance and the development of pulmonary arterial hypertension (PAH). Sildenafil, the PDE-5 inhibitor which indirectly potentiates the vasodilator action of NO by preventing inactivation of cGMP, causes marked reduction in pulmonary artery pressure, and is the drug of choice for PAH (*see* p. 328). Inhalation of diluted NO gas also lowers pulmonary artery pressure in PAH, and is the 1st line therapy in newborns with severe respiratory distress and raised pulmonary artery pressure. Inhaled NO relaxes bronchial smooth muscle as well.

Nitric oxide donors

These are compounds which contain a NO or similar moiety in their structure, that is released in the body, mostly enzymatically, to elicit smooth muscle relaxation. Organic nitrates, nitrites and sodium nitroprusside are the clinically useful NO donors. They are also called 'nitro-dilators'. However, the pattern of vasodilatation produced by different NO donors differs according to the NO species that is released and the mechanisms involved in the release process.

Glyceryl trinitrate (GTN): It is a rapidly acting antianginal drug (*see* Ch. 40) which mainly dilates veins and coronary arteries. Mitochondrial aldehyde dehydrogenase is the most important enzyme which releases NO from GTN. This enzyme is abundantly expressed in veins, offering an explanation for the preferential venodilator action of GTN.

Isosorbide dinitrate and *Isosorbide mononitrate* generate a related NO species by process/enzymes that are not well characterized. They are slower acting, but the pattern of action is similar to GTN. When administered continuously, organic nitrates produce rapidly developing tolerance (within few hours), which also weans off rapidly. Though the processes involved in rapid nitrate tolerance are incompletely understood, it is believed that the reactive oxygen species generated during metabolism of organic nitrates inhibit mitochondrial aldehyde dehydrogenase and other enzymes which produce the NO species, limiting further action.

Platelets do not have the enzymes to denitrate GTN and other nitrates. Therefore, organic nitrates

do not significantly inhibit platelet aggregation. This is in contrast to NO, which has potent antiaggregatory action.

Amyl nitrite: It is the only organic nitrite that was used for angina pectoris. Inhaled amyl nitrite rapidly dilated both veins and arteries, including coronaries, and produced throbbing headache. Like nitrates, it also needs conversion to a NO species, but the enzymatic mechanism has not been elucidated. Nitrate-like rapid tolerance has not been observed with amyl nitrite.

Sodium nitroprusside: Administered by i.v. infusion, nitroprusside equally dilates arterioles and veins by releasing NO as well as by directly activating guanylyl cyclase. It rapidly lowers BP and the action is titratable. The breakdown of nitroprusside into NO and CN moieties is both enzymatic and non-enzymatic; the latter by reaction with glutathione (*see* Ch. 41). Not only endothelial cells, but RBCs and some other cells can split nitroprusside. However, the enzymes involved have not been identified. Nitrate-like tolerance is absent even after continuous infusion. The released CN moiety is detoxified by forming thiocyanate, which is excreted slowly. Toxic amount of thiocyanate may accumulate if nitroprusside infusion is prolonged.

Nitic oxide as a therapeutic agent: Apart from being an important signal molecule, exogenously administered NO gas has limited therapeutic application as well. Inhaled NO is indicated in severe respiratory distress in neonates with elevated pulmonary arterial pressure. It dilates pulmonary vessels, particularly in areas of the lung that are better ventilated, reducing the ventilation-perfusion mismatch and improving gaseous exchange. The elevated pulmonary artery pressure is lowered and cardiopulmonary function is improved. Inhaled NO improves cardiopulmonary function in adult patients as well with severe PAH, but this can only be a short-term measure.

VASOACTIVE PEPTIDES

Over the past 50 years it has been realized that a large number of peptides are utilized by the body as signal molecules in the nervous system as well as for other cell-to-cell communications. Some of these have pronounced direct effects on the vasculature, and may be termed 'Vasoactive peptides'. These may be grouped into those which constrict and those which dilate blood vessels.

Vasoconstrictor peptides	*Vasodilator peptides*
1. Angiotensin II (Ang II)	1. Bradykinin and Kallidin (Kinins)
2. Vasopressin (AVP, ADH)	2. Natriuretic peptides (ANP, BNP)
3. Endothelins (ET)	3. Vasoactive intestinal peptide (VIP)
4. Neuropeptide Y (NPY)	4. Substance P
5. Urotensin	5. Calcitonin gene-related peptide (cGRP)
	6. Adrenomedullin

Angiotensin II (Ch. 36) and Vasopressin (Ch. 43) are considered in other chapters.

VASOCONSTRICTOR PEPTIDES

Endothelins (ETs)

Endothelins are three (ET-1, ET-2, ET-3) closely related 21 amino acid peptides having potent vasoconstrictor action. Vascular endothelium primarily generates ET-1 which is functionally the most relevant ET. It is also produced by nervous tissue, lungs, kidney, breast, endometrium and some other cells, while ET-2 and ET-3 have been located in kidney, brain and intestines. ET-1 is synthesized in the endothelial (and other) cells as a larger peptide called *prepro- endothelin-1 (prepro ET-1),* which is broken down first to a 38 amino acid peptide named '*Big ET-1*' and then by an *endothelin converting enzyme (ECE)* to ET-1 (*see* Fig. 37.3). Control of ET-1 synthesis is exercised at the level of expression of prepro ET-1 gene; synthesis is enhanced by transforming growth factor β (TGFβ), cytokines (mainly IL-1) and vasoconstrictors like angiotensin II, vasopressin (AVP). On the other hand, vasodilators like NO, prostacyclin (PGI_2) and atrial natriuretic peptide (ANP) suppress production of prepro ET-1. Synthesis of prepro ET-1 is immediately translated into ET-1 production and release from the cell.

Though ET-1 is released into the circulation, it primarily acts locally to serve as *paracrine*

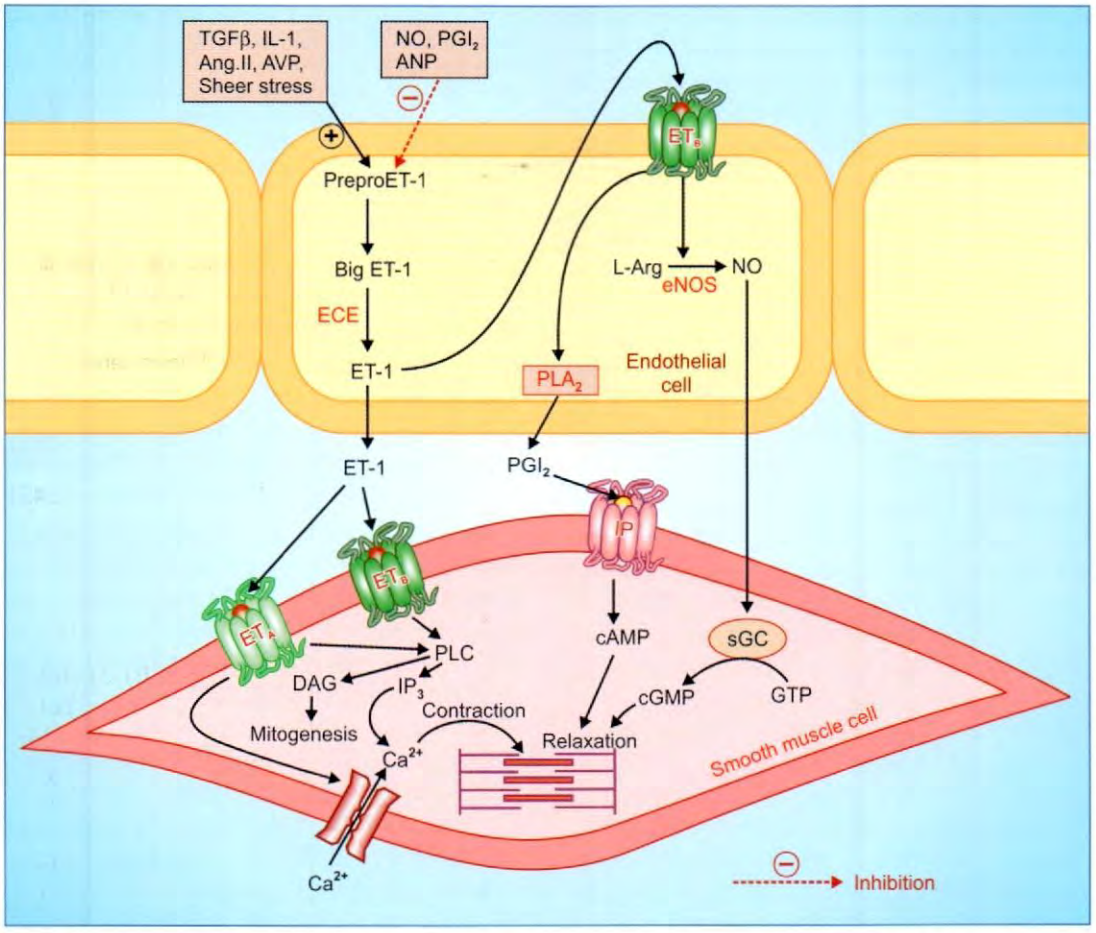


Fig. 37.3: Schematic depiction of endothelin-1 (ET-1) production in the endothelium, and its direct contractile (through ET_A + ET_S receptors), and indirect relaxant (through ET_B receptors) effects on vascular smooth muscle ECE—Endothelin converting enzyme; Ang II— Angiotensin II; TGFβ—Transforming growth factorβ; AVP—Argenine vasopressin; PGI_2— Prostacyclin; IP—prostacyclin receptor; ANP— Atrial natriuretic peptide; L-Arg—L-argenine; NO—Nitric oxide; sGC— soluble guanylyl cyclase; cGMP—cyclic GMP; cAMP—cyclic AMP; IL-1—Interleukin; PLA_2—Phospholipase A_2; eNOS—Endothelial nitric oxide synthase; IP_3— Inositol trisphosphate; DAG— Diacylglycerol.

or even *autocrine* signal molecule. ETs are rapidly cleared from blood (t½ 4–7 minutes) by peptidases in lungs and kidneys as well as by receptor binding.

Actions and roles of endothelins

The most prominent action of ET-1 is pronounced and relatively long lasting vasoconstriction in most vascular beds, including pulmonary, renal and coronary arteries. However, i.v. injection of ET-1 initially causes brief fall in BP (due to release of NO and P GI_2 from the endothelium) followed by more marked and sustained rise in BP due to direct action on arterial smooth muscle. ET-1 also increases heart rate and cardiac contractility which contributes to the rise in BP. Constriction of renal vessels reduces GFR and urine output. Acting on adrenals, ET-1 promotes aldosterone release which contributes to the salt and water retaining action. Action

of ET-1 in the lungs causes bronchoconstriction and rise in pulmonary artery pressure. Mitogenic action of ET-1 promotes proliferation of vascular smooth muscle, cardiac myocyte and perivascular fibroblasts as well as other connective tissue cells.

There is now evidence that ETs play a role in the regulation of BP in humans. Sustained overproduction of ETs has been implicated in the genesis of pulmonary arterial hypertension (PAH), systemic hypertension, cardiac and vascular hypertrophy, atherosclerosis, coronary artery disease, asthma and chronic renal disease. ET-1 levels are elevated in chronic heart failure, and this may contribute to the impairment of cardiac contractility.

Endothelin receptors: Two types of ET receptors have been identified, ET_A and ET_B. Both are GPCRs. The ET_A receptor is distinguished by its higher affinity for ET-1 compared to ET-2 or ET-3, whereas all 3 ETs have similar affinity for the ET_B receptor. Vascular and other smooth muscles express mainly ET_A and few ET_B receptors. Activation of both results in PLc—IP_3/DAG—Ca^{2+} release mediated contractile response (Fig. 37.3). On the other hand, vascular endothelium expresses ET_B receptor, activation of which indirectly elicits vasodilatation by releasing NO and PGI_2.The transient initial vasodepressor response to i.v. ET-1 is due to this action. Sustained activation of both ET_A and ET_B receptors is mitogenic and results in vascular/cardiac myocyte, perivascular fibroblast and other connective tissue cell hyperplasia. Several organs, *viz* adrenals, kidney, intestines and brain express more ET_B than ET_A receptors.

Endothelin receptor antagonists (ERAs): Characterization of ET_A and ET_B receptors and appreciation of the etiological role of ETs in several cardiovascular and pulmonary disorders prompted efforts to develop ERAs, and have resulted in the approval of 3 ERAs for clinical use over the past 15 years. Though these ERAs are being tried in several conditions, the only approved indication so far is pulmonary arterial hypertension (PAH).

PAH is an uncommon condition characterized by severe remodeling of small pulmonary arteries causing rise in pulmonary artery pressure above 25 mm Hg, right heart failure and early death. Etiologically, it may be idiopathic, heritable, or PAH associated with connective tissue disease or HIV infection or that due to congenital heart disease, etc. ET_A receptors are richly expressed in pulmonary artery smooth muscle, airway muscle and lung fibroblasts, more so in PAH patients. ET-1 is a potent pulmonary vasoconstrictor and smooth muscle mitogen. ERAs and drugs that augment NO (sildenafil) or PGI_2 (epoprostenol) action are the mainstay in the treatment of PAH. However, therapy with these drugs is only palliative.

ERAs can be divided into:

Dual ET_A-ET_B antagonist: Bosentan, Macitentan

Selective ET_A antagonist: Ambrisentan

Sitaxsentan another selective ET_A blocker has been withdrawn due to fatal hepatotoxicity.

Both dual ERAs and selective ET_A antagonist produce similar pharmacodynamic effects. In PAH patients they lower pulmonary artery pressure, improve haemodynamic parameters and increase exercise capacity. Follow up of patients in clinical trials has shown that risk of worsening of clinical condition in PAH patients is decreased and deterioration delayed. Significant reduction in mortality compared to placebo is also reported. Efficacy of all 3 ERAs is comparable, but they differ in pharmacokinetics, drug interaction potential and tolerability. All ERAs are nonpeptide and orally effective.

Bosentan: It is the first ERA to be approved for clinical use. Chemically it is a sulfamide and dual ET_A-ET_B antagonist. Both initial depressor and subsequent pressor response to i.v. ET-1 is blocked. Oral bioavailability of bosentan is ~50%. It is metabolized in liver by CYP2C9 and CYP3A4, and excreted in bile; plasma t½ is 6 hours. One of the metabolites is active. No dose adjustment is needed in renal disease, but it is contraindicated in liver disease, because it causes dose-dependent elevation of hepatic aminotransferases and carries risk of hepatic injury. Monthly monitoring of liver function test is mandatory. Bosentan induces microsomal CYP2C9 and CYP3A4 isoenzymes, and can interact with many drugs, including warfarin, oral contraceptives, glibenclamide and simvastatin.

It auto-induces own metabolism; the initial dose of 62.5 mg BD is mostly doubled to 125 mg BD after 4 weeks. Ketoconazole doubles blood levels of bosentan, and rifampin lowers its blood level. Due to the above problems, the other ERAs have overtaken bosentan.

BOSENTAS, LUPIBOSE, BOZTAN 62.5, 125 mg tabs.

Ambrisentan: Developed after bosentan, it is the only selective ET_A receptor antagonist currently available, and has the theoretical advantage of retaining the vasodilator function through the ET_B receptor. However, no enhancement of clinical efficacy has been demonstrated. It is not a sulfamide derivative, and carrys a low risk of hepatic aminotransferase elevation. Ambrisentan is rapidly absorbed with oral bioavailability of 90%; metabolized by CYP3A4 and glucuronidation. It is excreted mainly in bile; only 20% in urine. The t½ is 12–15 hours, permitting once daily dosing. It is not an enzyme inducer, has low potential for drug interactions (contrast bosentan); has been safely given with warfarin, sildenafil and oral contraceptives without dose modification.

Ambrisentan is generally well tolerated; peripheral edema is the most common side effect. In clinical trials liver enzymes were raised only in 2% patients. This was reversible and comparable to that with placebo.

Ambrisentan has been combined with tadalafil (a PDE-5 inhibitor), and this has improved efficacy as well as reduced the risk of clinical failure (AMBITION trial) in PAH patients.

Dose: 5–10 mg OD.

PULMONEXT, AMBRICAN, ENDOBLOC, ZAMBRI 5 mg, 10 mg tabs.

Macitentan: It is a new dual ERA with higher affinity for ET_A than for ET_B receptors. Macitentan has been found to bind tightly to the ETa receptor producing unsurmountable blockade, which probably contributes to its enhanced activity. Oral absorption of macitentan is slow, takes 8–10 hours. It is oxidized by CYP3A4 to an active metabolite which has a much longer t½ than the 17 hours t½ of macitentan itself. Excretion is largely urinary and the remaining in bile. No clinically relevant drug interactions have been noted with macitentan despite its enzyme inducing potential. No modification of warfarin and sildenafil (which are also given in PAH) dose was needed. In clinical trials it has reduced mortality in PAH patients by 45%, and is approved both for monotherapy as well in combination with a PDE-5 inhibitor or i.v. epoprostenol (PGI_2). Macitentan has a good tolerability profile; frequent side effects are headache, nasopharyngitis and anaemia.

Peripheral edema and aminotransferase elevation were similar to placebo group.

Dose: 10 mg OD.

Adverse effects of ERAs

The *general side effects* of ERAs are due to their vasodilator property, producing headache, nasal congestion, flushing and palpitation. Peripheral edema is common, especially with ambrisentan.

Elevation of aminotransferase levels is the major adverse effect, more common with bosentan, but is reversible. With ambrisentan and macitentan, the incidence is similar to that with placebo.

Anaemia: A mild (0.5–0.8%) lowering of Hb% and haematocrit occurs with all ERAs. It is probably due to fluid retention and haemodilution.

Teratogenicity: All ERAs are teratogenic in animals. In clinical trials, ERAs have not been given to pregnant women, and there is no human data, but all ERAs are contraindicated in pregnancy.

Orally administered ERAs are now a first line well tolerated option for the treatment of PAH of various etiologies. They compare favourably with oral PDE-5 inhibitors (sildenafil, tadalafil) and can be combined with them for enhanced efficacy. Continuous long term i.v. infusion of epoprostenol (PGI_2 analogue) has been shown to afford relief as well as reduce mortality in PAH cases nonresponsive to oral

medication or those with severe (functional class III or IV) disease.

ERAs are also being evaluated for use in refractory chronic heart failure.

Neuropeptide Y (NPY)

Neuropeptide Y (NPY) first isolated from pig brain in 1982, is one of the most abundant neuropeptides in the brain and is also present in peripheral sympathetic nerves. It is the leading member of a family of three 36 amino acid peptides, the other two are *pancreatic polypeptide (PP)* and *peptide YY (PYY)*. While NPY is a neurotransmitter, PP and PYY are hormones. PP is secreted by pancreatic islets in response to food ingestion and acts in the CNS as well as on gut to suppress appetite, delay gastric emptying and promote fuel utilization. Hormonal cells in the ileum secrete PYY according to the quantity of food, and it serves to regulate appetite.

In the periphery NPY is mainly localized in the sympathetic nerves, especially those innervating blood vessels. It is stored in separate synaptic vesicles than those storing NA (*see* Fig. II.3B). Nerve impulse releases NPY along with NA, and it appears to serve both as transmitter as well as cotransmitter (*see* p. 108). NPY exerts postjunctional as well as prejunctional actions. The postjunctional action in the vasculature is a direct slow but longlasting contractile effect, as well as potentiation of NA-induced vasoconstriction. The prejunctional action is inhibition of nerve impulse induced transmitter release. Not only NA release from sympathetic nerve endings, but also ACh release from parasympathetic nerves is attenuated.

NPY causes vasoconstriction in nearly all vascular beds, especially renal and cerebral vessels. It has a direct positive inotropic and chronotropic effect on heart and increases Na^+ and water excretion by the kidney, despite renal vasoconstriction. In the brain, NPY is present in several cortical and subcortical areas and plays a key role in regulating food intake (NPY strongly promotes feeding), energy homeostasis, stress response, autonomic out flow, HPA axis activation and several other functions. The presynaptic action of NPY in the brain is to inhibit release of various neurotransmitters, *viz.* NA, DA, 5-HT, glutamate, GABA, as well as that of hypothalamic GnRH, AVP and oxytocin.

NPY receptors: In humans, four types of Y receptors (Y_1, Y_2, Y_4, Y_5) have been characterized for NPY and related peptides, of which NPY has high affinity for three (Y_1, Y_2, Y_5), while Y_4 has preferential affinity for PP; so that it may be regarded as PP receptor. The original Y_3 receptor is now considered to be CXC chemokine receptor and not a Y receptor. All Y receptors are GPCRs, which transduce their response by raising cytosolic Ca^{2+} or by inhibiting adenylyl cyclase. The vasoconstrictor and other peripheral post junctional actions of NPY are mediated mainly by Y_1 receptor, while Y_2 is the prejunctional receptor for NPY in the periphery as well as in the brain. Both Y_1 and Y_2 receptors are expressed in many areas of the brain. The Y_5 receptor is restricted to the brain, in areas which control food intake or hypothalamo-pituitary function and in limbic areas.

Several selective nonpeptide Y_1 receptor antagonists have been produced which block vasoconstrictor action of NPY. Their use has indicated that NPY is probably not involved in the regulation of normal BP or cardiac function, but that it may play a role in the development of hypertension or heart failure. Selective Y_2 and Y_5 antagonists have also become available for investigation. Some of the Y_1 and Y_5 antagonists are orally active and have undergone limited clinical trial as antiobesity agents, but none has been approved for clinical use.

Urotensin II (UII)

Urotensin II (UII) is a 11 amino acid cyclic vasoconstrictor neuropeptide identified in 1980 from the urophysis of teleost fish and later demonstrated to be present in mammals including humans. It has been located in the cholinergic neurones of the brainstem and spinal cord as well as in kidney, heart and lungs. UII strongly contracts arterial smooth muscle with less effect on veins, and depresses the heart. A variety of other actions on the CNS as well as on peripheral organs have been shown, but their physiological relevance is uncertain. Though UII circulates in blood, it does not appear to play significant role in the regulation of BP.

The receptor for UII has been identified as a cell surface GPCR and named *UT receptor*. It is coupled to Gq protein and produces vasoconstriction (as well as other effects) through the IP_3/DAG – intracellular Ca^{2+} release pathway. The UT receptor is widely expressed in the CNS, heart, blood vessels, lung, kidney and adrenal medulla.

Though UII appears to be physiologically unimportant in man, it may play a role in certain cardiovascular

and other diseases. Raised UII levels have been noted in hypertension, advanced heart failure, diabetic renal failure, etc. Many peptide and nonpeptide UT receptor antagonists have been produced, and some have been clinically tested, particularly in diabetic nephropathy and in asthma, but none has been developed as a drug.

VASODILATOR PEPTIDES

Bradykinin and Kallidin (Plasma kinins)

Plasma kinins are polypeptides split off from a plasma globulin *Kininogen* by the action of specific enzymes *Kallikreins*. The two important plasma kinins, *Kallidin* (decapeptide) and *Bradykinin* (nonapeptide) were discovered around 1950 by two independent lines of investigation into the hypotensive activity of urine and certain snake venoms. These and some other biological fluids were found to act indirectly: they contained enzymes which generated vasodilator substances in the plasma.

Kinins are generated by proteolytic reactions triggered by tissue injury, inflammation, allergic reaction, etc., and play important mediator roles.

Generation and metabolism Kininogens are α_2 globulins present in plasma which also contains inactive kininogenase *prekallikrein*.

Prekallikrein is activated by Hageman factor (factor XII) which itself is activated by tissue injury and contact with surfaces having negative charge, e.g. collagen, basement membrane, bacterial liposaccharides, urate crystals, etc. *Plasmin* facilitates contact activation of Hageman factor (Fig. 37.4). Kinins are also generated by trypsin, proteolytic enzymes in snake and wasp venoms and by kallikrein present in kidney, pancreas and other tissues. Bradykinin is generated from high molecular weight (HMW) kininogen by the action of plasma kallikrein, because HMW-kininogen does not cross the capillaries. On the other hand, kallidin can be produced from both low molecular weight (LMW) kininogen as well as HMW-kininogen by the action of tissue kallikreins. Bradykinin can also be generated from kallidin on the removal of lysine residue by an aminopeptidase.

Plasma and tissues also contain kininogenase inhibitory factors of which *complement (C1) esterase inhibitor (C1 Inh)* is the most important. Moreover, kallikreins are normally present in their inactive zymogen forms. Thus, physiologically only small amounts of kinins are generated in plasma and tissues.

Kinins are very rapidly degraded, primarily in lungs, but also in other tissues and have a t½ of < 1 min. The principal degrading enzyme is *Kininase* II, also known as 'angiotensin-II converting enzyme' (ACE) which splits off 2 amino acids from the carboxyterminal of the peptide chain. Another carboxypeptidase *Kininase I* removes only one amino acid (arginine) producing selective B_1 receptor agonistic metabolites (desArg bradykinin and desArg kallidin) which are further degraded by other peptidases.

Actions

Bradykinin and kallidin have similar actions.

1. *Blood vessels* Kinins are more potent vasodilators than ACh and histamine. The dilatation is mediated through endothelial NO and PGI_2 generation, and involves mainly the arterioles. In contrast, large arteries, most veins and

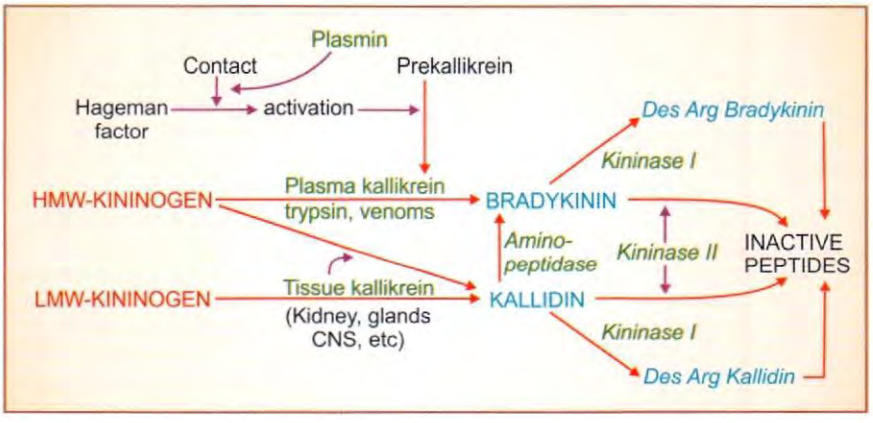


Fig. 37.4: Generation and degradation of bradykinin and kallidin
HMW—high molecular weight; LMW—low molecular weight.

vessels with damaged endothelium are constricted by direct action of kinins on the smooth muscle. In addition, they can release histamine and other mediators from mast cells. Injected i.v. kinins cause flushing, throbbing headache and fall in BP. They markedly increase capillary permeability due to separation of endothelial cells → exudation and inflammation occurs if they are injected in a tissue. Intradermal injection produces wheal and flare (similar to histamine).

Kinins have no direct action on heart; reflex stimulation occurs due to fall in BP.

2. *Smooth muscle* Kinins induce contraction of intestine which is characteristically slow (*bradys*—slow, *kinein*—to move). They cause marked bronchoconstriction in guineapigs and in asthmatic patients. Action on other smooth muscles is not prominent. Some smooth muscles may be relaxed.

3. *Neurones* Kinins strongly stimulate nociceptive afferents and produce a burning sensation. Applied to blister base or injected intraperitoneally or in the brachial artery, bradykinin produces intense, transient pain and has been used in analgesic testing.

Kinins release CAs from adrenal medulla. Injected directly in brain they produce a variety of effects including enhanced sympathetic discharge. They increase permeability of the blood-brain barrier.

4. *Kidney* Kinins increase renal blood flow as well as facilitate salt and water excretion by action on tubules. The diuretic effect of furosemide is reduced by kinin B_2 receptor antagonists, indicating participation of locally generated kinins in this response.

Kinin receptors Existance of two types of kinin receptors (B_1, B_2) has been established. Both are GPCRs. Bradykinin and Kallidin are selective agonists of B_2 receptors, while their des-Arg metabolites generated by the action of kininase I are selective agonists of B_1 receptor. Most of the kinin actions in noninflamed tissues are mediated by B_2 receptors which are constitutively present on:

- Visceral smooth muscle—contraction of intestine, uterus, airway.
- Vascular endothelium—NO release, vasodilatation, increased permeability.
- Sensory nerves—acute pain.

The B_2 receptor is coupled to Gq and Gi proteins which utilizes the phospholipase C—IP_3/DAG—intracellular Ca^{2+} mobilization transducer mechanism. Endothelial NO synthase (eNOS) is activated causing vasodilatation. Certain responses to kinins, e.g. bronchoconstriction, renal vasodilatation and activation of pain nerve endings appear to be mediated by stimulation of phospholipase A and generation of PGs at the local site. The activated Gq protein also mediates production of NFκB which triggers MAP kinase pathway leading to generation of proinflammatory mediators.

The B_1 kinin receptors are minimally expressed in normal tissues, but are induced by inflammation and colocalize with kininase I enzyme, so that the B_1 agonistic des-Arg kinins are produced at the same site. Activated B_1 receptor also transduces through Gq and Gi proteins and cause contraction of veins, large vessels, enhanced PG synthesis, leukocyte recruitment, generation of inducible NOS (iNOS) and chronic pain in inflammed tissues.

Pathophysiological roles

1. *Mediation of inflammation* Kinins produce all the signs of inflammation—redness, exudation, pain and leukocyte mobilization. Tissue injury can cause local kinin production which then sets in motion the above defensive and reparative processes. Activation of B_1 receptors on macrophages induces production of IL-1, TNF-α and other inflammatory mediators.

2. *Mediation of pain* By directly stimulating pain nerve endings and by increasing PG production, kinins appear to serve as mediators of pain. The B_2 antagonists block acute pain produced by bradykinin, but induced B_1 receptors appear to mediate pain of chronic inflammation.

3. *Functional hyperemia* (in glands during secretion) and *regulation of microcirculation*—especially in kidney may be occurring through local kinin production.

4. *Hereditary angioedema* This rare hereditary disorder is due to quantitative or functional deficiency of C-1 esterase inhibitor which is the most important natural kininogenesis inhibitor. As a result plasma bradykinin levels rise manifesting as unpredictable episodes of swelling of lips, tongue, face, respiratory and g.i. tracts, hands, feet, etc. Inhibitors of kinin production and B_2 kinin receptor antagonists afford, symptomatic relief.

5. Kinins appear to play no significant role in the regulation of normal BP. However, they may serve to oppose overactive RAS and exert antiproliferative influence on cardiac and vascular muscle in hypertensive states.

Ischaemic preconditioning which limits tissue damage during myocardial infarction appears to involve kinins.

6. Kinins cause closure of ductus arteriosus, dilatation of foetal pulmonary artery and constriction of umbilical vessels. Thus, they may be involved in adjusting from foetal to neonatal circulation.

7. Kinins play a major role in the development of angioedema. They also appear to be involved in *shock, rhinitis, asthma, ACE inhibitor induced cough, carcinoid, postgastrectomy dumping syndrome,* fluid secretion in *diarrhoea, acute pancreatitis* and certain *immunological* reactions.

Because of evanescent and unpleasant actions, kinins have no clinical use.

Bradykinin antagonists

After characterization of B_1 and B_2 kinin receptors, and in view of prominent pathophysiological roles of kinins, several peptide and nonpeptide kinin antagonists have been produced and tested for clinical use. However, only one (Icatibant) has been marked so far in UK and Europe.

Icatibant: It is a synthetic decapeptide bradykinin B_2 receptor antagonist which is resistant to kinin degrading enzymes, and has a duration of action upto 6 hours after s.c. injection. It effectively reverses the swelling and other symptoms in hereditary angioedema, and is currently the best treatment option for this condition. Its utility in treating drug induced angioedema, burns, pancreatitis and other conditions involving kinins, is being explored.

A recent controlled trial has reported icatibant injected s.c. to be more effective in resolving ACE inhibitor induced angioedema than the standard therapy with i.v. prednisolone and an antihistaminic.

(Icatibant is marketed in UK, Europe as FIRAZYR 30 mg/3 ml prefilled syringe for s.c. injection in abdominal area). Compound 173657, comp. SSR 240612 and few other orally active nonpeptide B_2 antagonists have undergone trials and are being developed as analgesics, antiinflammatory drugs, and for treating pancreatitis, head injury, etc.

Natriuretic peptides (ANP, BNP, CNP)

Natriuretic peptides (NPs) are a family of 3 cyclic peptides, namely atrial NP (ANP), brain NP (BNP) and c-type NP (CNP), all having natriuretic, diuretic and vasodilator property. They have a common 17 amino acid ring with differing straight chains.

ANP: It is a 28 amino acid peptide produced, mainly by atrial myocytes; also by ventricles, certain neurones and lungs. ANP is the major circulating NP. Atrial and ventricular distention perceived by stretch receptors is the primary stimulus for ANP (also BNP) release, which is triggered by blood volume expansion, sympathetic stimulation (α_1 receptor mediated), AngII, endothelin, vasopressin and aldosterone as well. Plasma ANP level is raised in CHF, renal failure, primary aldosteronism and in inappropriate ADH secretion syndrome. ANP is synthesized in cardiac myocytes as a large peptide *prepro-ANP*, which is then split to *pro ANP* and finally to ANP which is released.

BNP: Produced mainly by ventricles, also by brain and some other organs, BNP exists in 2 forms—either 32 or 26 amino acids. It is also first synthesized as prepro BNP, and then broken down to BNP in 2 steps. Releasing stimuli for BNP are the same as for ANP, and the actions of the two peptides are identical. However, circulating levels of BNP are lower than those of ANP.

CNP: This 22 amino acid NP is produced mainly by vascular endothelium and neurones in the CNS; also by kidneys and intestines. Circulating levels of CNP are very low. The primary action of CNP is vasodilatation, while natriuresis and diuresis is mild. The physiological role of CNP is not clear.

Clearance of NPs: Occurs both by enzymatic degradation as well as by receptor mediated internalization followed by intracellular breakdown (see below).

A neutral endopeptidase (NEP; also called Neprilysin) present in kidney, lungs and liver rapidly degrades NPs. The plasma t½ of ANP is short (2–5 min in humans), BNP has a longer t½, (4–20 min) probably due to less efficient receptor mediated removal, while that of CNP is the shortest due to more marked receptor mediated removal.

Actions and roles: The NPs produce two major actions, *viz* vasodilatation and natriuresis-diuresis (*see* box), and are involved in the regulation of Na^+ and water balance, blood volume and arterial pressure. By directly dilating veins, NPs lower central venous pressure and preload on the heart, which tends to reduce cardiac output in normal subjects, but may improve it in decompensated heart. NPs also dilate arteries reducing systemic vascular resistance, and BP.

Vascular and renal actions of ANP/BNP

- Systemic arterial and venous dilatation
- ↓Sympathetic flow
  - ↓Venous pressure and preload on heart
  - ↓Systemic arterial pressure
- Natriuresis and diuresis
- ↑Renal blood flow
- ↑Glomerular filtration rate and filtration fraction
- ↓Proximal tubular Na^+ reabsorption
- ↓Renin release from kidney
  - ↓Plasma angiotensin II
  - ↓Plasma aldosterone

In addition to direct vasodilator action, NPs decrease sympathetic flow by acting in the CNS as well as by reducing NA release from sympathetic nerve terminals.

Acting on the kidneys, NPs increase renal blood flow, GFR and filtration fraction. They also decrease proximal tubular Na^+ reabsorption resulting in natriuresis and diuresis. Moreover, they inhibit renin release from the kidney which translates into lowered plasma AngII reducing aldosterone production. This also contributes to the natriuresis (Fig. 37.5). In contrast to furosemide and thiazide induced natriuresis, the ANP induced natriuresis is not accompanied by K^+ loss, because it also suppresses the renin-AngII-aldosterone mechanism. Lowered circulating AngII contributes to the hypotensive action as well.

Overall, the NPs seem to act as a counter regulatory system to the renin-AngII-aldosterone system to maintain blood volume and blood pressure homeostasis, as well as Na^+-K^+ balance.

NP receptors: The NPs act by combining with specific cell surface receptors, three subtypes of which have been identified, namely ANP_A (or NPR_1), ANP_B (or NPR_2) and ANP_C (or NPR_3).

ANP_A and ANP_B receptors: Both these receptors are transmembrane enzyme-linked receptors (*see* p. 58–59) and Fig. 4.8) which have guanylyl cyclase activity at the cytosolic domain and are

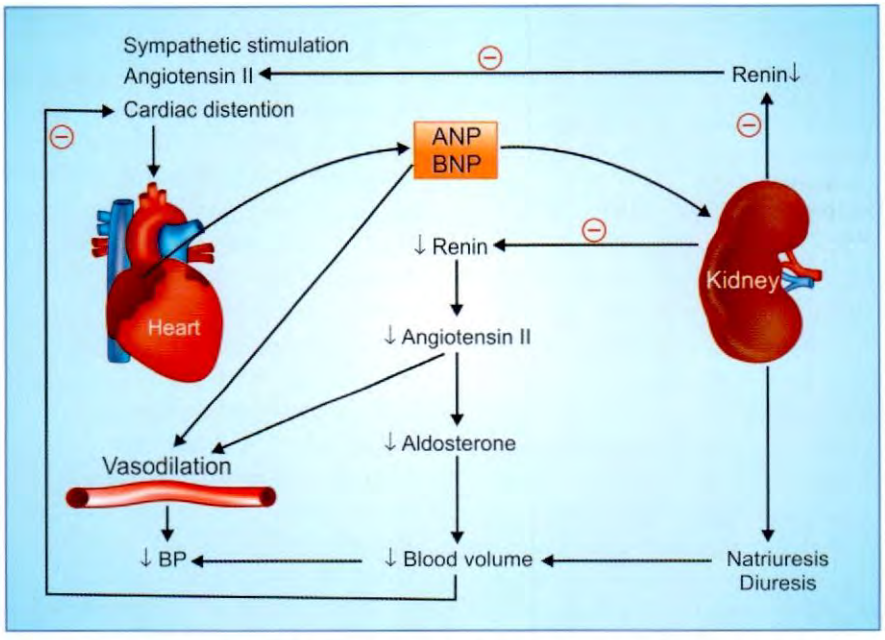


Fig. 37.5: Counter-regulatory operation of natriuretic peptides against the renin-angiotensin II-aldosterone system to maintain blood volume, blood pressure, salt and water homeostasis
ANP—atrial natriuretic peptide; BNP—brain natriuretic peptide.

located on the surface of target cells. Binding of ANP or BNP at the extracellular domain promotes receptor dimerization and activation of the guanylyl cyclase. The raised cytosolic cGMP activates PK_G which brings about vascular smooth muscle relaxation, natriuresis and other responses by lowering intracellular Ca^{2+} and dephosphorylating MLCK (*see* Fig. 40.3). While ANP_A receptor has equal affinity for ANP and BNP, the ANP_B subtype has high affinity for CNP and is involved mainly in causing vasodilatation.

ANP_C receptor: Located mostly on vascular endothelium, it primarily serves as a clearance receptor, and has equal affinity for ANP, BNP and CNP.

On binding the NP, the receptor dimerizes and is internalized. The peptide is broken down intracellularly and the receptor is returned to the surface. The ANP_C receptor is also linked to adenylyl cyclase inhibition and PL_C activation, but the physiological consequences of these are not well understood.

Clinical application: A recombinant form of BNP called *Nesiritide* is used clinically to a limited extent because of need for i.v. administration and brief life-span in the body. Continuous i.v. infusion of nesiritide is occasionally employed to treat severely decompensated patients of CHF. It benefits by causing natriuresis-diuresis, vasodilatation—reduction in cardiac pre- and after-load and lowering of renin-AngII-aldosterone levels. However, hypotension and renal injury are the risks, and cost is prohibitive.

Serial measurements of plasma BNP levels have been used to monitor progression of heart failure, and to assess response to therapy: levels fall with improvement.

Neutral endopeptidase (NEP; neprilysin) inhibitors: This is a new class of drugs which inhibit NEP enzymes that degrade NPs, bradykinin, substance P and adrenomedullin. By raising levels of natriuretic and vasodilator peptides they have potential utility in CHF. A nonpeptide NEP inhibitor *Sacubitril* has been approved (in 2015) for the treatment of class II to IV CHF when combined with the ARB valsartan.

Sacubitril: It is an orally active NEP inhibitor which increases the blood levels of NPs and other vasodilator peptides resulting in natriuresis, diuresis, vascular relaxation, lowering of AngII as well as aldosterone levels. Combined with valsartan, it affords symptomatic improvement in CHF patients. Sacubitril is a prodrug that is absorbed after oral ingestion and rapidly activated by esterases to *sacubitrilat*. The absolute oral bioavailability is 60%, and food does not alter absorption. Passage of sacubitrilat across blood-brain barrier is limited and it is not significantly metabolized further. Excreted in both urine and faeces, the plasma t½ of sacubitrilat is ~12 hours. No significant drug interactions with drugs generally used in CHF have been observed.

In a large multicentric randomized clinical trial (PARADIGM-HF, 2014), a 1:1 combination of sacubitril + valsartan (200 mg BD) was compared with enalapril (10 mg BD) in 8442 patients of class II to class IV CHF already receiving CHF therapy with one or more of diuretics, β blockers and aldosterone antagonist. The sacubitril-valsartan combination caused 20% greater reduction in death or hospitalization for heart failure than enalapril. The most common side effects were hypotension, hyperkalemia and renal impairment. Angioedema was infrequent, and its tolerability profile was similar to enalapril.

Thus, sacubitril-valsartan appears to be a more effective and well tolerated alternative to ACE inhibitors for reducing morbidity and mortality in patients with advanced heart failure. However, it is expensive.

ENTRESTO, VYMADA 50, 100, 200 mg tabs. (containing 24 + 26 mg or 49 + 51 mg or 97 + 103 mg sacubitril + valsartan.

Vasoactive intestinal peptide (VIP)

First isolated from intestines this 28 amino acid neuropeptide is broadly expressed in the CNS, peripheral cholinergic and peptidergic neurones in the ANS, especially those innervating blood vessels, heart, intestines, pancreas, urogenital tract and in some immunological cells. VIP is also a cotransmitter with ACh in many parasympathetic nerves (*see* Fig. II.3, p. 108). It produces a slow, but long lasting response. Though present in circulation, the t½ of VIP in blood is very short (~ 2 min), and it appears to function mainly as a paracrine transmitter rather than as a hormone.

VIP is a potent vasodilator; coronaries and most vessels are dilated; BP falls on i.v. injection of VIP. Cardiac contractility and heart rate are increased. Intestinal, biliary, bronchial and genitourinary smooth muscle is relaxed. Secretion of salt and water across intestinal mucosa is increased; overactivation may cause watery diarrhoea. VIP promotes glycogenolysis in liver and appears to regulate certain metabolic processes. A role in modulating immune function has also been ascribed to VIP.

Two subtypes, $VPAC_1$ and $VPAC_2$ of VIP receptors have been designated. Both are GPCRs and are richly expressed in the CNS, heart, blood vessels, intestines, pancreas and immune cells. These GPCRs are linked to the Gs protein; vasodilatation, cardiac stimulation, smooth muscle relaxation and many other responses are mediated by adenylyl cyclase activation and generation of cAMP. Some other responses are produced *via* generation of IP_3 and mobilization of cytosolic Ca^{2+}.

Because of very short lifespan, VIP as such is not suitable for clinical use. Some stable analogues have been produced and their clinical application in cardiovascular, neurological, gastrointestinal and inflammatory diseases, as well as in COPD and diabetes is being explored, but none has been found satisfactory yet. VIP antagonists are also being investigated.

Substance P (SP)

A substance that contracted intestinal smooth muscle was detected in certain tissue extracts by Von Euler and Gaddum in 1931 and named substance P. Later it was found to be a 11 amino acid neuropeptide distributed widely in the brain, spinal cord, peripheral sensory nerves, enteric nervous system, blood vessels and skin. Two other related decapeptides *Neurokinin A (NKA)* and *Neurokinin B (NKB)* have also been found, and together they constitute the *Tachykinin* (contrast *bradykinin* which produces slow contraction) family. All three have similar actions, but SP is the dominant member. SP, NKA and NKB are produced by the cleavage of a large polypeptide *preprotachykinin* and all three serve as neurotransmitter or neuromodulator in the CNS as well as in the periphery, where SP is primarily associated with pain and inflammation.

Tachykinin receptors: SP and others act by binding to three subtypes of tachykinin receptors NK_1, NK_2 and NK_3; all of which are GPCRs coupled to Gq protein. The responses are transduced by generation of IP_3 and mobilization of intracellular Ca^{2+} triggering smooth muscle contraction, glandular secretion, release of NO and other messengers, cell proliferation, production of afferent impulse, etc. The NK_1 receptor (NK_1R) has the highest affinity for SP and serves as its major receptor. Binding of SP to NK_1R also leads to receptor internalization into endosomes where SP is degraded and the NK_1R is returned to the surface.

Actions and role of substance P: SP is a potent arteriolar dilator; acts on endothelial NK_1 receptors to release NO which than relaxes the underlying smooth muscle. Rapid fall in BP occurs when SP is injected i.v. Subcutaneous injection produces red spot, wheal and flare by local vasodilatation, exudation and axon reflex. However, veins are often contracted due to direct action on their smooth muscle. Intestinal, bronchial and other smooth muscles are rapidly and strongly contracted. Secretion from salivary glands and intestinal mucosa is increased. Acting on the kidney, SP promotes natriuresis and diuresis.

In the brain, SP and NK_1R are particularly localized in the hypothalamus, amygdala, periaqueductal gray, nucleus tractus solitarius (NTS), area postrema, and appear to be involved in mood, behaviour, anxiety, stress response, depression, reinforcement, nociception, etc. The chemoreceptor trigger zone (CTZ) and NTS express NK_1R along with $5\text{-}HT_3$ and other receptors which respond to noxious stimuli and coordinate the act of vomiting. It has been found that SP is released along with other mediators in response to tissue injury, especially that due to cancer chemotherapy and radiotherapy. The SP reaches CTZ and NTS which are not protected by blood-brain barrier and participates in triggering nausea and vomiting. Accordingly, the NK_1R antagonists have antiemetic property.

SP is involved in pain perception at various levels. It is elaborated by pain nerve endings in response to injury, and can trigger neurogenic inflammation. SP is released from primary pain afferents in the dorsal horn of spinal cord, and together with glutamate serves to transmit pain impulses. SP is one of the first responders to noxious stimuli. It initiates expression of cytokines which in turn induce SP and NK_1R, thus sustaining the reaction and inducing cellular proliferation. As such, SP has a role in inflammatory response. Recently, it has been found that SP and NK_1R, are richly

expressed on certain tumour cells, and that SP along with cytokines induced by it stimulate growth, proliferation and angiogenesis in these tumours. Thus, NK_1R antagonists may have potential utility in certain cancers.

SP (NK_1R) antagonists: Realizing the pathophysiological importance of SP, several nonpeptide orally active NK_1R antagonists have been produced and are being tested as potential drugs for anxiety, mood disorders, depression, inflammatory bowel disease, arthritis, eczema and cancer. However, the only drug that has succeeded clinically so far is *Aprepitant* (and its parenteral prodrug *Fosaprepitant*) which is being used as an adjuvant antiemetic for cancer chemotherapy induced vomiting and for postoperative nausea and vomiting (*see* Ch. 48).

Calcitonin gene-related peptide (CGRP)

Discovered ~30 years ago in medullary thyroid carcinoma, it is a 37 amino acid neuropeptide produced by alternative processing of the calcitonin gene. CGRP is co-located with calcitonin in the C cells of thyroid, but is primarily produced by neurones in the central and peripheral nervous system; also in enteric neurones, around blood vessels and in lungs. There are two (α and β) forms of CGRP which have similar biological activity, but are products of separate genes.

CGRP acts on an unusual type of receptor which has two parts, a *calcitonin receptor-like receptor (CLR)* and a *receptor activity modifying protein (RAMP)* needed for the receptor to function. CGRP is a very potent vasodilator which acts *via* the adenylyl cyclase—cAMP mechanism in the vascular smooth muscle, and not through endothelial NO release. Injected i.v. CGRP causes fall in BP and tachycardia by dilating arteries, especially coronaries. CGRP is released mainly from the sensory C and Aδ fibres (where it is mostly colocated with SP). The periarterial nerves are rich in CGRP, and it appears to serve both afferent (nociceptive) as well as efferent (neurogenic inflammation) function. CGRP is also found in the dorsal horn of spinal cord and may be an important link in pain transmission. Injected in the brain CGRP produces a variety of effects.

Several lines of evidences have pointed to a role of CGRP in migraine. It appears that sensory neurones of the trigeminal ganglion release CGRP around meningeal vessels—cause dilatation, plasma extravasation and mast cell degranulation→neurogenic inflammation is triggered and a migraine attack is precipitated. Cranial CGRP level is increased during migraine, and sumatriptan treatment normalizes it. CGRP injected i.v. has been found to produce headache in individuals susceptible to migraine.

Some peptide as well as nonpeptide CGRP antagonists have been produced, and two agents *olcegepant* and *telcagepant* have been tested clinically in migraine, and found to be effective. However, olcegepant has very low bioavailability, and telcagepant was withdrawn after phase III trial due to hepatotoxicity.

Erenumab It is a fully human monoclonal antibody which blocks CGRP receptor, and has been approved by US-FDA (May 2018) for prophylaxis of migraine. Administered as 70 mg once a month s.c. injection through a single-use prefilled autoinjector, erenumab (marketed as AIMOVIG inj.) significantly reduced the number of migraine days per month in those suffering 4-14 migraine days per month. In some patients the reduction in migraine days was > 50%, and few patients required a double dose (140 mg/month). Erenumab has been well tolerated; injection site reaction was the most common adverse effect.

A protective role of CGRP against development of hypertension has been proposed. Due to presence in enteric nervous system, CGRP has been implicated in visceral painful disorders like irritable bowel syndrome.

Adrenomedullin (AM)

Adrenomedullin (AM) is a 52-amino acid peptide belonging to the calcitonin family that was first obtained from human pheochromocytoma. It is now known to be present in normal adrenal medulla, hypothalamus, anterior pituitary, heart, lungs, blood vessels, kidneys and intestines, as well as circulates in blood. AM produces long-lasting vasodilatation in majority of vascular beds resulting in hypotension and reflex tachycardia. Direct cardiac stimulation and centrally mediated increased sympathetic outflow also occurs. Other actions are natriuresis and renin release.

The AM receptor is structurally and functionally very similar to the CGRP receptor, i.e. it is a GPCR consisting of a CLR part coupled to a subtype of RAMP. On activation by AM, the receptor interacts with Gs protein to increase cAMP production in target cells, including vascular smooth muscle, and releases NO from endothelium. Though the physiological significance of AM is still not defined, it has been hypothesized to be playing a counterbalancing role to the RAS and endothelin system. Raised AM levels have been found in systemic and pulmonary hypertension, CHF, kidney failure and in acute myocardial infarction, where AM may be serving as a protective mechanism. No AM based clinically useful drug has been developed so far.

Chapter 38 Cardiac Glycosides and Drugs for Heart Failure

CARDIAC GLYCOSIDES

These are glycosidic drugs having *cardiac inotropic* property. They increase myocardial contractility and output in a hypodynamic heart without a proportionate increase in O_2 consumption. Though other drugs are now more important in the treatment of congestive heart failure (CHF), the cardiac glycosides were the primary drugs till the 1970s, and are still valuable for many patients, when combined with others.

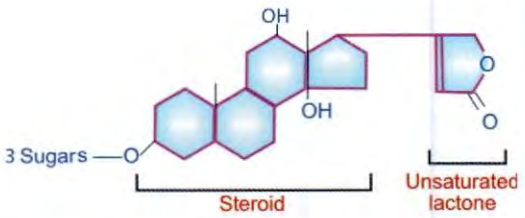
William Withering, a Birmingham physician, tried an extract of 'foxglove' (*Digitalis*) and found it to be remarkably effective in some cases of dropsy (edema). He published his classic monograph in 1785 and ascribed the beneficial effect to an action on the kidney. Cushney and Mackenzie, in the beginning of 20th century, established its action on the heart and its use in congestive heart failure (CHF).

Cardiac glycosides are found in several plants and in toad skin *(Bufotoxin)*. *Digitalis lanata* is the source of *Digoxin*, the only glycoside that is currently in use. Others like *Digitoxin* (from *Digitalis purpurea*) and *Ouabain* (from *Strophanthus gratus*), etc. are no longer clinically used or marketed.

By convention the term, 'Digitalis' has come to mean 'a cardiac glycoside'.

Chemistry

The cardiac glycosides consist of an *aglycone (genin)* to which are attached one or more *sugar* (glucose or digitoxose) moieties.



DIGOXIN

The aglycone consists of a cyclopentanoperhydrophenanthrene (steroid) ring to which is attached a 5 or 6 membered unsaturated lactone ring.

Pharmacological actions

All digitalis glycosides have qualitatively similar action. Digoxin is described as prototype.

1. Heart Digoxin has direct effects on myocardial contractility and electrophysiological properties. In addition, it has vagomimetic action, reflex effects due to alteration in haemodynamics and direct CNS effects altering sympathetic activity.

Force of contraction Digoxin causes a dose dependent increase in force of contraction of heart—a positive inotropic action. This is especially seen in the failing heart which is exquisitely sensitive. Systole is shortened, diastole is prolonged. When a normal heart is subjected to increased impedance to outflow, it generates increased tension so that stroke volume is maintained upto considerably higher values of

impedance (Fig. 38.1), while the failing heart is not able to do so and the stroke volume progressively decreases. The digitalized failing heart regains some of its capacity to contract more forcefully when subjected to increased resistance to ejection. There is more complete emptying of failing and dilated ventricles—cardiac output is increased and end-diastolic volume is reduced.

Rate Heart rate is decreased by digoxin. Bradycardia is more marked in CHF patients because improved circulation (due to positive inotropic action) restores the diminished vagal tone and abolishes sympathetic overactivity. In addition, digitalis slows the heart by vagal (increase in vagal tone) and extravagal (direct depression of SA and AV nodes) actions.

Electrophysiological properties

(a) ***Action potential (AP):*** The effects are illustrated diagrammatically in Fig. 38.2.

- The resting membrane potential (RMP) is progressively decreased (to less negative values) with increasing doses.
- The rate of 0 phase depolarization is reduced resulting in slowing of conduction. This action is most marked in A-V node and bundle of His.
- The slope of phase-4 depolarization is increased in the PFs—ectopic automaticity is enhanced—latent pacemakers become overt at high doses producing extrasystoles. High doses of digoxin produce coupled beats by another mechanism: the RMP shows oscillations during phase-4; when their magnitude is sufficient enough, delayed after-depolarizations result (*see* Fig. 39.1). The SA and A-V node automaticity is reduced at therapeutic concentrations by vagal action which hyperpolarizes these cells and reduces their phase-4 slope.
- The action potential duration (APD) is reduced (primarily at phase-2) and amplitude of AP is diminished.

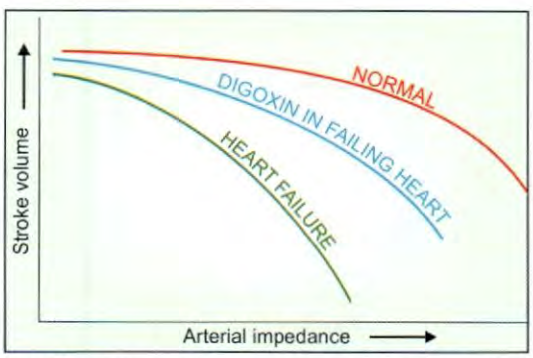


Fig. 38.1: Relationship between peripheral resistance and stroke output in normal and failing heart, and the action of digoxin on failing heart

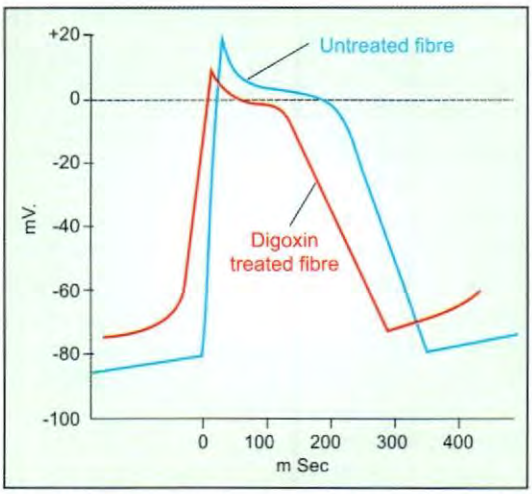


Fig. 38.2: Effect of digoxin on Purkinje fibre action potential

(b) Effective refractory period (ERP):

Atrium
- decreased by vagal action
- increased by direct action

} Vagal action normally predominates, causes inhomogeneity; allows the atria to respond at a higher rate and in an asynchronous manner.

A-V node and bundle of His } Increased by direct, vagomimetic and antiadrenergic actions; the maximum rate at which impulses can be transmitted is reduced.

Ventricle—ERP is abbreviated by direct action.

(c) ***Conduction:*** A-V conduction is demonstrably slowed by therapeutic doses. At high doses, intraventricular conduction in PFs is also depressed by uncoupling of gap junctions.

(d) ***ECG*** : Therapeutic doses of digoxin produce changes in the ECG. These are accentuated at high doses which may also produce arrhythmias.

- Decreased amplitude or inversion of T wave.
- Increased P-R interval (due to slowing of A-V conduction), A-V block at toxic doses.

CHAPTER 38

- Shortening of Q-T interval (reflecting shortening of systole).
- Depression of ST segment (at high doses—due to interference with repolarization).

Mechanism of action Digitalis increases force of cardiac contraction by a direct action independent of innervation. It selectively binds to extracellular face of the membrane associated Na^+K^+ ATPase of myocardial fibres and inhibitis this enzyme (Fig. 38.3). Inhibition of this cation pump results in progressive accumulation of Na^+ intracellularly. This indirectly results in intracellular Ca^{2+} accumulation due to diminished Ca^{2+} extrusion.

During depolarization Ca^{2+} ions enter the cell driven by the steep Ca^{2+} gradient (>1 mM extracellular to < 100 nM cytosolic during diastole) through voltage sensitive L type Ca^{2+} channels. This triggers release of larger amount of Ca^{2+} stored in sarcoplasmic reticulum (SR) through a calcium-activated calcium channel known as *Ryanodine receptor calcium channel 2* (*RYR2*) → cytosolic Ca^{2+} increases transiently to about 500 nM (calcium transients) triggering contraction by activating troponin C on myofibrils. The *sarcoplasmic-endoplasmic reticular Cal. ATPase 2* (*SERCA2*) is then activated which pumps Ca^{2+} back into the SR, where it is stored loosely bound to calsequestrin (CalS). In the normal state SERCA remains inhibited by a cytosolic protein phospholamban (PLN). Phosphorylation of PLN by PK_A removes this inhibition and SERCA becomes active. A fraction of Ca^{2+} (equal to that which entered from outside during depolarization) is extruded mainly by $3Na^+/1Ca^{2+}$ exchange transporter (*NCX-antiporter*) and to a lesser extent by sarcolemmal Ca^{2+} pump (Ca^{2+} ATPase). During phase 3 of AP, membrane Na^+K^+ATPase moves 3 intracellular Na^+ ions for 2 extracellular K^+ ions. The slight (1–1.5 mM) increase in cytosolic Na^+ over normal (8–10 mM) due to

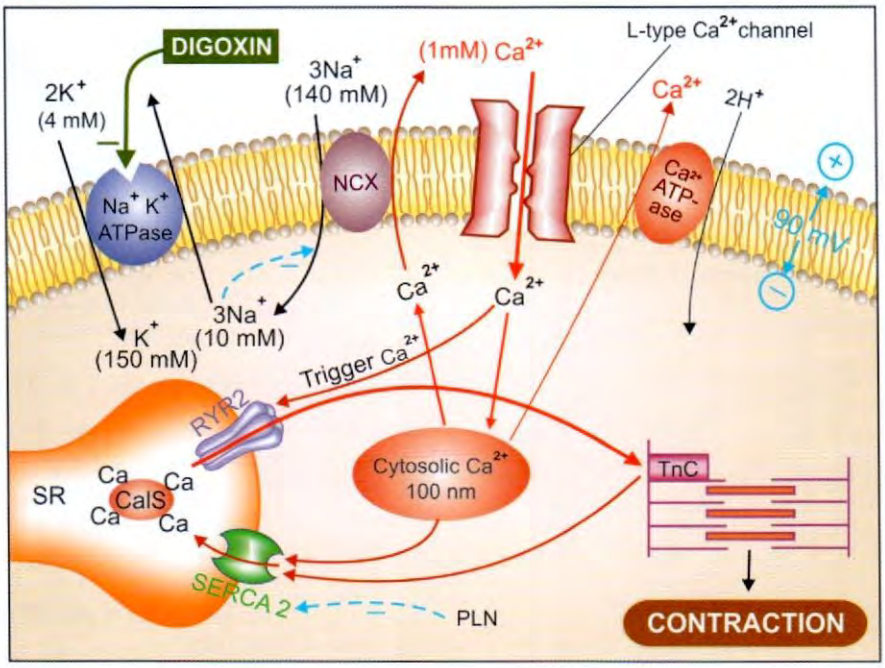


Fig. 38.3: Mechanism of positive inotropic action of digoxin
SR—Sarcoplasmic reticulum; TnC—Troponin C; NCX—Na^+-Ca^{2+} exchanger; RyR2—Ryanodine receptor calcium channel 2; PLN—Phospholamban; SERCA2—Sarcoplasmic-endoplasmic reticulum calcium ATPase 2, CalS—Calsequestrin.

partial inhibition of Na^+K^+ATPase by digoxin reduces transmembrane gradient of Na^+ which drives the extrusion of Ca^{2+}. The excess Ca^{2+} remaining in cytosol is taken up into SR which progressively get loaded with more Ca^{2+} so that subsequent calcium transients are augmented.

The relationship of cytosolic [Na^+] and [Ca^{2+}] is such that a small percentage increase in Na^+ concentration leads to a large percentage increase in Ca^{2+} concentration. Moreover, raised cytosolic Ca^{2+} induces greater entry of Ca^{2+} through voltage sensitive Ca^{2+} channels during the plateau phase. It has been shown that 1 mM rise in cytosolic [Na^+] results in 20–30% increase in the tension developed by ventricular fibres.

Binding of glycoside to Na^+K^+ATPase is slow. Moreover, after Na^+K^+ATPase inhibition, Ca^{2+} loading occurs gradually. As such, inotropic effect of digitalis takes hours to develop, even after i.v. administration.

Inhibition of Na^+K^+ ATPase is clearly involved in the toxic actions of digitalis. At high doses, there is depletion of intracellular K^+; and digitalis toxicity is partially reversed by infusing K^+, because K^+ decreases binding of glycoside to Na^+K^+ ATPase. Excessive Ca^{2+} loading of SR results in spontaneous cycles of Ca^{2+} release and uptake producing oscillatory delayed after-depolarizations and after-contractions. Since both therapeutic and toxic effects of digoxin are due to myocardial Ca^{2+} loading, these are inseparable and therapeutic index of digoxin is low.

2. Blood vessels Digoxin has weak direct vasoconstrictor action—peripheral resistance is increased in normal individuals. However, in CHF patients this is more than compensated by the indirect effect of improvement in circulation, i.e. reflex sympathetic overactivity is withdrawn and a net decrease in peripheral resistance occurs.

Digoxin has no prominent effect on BP: systolic BP may increase and diastolic may fall in CHF patients—pulse pressure increases. Hypertension is no contraindication to the use of digoxin.

Therapeutic doses of digoxin have no significant effect on coronary circulation—coronary insufficiency is no contraindication to its use.

3. Kidney Digoxin promptly causes diuresis in CHF patients, secondary to improvement in circulation and renal perfusion. The retained salt and water is gradually excreted. No diuresis occurs in normal individuals or in patients with edema due to other causes.

4. CNS Digoxin has little apparent CNS effect in therapeutic dose. Higher doses cause CTZ activation inducing nausea and vomiting. Still higher doses produce hyperapnoea, central sympathetic stimulation, mental confusion, disorientation and visual disturbances. Effects on the g.i.t. are only of toxicological nature (*see* adverse effects).

Pharmacokinetics

The pharmacokinetic features of digoxin are listed in Table 38.1.

Bioavailability of digoxin tablets from different manufacturers may differ. Presence of food in stomach delays absorption of digoxin. The volume of distribution is large (6–8 L/Kg). It is concentrated in the heart (~20 times than plasma), skeletal muscle, liver and kidney.

Table 38.1: Pharmacokinetic features of digoxin

		DIGOXIN
1.	Oral absorption	60–80%
2.	Plasma protein binding	25%
3.	**Time course of action***	
	–Onset	15–30 min
	–Peak	2–5 hr
	–Duration	2–6 days
4.	Plasma t½	40 hr
5.	Therapeutic concn.	0.5–1.4 ng/ml
6.	Toxic concn.	> 2 ng/ml
7.	Daily maintenance dose	0.125–0.5 mg
8.	Daily elimination**	35%
9.	Route of elimination (predominant)	Renal excretion
10.	Route of administration	Oral, i.v.

* Of full digitalizing dose given i.v.;
** fraction of total amount present in the body.

Digoxin is primarily excreted unchanged by the kidney: mainly by glomerular filtration; rate of excretion is altered parallel to creatinine clearance. Its t½ is prolonged in elderly patients and in those with renal insufficiency: dose has to be reduced.

Digoxin is a cumulative drug. When maintenance doses are given from the beginning, steady state levels and full therapeutic effect are attained after 4 × t½, i.e. 6–7 days.

Digoxin: DIGOXIN 0.25 mg tab., 0.05 mg/ml pediatric elixir, 0.5 mg/2 ml inj. LANOXIN, SANGOXIN 0.25 mg tab, CARDIOXIN 0.25 mg tab, 0.5 mg/2 ml inj.

Adverse effects

Toxicity of digitalis is high, margin of safety is low (therapeutic index 1.5–3). About 25% patients receiving digoxin therapy develop one or other toxic symptom. The manifestations are:

Extracardiac Anorexia, nausea, vomiting and abdominal pain are usually reported first: are due to gastric irritation, mesenteric vasoconstriction and CTZ stimulation. Diarrhoea can also occur. Fatigue, malaise, headache, mental confusion, restlessness, hyperapnoea, disorientation, psychosis and visual disturbances are the other complaints. Skin rashes and gynaecomastia are rare.

Cardiac Almost every type of arrhythmia can be produced by digoxin: pulsus bigeminus is common; others are nodal and ventricular extrasystoles, ventricular tachycardia and terminally ventricular fibrillation. Partial to complete A-V block may be the sole cardiac toxicity, or it may accompany other arrhythmias. Severe bradycardia, atrial extrasystoles, AF or AFl have also been noted. In about 2/3 patients showing toxicity, extracardiac symptoms precede cardiac toxicity.

Treatment Further doses of digoxin must be stopped at the earliest sign of toxicity; nothing more needs to be done in many patients, especially if the manifestations are only extracardiac.

(a) For tachyarrhythmias When caused by chronic use of digoxin and diuretics (both induce K^+ depletion)—infuse KCl 20 m.mol/hour (max. 100 m.mol) i.v. or give orally in milder cases. High extracellular K^+ decreases binding of the glycosides to Na^+K^+ATPase by favouring a conformation of the enzyme that has lower affinity for the glycoside, and K^+ tends to antagonize digitalis induced enhanced automaticity. When toxicity is due to acute ingestion of large doses of digoxin, plasma K^+ may be high; it should not be given from outside. In any case, it is desirable to measure serum K^+ to guide KCl therapy. K^+ is contraindicated if higher degree of A-V block is present, because complete A-V block and ventricular asystole may be precipitated.

(b) For ventricular arrhythmias Lidocaine i.v. repeated as required is the drug of choice. It suppresses the excessive automaticity, but does not accentuate A-V block. Quinidine, procainamide and propafenone are contraindicated.

(c) For supraventricular arrhythmias Propranolol may be given i.v. or orally depending on the urgency.

(d) For A-V block and bradycardia The treatment of choice is cardiac pacing through a temporarily inserted pacemaker. Atropine 0.6–1.2 mg i.m. may help.

Cardioversion by DC shock is contraindicated because severe conduction defects may be unmasked in the digitalis intoxicated heart.

Digoxin antibody Digoxin specific antibody is highly effective in reversing cardiotoxicity due to digoxin as well as many other related glycosides. The Fab fragment has been marketed in Europe as DIGIBIND (38 mg vial), DIGIFAB (40 mg/vial). It is nonimmunogenic because it lacks the Fc fragment. Given by i.v. infusion it has markedly improved the survival of seriously digitalis intoxicated patients.

Precautions and contraindications

- *Hypokalemia*: enhances digitalis toxicity.
- *Elderly, renal or severe hepatic disease*: patients are more susceptible to digoxin toxicity.
- *Thyrotoxicosis*: patients are more prone to develop digitalis arrhythmias, while digoxin elimination is slowed in hypothyroid patients.
- *Ventricular tachycardia*: digitalis is contraindicated because it may precipitate ventricular fibrillation.
- *Partial A-V block*: may be converted to complete A-V block by digoxin.
- *Wolff-Parkinson-White syndrome*: Digoxin is contraindicated because it decreases the ERP of bypass tract in 1/3 patients. In them rapid atrial impulses may be transmitted to ventricles → VF may occur. Digoxin can increase the chances of reentry by slowing

conduction in the normal A-V bundle and accelerating it in the aberrant pathway.

Interactions

1. *Diuretics*: cause hypokalemia which increases the risk of digitalis arrhythmias; potassium supplements should be given prophylactically.
2. *Calcium*: synergises with digitalis → precipitates toxicity.
3. *Quinidine*: reduces binding of digoxin to tissue proteins as well as its renal and biliary clearance by inhibiting efflux transporter P-glycoprotein → plasma concentration of digoxin is doubled → toxicity can occur. *Verapamil, diltiazem, captopril, propafenone* and *amiodarone* also increase plasma concentration of digoxin to variable extents.
4. *Adrenergic drugs*: can induce arrhythmias in digitalized patients; both increase ectopic automaticity.
5. Digoxin absorption may be reduced by *metoclopramide, sucralfate, antacids, neomycin, sulfasalazine.* Absorption of digoxin is increased by atropinic drugs, including tricyclic antidepressants.
6. *Propranolol, verapamil, diltiazem and disopyramide:* may additively depress A-V conduction and oppose positive inotropic action.

Uses

The two main indications of digoxin are heart failure and control of ventricular rate in atrial fibrillation/flutter. Its use in heart failure is described in the next section on treatment of heart failure.

Cardiac arrhythmias

Atrial fibrillation (AF), atrial flutter (AFl)
Digoxin can be used for controlling ventricular rate in AF and AFl, whether associated with CHF or not, but it is incapable of curing the arrhythmia, i.e. does not revert it to sinus rhythm. Often, AFl may be converted into AF because digoxin abbreviates atrial ERP and makes it more inhomogeneous.

Digoxin reduces ventricular rate in AF and AFl by decreasing the number of impulses that are able to pass down the A-V node and bundle of His. It increases ERP of A-V node by direct, vagomimetic and antiadrenergic actions: the minimum interval between consecutive impulses that can successfully traverse the conducting tissue is prolonged.

Digoxin may be used for long-term ventricular rate control in persistent or permanent AF/AFl, but is not the preferred drug for rapid control of heart rate. Oral or i.v. β blocker (e.g. metoprolol) or a non-DHP calcium channel blocker (CCB) diltiazem/verapamil given orally or i.v. (depending on the urgency) are the preferred drugs. The short-acting i.v. β blocker esmolol is preferred for haemodynamically unstable patients. Digoxin is not only slow to act (takes 1–6 hours even after i.v. injection), but also less effective. However, it is preferred when AF/AFl is attended by heart failure. Digoxin decreases ventricular rate in a dose dependent manner and abolishes the pulse deficit in AF. The maintenance dose in persistent or permanent AF/AFl can be determined by titrating with heart rate, which should not be allowed to decrease to ≤ 60 per min at rest. Digoxin can also be combined with the β blocker/CCB, if a single drug fails to lower the heart rate to the desired levels.

Paroxysmal supraventricular tachycardia (PSVT) It is a common arrhythmia with a rate 150–200/min and 1 : 1 A-V conduction. It is mostly due to reentry involving the A-V node. Digoxin may be injected i.v. It increases vagal tone and depresses the path through the A-V node, or the ectopic focus, and terminates the arrhythmia (success in 1/3 cases). Adenosine, verapamil or esmolol injected i.v. are more effective, less toxic and act faster, therefore preferred.

TREATMENT OF HEART FAILURE

Heart failure occurs when cardiac output is insufficient to meet the demands of tissue perfusion, or is able to do so only by elevating filling pressure. It is a progressive disease with gradually deteriorating cardiac performance. Heart failure may primarily be due to systolic dysfunction or diastolic dysfunction.

Systolic dysfunction This refers to deficient pumping action of ventricles, i.e. ventricles are unable to develop sufficient wall tension to eject adequate quantity of blood and get progressively dilated. This makes the ventricle further inefficient according to the Laplace equation:

Wall tension = Intraventricular pressure × ventricular radius

i.e. to generate the same ejection pressure a dilated ventricle has to develop higher wall tension. Thus, a self-perpetuating vicious cycle is set up and ejection fraction (EF) is progressively reduced (usually to <40%). The most important cause of systolic dysfunction is coronary artery disease (CAD), myocardial infarction (MI) and loss of functioning myocardium. Other causes are valvular incompetence, dilated cardiomyopathy, viral (including HIV) myocarditis, tachyarrhythmias (mostly AF), etc.

Diastolic dysfunction The ventricular wall is thickened and unable to relax normally during diastole; ventricular filling is impaired and stroke volume is reduced, but the EF may be normal.

Long standing hypertension is the most common cause of left ventricular hypertrophy (LVH) and subsequent diastolic dysfunction. It is mostly associated with ageing and myocardial stiffening. Aortic stenosis, hypertrophic cardiomyopathy, A-V shunts and congenital heart disease are the other important causes.

However, most patients, especially long standing cases, have both systolic and diastolic dysfunction. Symptomatically also both are similar. Several compensatory mechanisms are brought into action to overcome the reduced cardiac output (CO). These include:

- Elevation of filling pressure by Frank-Starling compensation to increase stroke volume (*see* Fig. 38.4); but this may produce congestive symptoms, i.e. venous engorgement, hepatic enlargement, peripheral edema, pulmonary congestion → dyspnoea, renal congestion → oliguria.
- Augmentation of sympathetic tone resulting in β receptor mediated cardiac stimulation and α receptor mediated vasoconstriction. However, prolonged β receptor activation promotes cardiac myocyte apoptosis and fibrotic change. Vasoconstriction increases cardiac afterload and tends to restrict CO.
- Activation of RAS causes further vasoconstriction and LVH. Myocardial remodeling, cell death and fibrotic transformation are direct consequences of long term exposure to raised Ang II.
- Over production of aldosterone promotes Na^+ retention, K^+ loss and fibroblast proliferation which contributes to ventricular remodeling.
- Endothelin production is also increased which reinforces vasoconstriction as well as cardiac and vascular myocyte proliferation followed by fibrotic change.
- Heart failure also triggers release of natriuretic peptides ANP and BNP due to atrial and ventricular distention, which tend to oppose vasoconstriction and Na^+ retention.

After initial haemodynamic benefit, the compensatory ventricular hypertrophy becomes counter productive, because it alters ventricular geometry, hampers ventricular filling and predisposes to ischaemia. Nevertheless, the counter-regulatory neurohumoral mechanisms described above do provide targets for drug therapy to retard the progression of disease in heart failure.

There are two distinct goals of drug therapy in heart failure:

A. Relief of congestive/low output symptoms, restoration of cardiac performance and treatment of acute decompensation. This can be achieved by:

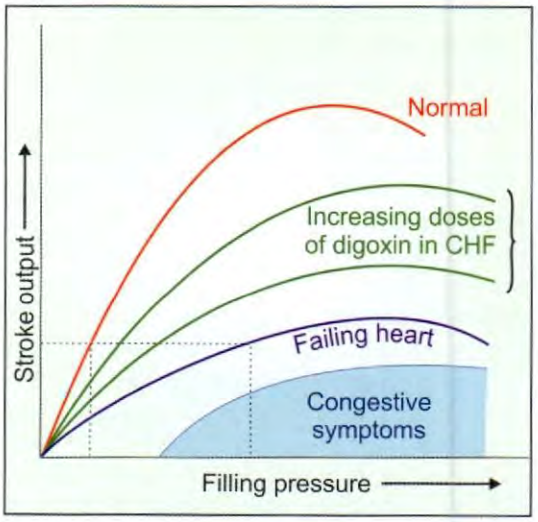


Fig. 38.4: Relationship between filling pressure and cardiac output in normal and failing heart. Digoxin tends to shift the curve towards normal

Inotropic drugs—Digoxin, dobutamine/dopamine, inamrinone/milrinone
Diuretics—Furosemide, thiazides, metolazone
RAS inhibitors—ACE inhibitors/ARBs
Vasodilators—Hydralazine, nitrate, nitroprusside
Synthetic BNP—Nesiritide
β blocker—Metoprolol, bisoprolol, carvedilol, nebivolol

B. Arrest/reversal of disease progression and prolongation of survival. This is possible with:
ACE inhibitors/ ARBs,
β blockers
Aldosterone antagonist—Spironolactone, eplerenone
Neprilysin inhibitor—Sacubitril

Till 1980 drugs available for heart failure (digitalis and diuretics) addressed only the consequences of CHF, but not its genesis. As such, these drugs while affording symptomatic relief, did not modify the course of heart failure. Drugs developed thereafter (ACE inhibitors/ARBs, β adrenergic blockers, aldosterone antagonists, etc.) impact the neurohumoral perpetrators of heart failure, myocardial apoptosis, fibrosis, remodeling, matrix abnormalities, etc. in addition to haemodynamic effects, and have become the primary therapeutic modality.

The pathophysiological mechanisms that perpetuate heart failure and contribute to disease progression, along with site of drug action are depicted in Fig. 38.5. The current pattern of use of drugs in various stages of heart failure is summarized in Fig. 38.6.

Diuretics

Almost all cases of symptomatic heart failure are treated with a diuretic. *High ceiling diuretics* (furosemide, bumetanide) are the diuretics of choice for mobilizing edema fluid; later they may be continued in low doses. However, resistance may develop to even high ceiling diuretics after prolonged use in advanced heart failure. Addition of metolazone or spironolactone to furosemide may overcome the resistance. Thiazide alone has very limited role in CHF. Diuretics:

- Decrease preload and improve ventricular efficiency by reducing circulating volume.

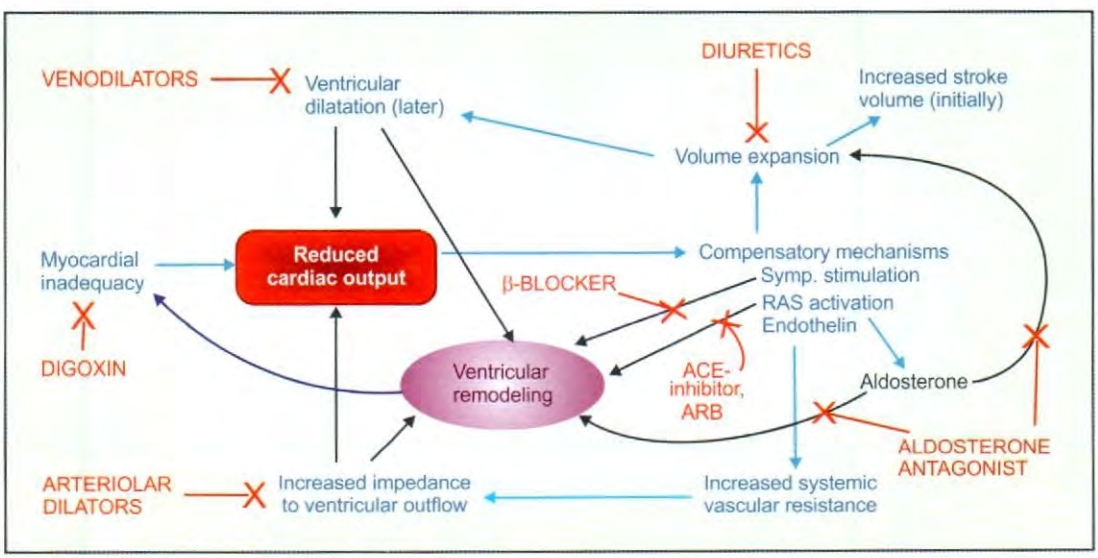


Fig. 38.5: The vicious cycle in heart failure: compensatory mechanisms evoked in response to reduced cardiac output themselves perpetuate failure and contribute to remodeling responsible for disease progression. The parameter which is improved by different therapeutic measures is indicated
ACE—Angiotensin convertnig enzyme; ARB—Angiotensin receptor blocker; RAS—Renin-angiotensin system

- Remove peripheral edema and pulmonary congestion.

Intravenous furosemide promptly increases systemic venous capacitance and produces rapid symptomatic relief in acute left ventricular failure. It has, in conjunction with vasodilators, virtually obviated the need for i.v. digoxin. On the other hand, most mild cases of heart failure can be maintained symptom free on diuretics without recourse to any other medication, though concurrent use of ACE inhibitor. ARB is recommended to retard disease progression. However, diuretics have no role in asymptomatic left ventricular dysfunction, and brisk diuresis can worsen some cases whose cardiac output is critically dependent upon volume overload. Diuretics do not influence the disease process in CHF, though they may dramatically improve symptoms. Despite decades of experience, no prognostic benefit has been demonstrated for diuretics. Moreover, they may cause activation of RAS (if hypovolemia occurs) which has adverse cardiovascular consequences. Chronic diuretic therapy tends to cause hypokalaemia, alkalosis and carbohydrate intolerance. Current opinion is to treat mild systolic heart failure with ACE inhibitors/ARBs ± β blockers only, because they afford survival benefit, while diuretics may be added intermittently for symptom relief. Chronic diuretic therapy should be reserved for relatively advanced cases with tendency to fluid retention on discontinuation of the diuretic. Diuretics are the primary drugs for heart failure with preserved EF (diastolic dysfunction), because these patients have prominent fluid retention. Dose should be titrated to the lowest that will check fluid retention, but not cause volume depletion to activate RAS.

Renin-angiotensin system (RAS) inhibitors

Since RAS activation is pivotal to development of symptoms and disease progression in heart failure, the ACE inhibitors and ARBs are the sheet anchor of drug therapy in CHF (*see* p. 534 and 537). They afford symptomatic as well as disease modifying benefits in heart failure by causing vasodilatation, retarding/preventing ventricular hypertrophy, myocardial cell apoptosis, fibrosis, intercellular matrix changes and remodeling. In addition to decreasing Ang II production, ACE inhibitors raise the level of kinins which stimulate generation of cardioprotective NO and PGs. Symptomatic and prognostic benefits of ACE inhibitors/ARBs have been established in mild to severe (NYHA class I to IV) CHF with reduced EF, as well as in subjects with asymptomatic systolic dysfunction. An overall 20% reduction in mortality has been obtained by the use of ACE inhibitors in heart failure. They are thus recommended for all grades of CHF, unless contraindicated, or if renal function deteriorates by their use (mainly in those with renal artery stenosis). However, no prognostic benefit or improved outcome has been obtained with them in patients of heart failure with preserved EF.

ACE inhibitor therapy is generally started at low doses (to avoid initial hypotension) which are gradually increased to obtain maximum benefit or to near the highest recommended doses.

The ARBs are an alternative to ACE inhibitors, but differ in certain aspects. They appear to more completely block the AT_1 receptor mediated effects, because Ang II can be generated *via* pathways other than ACE. However, unlike ACE inhibitors, they do not raise tissue bradykinin, PGI_2 and NO levels that may also contribute to the beneficial effect in heart failure. The current relative status of ARBs compared to ACE inhibitors in heart failure therapy is discussed on p. 537.

Cardiac glycosides

The only cardiac glycoside in clinical use today is digoxin. Once a pivotal drug for heart failure, it is no longer a first line drug, and is used only in conjunction with other drugs in selected cases. Digoxin is a positive inotropic drug which affords symptomatic relief, primarily in systolic dysfunction or when CHF is due to AF with rapid heart rate. It is incapable of

reversing or retarding the pathological changes of heart failure or affording prognostic benefit.

Digoxin induced enhancement of contractility increases ventricular ejection and shifts the curve relating stroke output to filling pressure towards normal, so that adequate output may be obtained at a filling pressure that does not produce congestive symptoms (*see* Fig. 38.4). Improved tissue perfusion results in withdrawal of sympathetic overactivity → heart rate and central venous pressure (CVP) are lowered towards normal. Compensatory mechanisms retaining Na^+ and water are inactivated, diuresis occurs and edema is cleared. Liver regresses, pulmonary congestion is reduced → dyspnoea abates, cyanosis disappears. Low output symptoms like decreased capacity for muscular work are mitigated. Thus, digoxin is the most effective drug capable of relieving symptoms of systolic failure and restoring cardiac compensation, especially in patients with dilated heart and low EF. However, patients with preserved EF and heart failure due to diastolic dysfunction usually do not respond to digoxin or to other inotropic drugs. All patients with low EF who remain symptomatic while receiving ACE inhibitor/ARB + diuretic ± β blocker should be treated with digoxin.

Randomized multicentric clinical trials have shown that after compensation has been restored digoxin therapy could be withdrawn without haemodynamic deterioration in a significant number of patients who are in sinus rhythm and who continue taking ACE inhibitor + diuretic. However, digoxin should be reinstituted if symptoms reappear or cardiac status declines. Continued digoxin therapy is the best course in CHF patients with atrial fibrillation who need ventricular rate control.

Large studies including those by Digoxin Investigation Group (DIG) have found no evidence that digoxin decreases overall mortality in CHF patients, though episodes of decompensation and heart failure deaths are reduced, but incidence of sudden death may increase. The two major limitations in the use of cardiac glycosides are low margin of safety and lack of effect on neurohumoral contributors to pathogenesis of heart failure.

Dosage Digoxin therapy is now initiated with the estimated maintenance doses (0.125–0.25 mg/day) without any loading dose. Full response takes 5–7 days to develop when steady-state is reached. In case of inadequate response, the dose is increased to 0.375 and 0.5 mg/day at weekly intervals. Reduction in heart rate and relief of heart failure symptoms are the best guide to dosing.

If an early response is required, a loading dose of 0.75–1.25 mg spread over 24–48 hours may be given in the beginning, but requires close monitoring.

Vasodilators

The direct acting vasodilators are primarily useful in the treatment of acute heart failure that occurs episodically in advanced cases, or that follows acute MI, and are infused i.v. for short periods to tide over crisis. The utility of long-term oral vasodilator therapy in chronic heart failure is quite limited. Vasodilators can be differentiated into those which primarily dilate veins (nitrates), or those which mainly dilate arterioles (hydralazine), or which dilate both (sod. nitroprusside).

(i) *Preload reduction: Nitrates* cause pooling of blood in systemic capacitance vessels to reduce ventricular end-diastolic pressure and volume. In a dilated ventricle, this improves effectiveness of myocardial fibre shortening to eject blood. Monitored i.v. infusion of glyceryl trinitrate affords rapid relief in acute left ventricular failure, particularly that due to myocardial ischaemia/infarction. It is indicated when the central venous pressure (CVP) is raised and in dilated cardiomyopathy. However, too much lowering of preload (by vasodilators + strong diuretics) may reduce output of a failing heart whose performance is dependent upon elevated filling pressure. Occurrence of nitrate tolerance limits their utility in routine treatment of CHF.

(ii) *Afterload reduction* *Hydralazine* dilates resistance vessels and reduces aortic impedance so that ventricle is able to pump more blood. It is effective in forward failure when cardiac index is low (< 2.5 L/min/m^2) without a marked increase in CVP (< 18 mm Hg). Marked tachycardia, worsening of myocardial

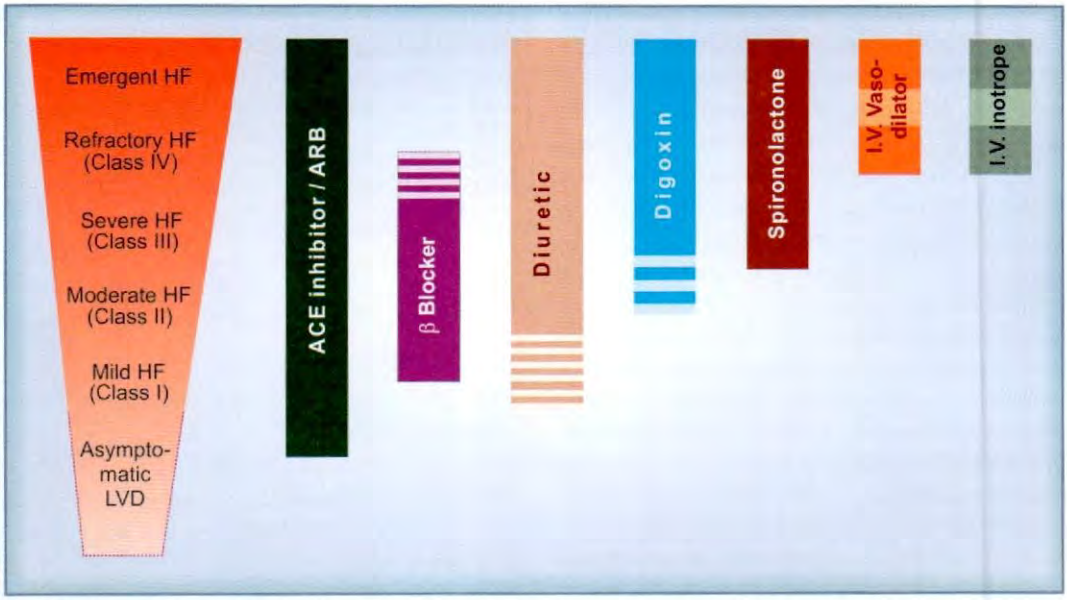


Fig. 38.6: Current pattern of clinical use of various classes of drugs in different stages of heart failure (HF)
LVD—Left ventricular dysfunction; ACE—Angiotensin converting enzyme; ARB—Angiotensin receptor blocker

ischaemia and fluid retention limit long-term use of hydralazine monotherapy.

(iii) *Pre- and after load reduction* *Sod. nitroprusside* is a high efficacy i.v. dilator with equal action on the two types of vessels. It reduces ventricular filling pressure as well as systemic vascular resistance. Cardiac output and renal blood flow are increased. The action is very fast and brief. Careful i.v. infusion of nitroprusside may be employed in conjunction with a loop diuretic + i.v. inotropic drug to tideover crisis in severely decompensated patients.

In the long term oral therapy, survival benefit has been obtained only with a combination of hydralazine + isosorbide dinitrate, but the ACE inhibitors and ARBs alone are clearly superior in this regard. Hydralazine causes more marked renal vasodilatation. Along with isosorbide dinitrate it may be selected for patients with renal insufficiency, low renal blood flow or renal artery stenosis, who cannot tolerate ACE inhibitors or ARBs. Isosorbide dinitrate and hydralazine supplement each other when combined. African-American patients with severe CHF who are already receiving ACE inhibitors + digoxin + diuretic have obtained extra survival benefit from addition of hydralazine + nitrate.

β-Adrenergic blockers

Extensive studies over the past 30 years have established the utility of β_1 blockers (mainly metoprolol, bisoprolol, nebivolol) and the nonselective β + selective α_1 blocker carvedilol in mild to moderate CHF treated with ACE inhibitor ± diuretic, digitalis. They afford survival benefit, and are now part of standard therapy of CHF.

A large number of randomized trials including Metoprolol in dilated cardiomyopathy trial (1993), US carvedilol trial (1996), MERIT-HF trial (1999), CIBIS-II trial (1999), CAPRICORN trial (2001), COPERNICUS trial (2002) have demonstrated subjective, objective, prognostic and mortality benefits of the above named β blockers over and above that afforded by ACE inhibitors + diuretic ± digitalis.

Though the early hemodynamic action of β blockers is to depress cardiac contractility and EF, these parameters gradually improve over weeks. After a couple of months EF is generally higher than baseline, and slow upward titration of dose

further improves cardiac performance. The hemodynamic benefit is maintained over long-term and hospitalization/mortality due to worsening cardiac failure, as well as all cause mortality is reduced. The benefits appear to be due to antagonism of ventricular wall stress enhancing, apoptosis promoting and pathological remodeling effects of excess sympathetic activity (occurring reflexly) in heart failure, as well as due to prevention of sinister arrhythmias. Incidence of sudden cardiac death as well as that due to worsening heart failure is decreased. β blockers lower plasma markers of activation of sympathetic, renin-angiotensin systems and endothelin-1.

However, β blocker therapy in heart failure requires caution, proper patient selection and observance of several guidelines:

- Greatest utility of β blockers has been shown in mild to moderate (NYHA class II, III) cases of dilated cardiomyopathy with systolic dysfunction in which they are now routinely coprescribed unless contraindicated. In one recent study (SENIORS, 2009) nebivolol has been found effective in both systolic as well as diastolic failure.
- Encouraging results (upto 35% decrease in mortality) have been obtained in class IV cases as well, but use in severe failure could be risky and needs constant monitoring.
- There is no place for β blockers in decompensated patients. β blockers should be stopped during an episode of acute heart failure and reinstituted gradually after compensation is restored. Conventional therapy should be continued along with them.
- Starting dose should be very low because the early negative inotropic action may precipitate failure. Dose is then titrated upward as tolerated to the target level (carvedilol 50 mg/day, bisoprolol 10 mg/day, metoprolol SR 200 mg/day) or near it, for maximum protection.
- In few patients any attempt to introduce a β blocker results in worsening of heart failure. β blockers should not be used in such patients.
- Survival benefit has been demonstrated with sustained release (SR) metoprolol which provides round-the-clock β blockade, but not with short acting metoprolol.
- There is no evidence of benefit in asymptomatic left ventricular dysfunction.

Aldosterone antagonist (Spironolactone, Eplerenone)

Over the past 2 decades it has been realized that rise in plasma aldosterone in heart failure, in addition to its well known Na^+ and water retaining action, is an important contributor to disease progression by direct and indirect effects:

(a) Expansion of e.c.f. volume → increased cardiac preload.

(b) Fibroblast proliferation and fibrotic change in myocardium → worsening systolic dysfunction and pathological remodeling.

(c) Hypokalemia and hypomagnesemia → increased risk of ventricular arrhythmias and sudden cardiac death.

The aldosterone antagonist spironolactone is a weak diuretic (*see* Ch. 42), but can benefit CHF by antagonizing the above effects of aldosterone.

Two large randomized trials (RALES, 1999 with spironolactone, and EPHESUS, 2003 with eplerenone) conducted on NYHA class III and IV heart failure have demonstrated the mortality and anti-remodeling benefit of these drugs over and above that of ACE inhibitors ± β blockers.

Though ACE inhibitors themselves lower aldosterone levels, this effect is incomplete and needs to be enhanced in moderate-to-severe heart failure with low EF. Current recommendation regarding spironolactone/eplerenone therapy in CHF is:

- They are to be used as add-on therapy to ACE inhibitors + other drugs in moderate-to-severe heart failure with reduced EF. Their role in patients with preserved EF is uncertain.
- They can retard disease progression, reduce episodes of decompensation and death due to heart failure as well as sudden cardiac deaths.

- Only low doses (12.5–25 mg/day) of spironolactone/eplerenone should be used to avoid hyperkalaemia.
- They may help restoration of diuretic response to furosemide when refractoriness has developed.

Gynaecomastia occurs in a number of male patients treated with spironolactone. This can be avoided by using eplerenone.

Ivabradine This pure bradycardia producing antianginal drug (*see* p. 600) has been approved recently for use in stable grade II to IV heart failure patients who are in sinus rhythm and have heart rate >70 per min with systolic dysfunction (ER <35%). It works by slowing the heart and improving ventricular filling. Ivabradine is specifically indicated for patients with contraindications to β blockers, or in those who do not achieve heart rate reduction to <75/min with an adequate dose of β blocker alone. It is given in addition to standard therapy with ACE inhibitor, diuretic, aldosterone antagonist, etc., and has been shown to decrease the composite end points of hospitalization and cardiovascular mortality (SHIFT trial 2010). However, it lacks the cardioprotective property of β blockers.

Sympathomimetic inotropic drugs (see Ch. 9)

Drugs with β adrenergic and dopaminergic D1 agonistic actions have positive inotropic property which may be utilized to combat emergency pump failure.

Dopamine and dobutamine (*see* p. 146–47) infused i.v. act promptly and afford additional haemodynamic support over and above vasodilators, digoxin and diuretics, but benefits are short-lasting. They are particularly useful when heart failure is accompanied by low BP. Due to development of tolerance and their cardiotoxic potential when used for prolonged therapy, these drugs have no role in the long-term management of CHF.

Phosphodiesterase 3 inhibitors

Inamrinone (amrinone) This bipyridine derivative is a selective phosphodiesterase 3 (PDE3) inhibitor. The PDE3 isoenzyme is specific for intracellular degradation of cAMP in heart, blood vessels and bronchial smooth muscles. Amrinone increases myocardial cAMP and transmembrane influx of Ca^{2+}. Both these actions may underlie its positive inotropic property.

The two most important actions of inamrinone are *positive inotropy* and direct *vasodilatation*. It has been called an 'inodilator'. Both preload and afterload on the heart is reduced. Compared to dobutamine, proportionately greater decrease in systemic vascular resistance is noted.

In CHF patients i.v. inamrinone acts rapidly and its action lasts for 2–3 hours; elimination t½ is 2–4 hours. It increases cardiac output and decreases peripheral vascular resistance, CVP and left ventricular end diastolic volume, accompanied by mild tachycardia and slight fall in BP.

Thrombocytopenia is the most prominent and dose related adverse effect, because of which inamrinone is seldom used now. Nausea, diarrhoea, abdominal pain, liver damage, fever and arrhythmias are the other adverse effects.

Use of oral inamrinone in maintenance therapy of CHF has been abandoned, because efficacy was lost and mortality was increased in comparison to placebo.

It is indicated only for short-term i.v. use in severe and refractory CHF, as an additional drug to conventional therapy with digoxin, diuretics and vasodilators.

AMICOR, CARDIOTONE 5 mg/ml (as lactate) 20 ml amp.

Milrinone Related to inamrinone, it has similar action but is more selective for PDE3, and is at least 10 times more potent. It is shorter-acting with a t½ of ~80 min.

Thrombocytopenia is not significant. In long term prospective trials, increased mortality has been reported with oral milrinone as well. Milrinone is preferred over inamrinone, but should be restricted to short-term use only.

Dose: 50 μg/kg i.v. bolus followed by 0.4–1.0 μg/kg/min infusion.

PRIMACOR IV 10 mg/10 ml inj.

Levosimendan

This inotropic drug acts by sensitizing myocardial troponin C to Ca^{2+}, as well as by inhibiting PDE3. As such, the inotropic effect occurs even in patients receiving β blockers, and is not associated with a change in cytosolic Ca^{2+} concentration. It also opens ATP-sensitive K^+ channels in vascular smooth muscle cells to cause vasodilatation. Thus, it is another 'inodilator', Haemodynamic improvement in heart failure is both due to increase in cardiac contractility as well as reduction in preload and afterload.

Levosimendan infused i.v. is primarily indicated for short-term treatment of acutely decompensated severe chronic heart failure. Though it relieved symptoms of heart failure, but survival rate was not improved. The most common side effect is hypotension which may last for few days due to its active metabolite that has long t½.

Nesiritide *(see p. 553)* This recombinant brain natriuretic peptide (BNP) is being used by continuous i.v. infusion to relieve dyspnoea and other symptoms in refractory CHF. It enhances salt and water excretion and is a potent vasodilator with profile of action similar to i.v. glyceryl trinitrate; i.e. reduces ventricular filling pressure. Added to the standard therapy, additional haemodynamic and symptomatic improvement can be obtained for short-periods, but no long-term benefits are evident in CHF.

Sacubitril-Valsartan combination

Sacubitril is an orally active neprilysin inhibitor which prevents the degradation of endogenous ANP, BNP and other vasodilator peptides, producing vasodilatation, natriuresis and diuresis. Combined with the ARB valsartan, it has been recently approved for use in advanced heart failure to decrease the incidence of death and acute decompensation (*see* p. 553). A greater reduction in hospitalization and mortality compared to enalapril has been reported.

Tolvaptan

This is an orally active nonpeptide vasopressin V_2 receptor antagonist introduced for the correction of water retention and hyponatremia occurring in 'syndrome of inappropriate ADH secretion' (SIADH) as well as in advanced CHF. In clinical trials on CHF patients with hyponatremia, tolvaptan has afforded short-term improvement by increasing water excretion, restoring serum Na^+ and relieving dyspnoea. However, no long-term benefit has been noted.

☞ PROBLEM DIRECTED STUDY

38.1 A 72-year-old man presents with swelling over ankle and feet, also noticeable over face in the morning, shortness of breath and palpitation on walking ~100 m, weakness, fatigue and cough at night. The pulse is 110/min, BP 114/78 mm Hg, there is pitting edema over feet, liver is enlarged 2 cm below costal margin, neck veins are filled upto 3 cm above clavicle, crepitations are heard at the base of lungs, apex beat is in the 6th intercostal space and heart sounds are muffled. Chest X-ray and echocardiography show enlarged cardiac shadow and an ejection fraction (EF) of 28%. A diagnosis of moderate grade heart failure due to dilated cardiomyopathy with reduced EF is made. The doctor prescribed bed rest, salt restriction and:

Tab enalapril 5 mg twice a day

Tab furosemide 40 mg in the morning

(a) Can the patient be prescribed any other drug to hasten relief of symptoms? If so, which drug and in what dosage?

(b) Should the dose of enalapril be changed over time or should it be withdrawn, if so when?

(c) Should a β adrenergic blocking drug be added to the treatment regimen concurrently?

(see Appendix-1 for solution)

Chapter 39 | Antiarrhythmic Drugs

These are drugs used to prevent or treat irregularities of cardiac rhythm.

Nearly 3 out of 4 patients of acute myocardial infarction (MI) and about half of those given a general anaesthetic exhibit at least some irregularity of cardiac rhythm. Arrhythmias are the most important cause of sudden cardiac death. However, only few arrhythmias need to be treated with antiarrhythmic drugs.

Abnormal automaticity or impaired conduction or both underlie cardiac arrhythmias. The generation and propagation of cardiac impulse and properties of excitability and refractoriness are described on p. 521–23. Ischaemia, electrolyte and pH imbalance, mechanical injury, stretching (due to heart failure), neurogenic and pharmacological influences, including antiarrhythmic drugs themselves, can cause arrhythmias by altering electrophysiological properties of cardiac fibres.

Important mechanisms of cardiac arrhythmias are:

A. Enhanced/ectopic pacemaker activity The slope of phase-4 depolarization may be increased pathologically in the automatic fibres or such activity may appear in ordinary fibres. Ectopic impulse may also result from current of injury. Myocardial cells damaged by ischaemia become partially depolarized: a current may flow between these and normally polarized fibres (injury current) and initiate an impulse.

B. After-depolarizations These are secondary depolarizations accompanying a normal or premature action potential (AP), Fig. 39.1.

Early after-depolarization (EAD) Repolarization during phase-3 is interrupted and membrane potential oscillates. If the amplitude of oscillations is sufficiently large, neighbouring tissue is activated and one or more extra impulses are

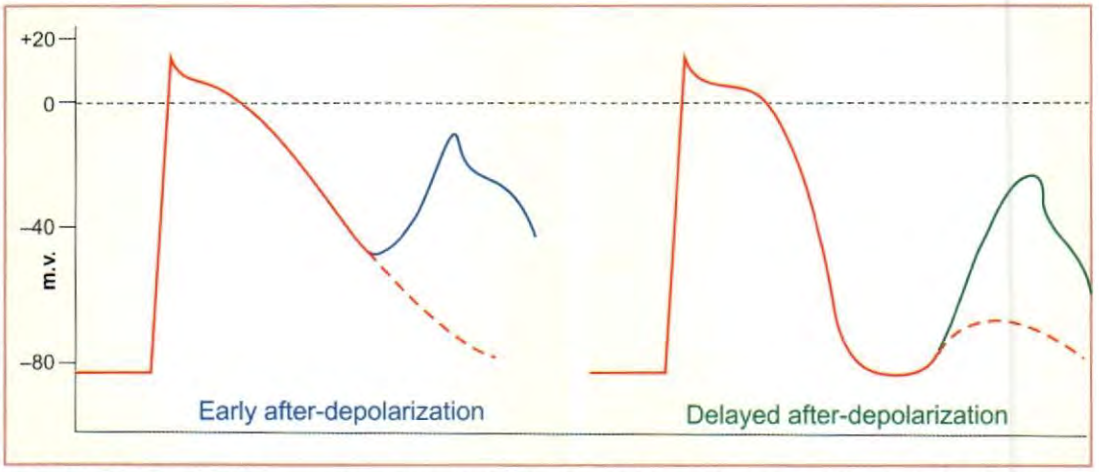


Fig. 39.1: Action potential in a nonautomatic ventricular fibre (in red) followed by early or delayed after-depolarizations.

propagated. EADs are frequently associated with long Q-T interval due to slow repolarization and markedly prolonged APs with slow heart rate. They result from depression of delayed rectifier K^+ current.

Delayed after-depolarization (DAD) After attaining resting membrane potential (RMP) a secondary deflection occurs during phase 4, which may reach threshold potential and initiate a single premature AP. This is more common with fast heart rate, and generally results from Ca^{2+} overload (e.g. in digitalis toxicity, ischaemia-reperfusion).

Because an AP is needed to trigger after-depolarizations, arrhythmias based on these have been called *triggered arrhythmias*.

C. Reentry Due primarily to abnormality of conduction, an impulse may recirculate in the heart and cause repetitive activation without the need for any new impulse to be generated. These are called *reentrant arrhythmias*.

(i) *Circus movement reentry* It occurs in an anatomically defined circuit. A premature impulse, temporarily blocked in one direction by refractory tissue, makes a one-way transit around an obstacle (natural orifices in the heart, A-V nodal region) or through an abnormal tract, finds the original spot in an advanced state of recovery and reexcites it, setting up recurrent activation of adjacent myocardium (Fig. 39.2). This type of reentry is often responsible for PSVT, atrial flutter and atrioventricular reciprocal rhythm in WPW.

Reentry occurring in an anatomically fixed circuit can be permanently cured by radiofrequency catheter ablation of the defined pathway.

(ii) *Functional reentry* In this type of reentry there is no fixed 'obstacle' or 'pathway'. Rather, a functional obstacle (core of the circuit) and unidirectional conduction pathway is created by a premature impulse which travels through electrophysiologically inhomogeneous myocardium. On encountering refractory tissue in one direction, the wavefront travels through partially recovered fibres—gets markedly slowed and can set up small reentry circuits which may constantly shift location. Functional reentry may be responsible for ventricular extrasystoles, polymorphic ventricular tachycardia, atrial/ventricular fibrillation.

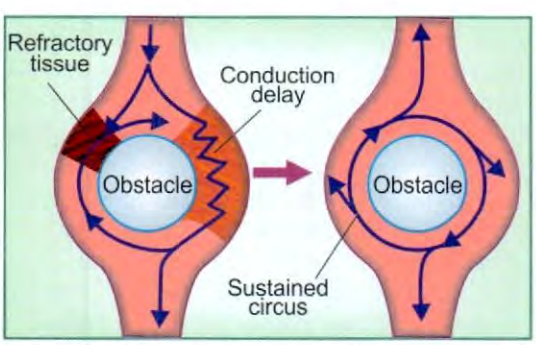


Fig. 39.2: Diagrammatic depiction of circus movement reentry in atrium

For reentry to occur, the path length of the circuit should be greater than the wave length (ERP × conduction velocity) of the impulse. Slow conduction in the reentrant circuit may be caused by:

(a) Partial depolarization of the membrane decreases the slope of phase 0 depolarization, i.e. depressed fast channel response.

(b) Cells changing over from fast channel to slow channel depolarization which conducts extremely slowly. When a fibre is depolarized to a RMP of about –60 mv, the Na^+ (fast) channels are inactivated, but the fibre can still develop Ca^{2+} (slow) channel response.

Reentry can be abolished both by marked slowing of conduction (converting unidirectional block to bidirectional block) as well as by acceleration of impulse (retrograde impulse reaches so early as to meet refractory tissue).

(iii) *Fractionation of impulse* When atrial ERP is brief and inhomogeneous (under vagal overactivity), an impulse generated early in diastole gets conducted irregularly over the atrium, i.e. it moves rapidly through fibres with short ERP (which have completely recovered) slowly through fibres with longer ERP (partially recovered) and not at all through those still refractory. Thus, asynchronous activation of atrial fibres occurs resulting in atrial fibrillation (AF). This arrhythmia must be initiated by a premature depolarization, but is self sustaining, because passage of an irregular impulse leaves a more irregular refractory trace and perpetuates the inhomogeneity of ERPs.

The important types of cardiac arrhythmias are:

1. *Extrasystoles (ES)* are premature ectopic beats due to abnormal automaticity or after-depolarization arising from an ectopic focus in the atrium (AES), A-V node (nodal ES) or ventricle (VES). The QRS complex in VES is broader and abnormal in shape.
2. *Paroxysmal supraventricular tachycardia (PSVT)* is sudden onset episodes of atrial tachycardia (rate 150–200/min) with 1:1 atrioventricular conduction: mostly due to circus movement type of reentry occurring within or around the A-V node or using an accessory pathway between atria and ventricle (Wolff-Parkinson-White syndrome or WPW).
3. *Atrial flutter (AFl)* Atria beat at a rate of 200–350/min and there is a physiological 2:1 to 4:1 or higher A-V block (because A-V node cannot transmit impulses faster than 200/min). AFl is mostly due to a stable reentrant circuit in the right atrium, but some

cases may be due to rapid discharge of an atrial focus.

4. *Atrial fibrillation (AF)* Atrial fibres are activated asynchronously at a rate of 350–550/min (due to electrophysiological inhomogeneity of atrial fibres), associated with grossly irregular and often fast (100–160/min) ventricular response. Atria remain dilated and quiver like a bag of worms. It is the most common chronic arrhythmia.
5. *Ventricular tachycardia (VT)* is a run of 4 or more consecutive ventricular extrasystoles. It may be a sustained or nonsustained arrhythmia, and is due either to discharges from an ectopic focus or after-depolarizations or single site (monomorphic) or multiple site (polymorphic) reentry circuits.
6. *Torsades de pointes* (French: twisting of points) is a life-threatening form of polymorphic VT with rapid QRS complexes which appear as undulating wave around the baseline in the ECG. Hypokalaemia and hypomagnesemia predispose to torsades de pointes, which is generally associated with long Q-T interval.
7. *Ventricular fibrillation (VF)* is grossly irregular, rapid and fractionated activation of ventricles resulting in incoordinated contraction of its fibres with loss of pumping function. It is fatal unless reverted within 2–5 min. VF is the most common cause of sudden cardiac death.
8. *Atrio-ventricular (A-V) block* is due to depression of impulse conduction through the A-V node and bundle of His, mostly due to vagal influence or ischaemia.

   First degree A-V block: Slowed conduction resulting in prolonged P-R interval (>0.21 sec).

   Second degree A-V block: Some supraventricular complexes are not conducted: drop beats.

   Third degree A-V block: No supraventricular complexes are conducted; ventricle generates its own impulse; also called complete heart block.

Proarrhythmic potential of antiarrhythmic drugs

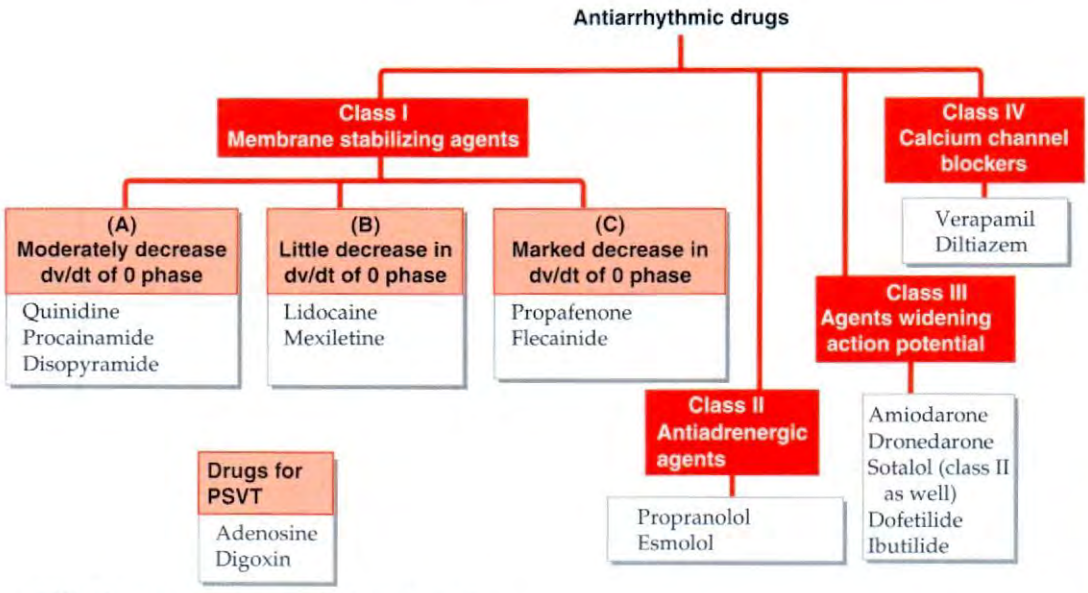
Most antiarrhythmics can themselves be the cause of serious arrhythmias, especially during long-term prophylactic use. Two multicentric trials 'Cardiac Arrhythmia Suppression Trial I and II' (CAST I, II, 1991, 1992) showed that post-MI patients randomized to receive encainide, flecainide, moricizine on a long-term basis had higher incidence of sudden death, though initially the same drugs had suppressed VES in these patients. It is possible that during transient episodes of ischaemia, the intraventricular conduction slowing action of these drugs gets markedly accentuated resulting in VT and VF. Similar increased mortality has been reported by the "Mortality in the survival with D-sotalol (SWORD) trial. It is therefore not prudent to try and suppress all extrasystoles/arrhythmias, especially those not causing symptoms, with chronic prophylactic antiarrhythmic therapy. Only the β blockers and amiodarone have been found to decrease cardiac mortality in the long term.

Drugs that prolong Q-T interval (have potential to precipitate Torsades de pointes)

1. *Antiarrhythmics*	:	Quinidine, procainamide, disopyramide, propafenone, amiodarone
2. *Antimalarials*	:	Quinine, mefloquine, artemisinin, halofantrine
3. *Antibacterials*	:	Sparfloxacin, moxifloxacin
4. *Antihistaminics*	:	Terfenadine, astemizole, ebastine
5. *Antidepressants*	:	Amitryptyline and other tricyclics
6. *Antipsychotics*	:	Thioridazine, pimozide, aripiprazole, ziprasidone
7. *Prokinetic*	:	Cisapride

CLASSIFICATION

Antiarrhythmic drugs act by blocking myocardial Na^+, K^+ or Ca^{2+} channels. Some have additional or even primary autonomic effects. Classification of antiarrhythmic drugs has been difficult, because many drugs have more than one action. Vaughan Williams and Singh (1969) proposed a 4 class system which takes into account the primary electrophysiological action of a drug that may serve to indicate the type of clinical effects and therapeutic utility. However, different drugs within a class have their own specific set of properties.



PSVT: Paroxysmal supraventricular tachycardia

A simplified clinical classification of antiarrhythmic drugs is given at the end of the chapter.

CLASS I

The primary action of drugs in this class is to limit the conductance of Na^+ (and K^+) across cell membrane—a local anaesthetic action. They also reduce rate of phase-4 depolarization in automatic cells.

The class I drugs bind easily to the activated and/or inactivated state of the Na^+ channel, but poorly to the resting state. As such, they block more when activation and inactivation is fast, i.e. in rapidly firing fibres. This is also called 'use dependent' blockade. Further, the partially depolarized fibres are blocked to a greater extent, because in them greater number of Na^+ channels are in the inactivated state.

SUBCLASS IA

The subclass IA containing the oldest antiarrhythmic drugs *quinidine* and *procainamide* are open state Na^+ channel blockers with little effect on resting channels. They also moderately delay channel recovery (channel recovery time $\tau_{recovery}$ 1–10s), suppress A-V conduction and prolong refractoriness. The Na^+ channel blockade is greater at higher frequency (premature depolarization is affected more). These actions serve to extinguish ectopic pacemakers that are often responsible for triggered arrhythmias and abolish reentry by converting unidirectional block into bidirectional block.

Quinidine

It is the dextro isomer of the antimalarial alkaloid quinine found in cinchona bark. In addition to Na^+ channel blockade, quinidine has cardiac antivagal action which augments prolongation of atrial ERP and minimizes RP disparity of atrial fibres. A-V node ERP is increased by direct action of quinidine, but decreased by its antivagal action; overall effect is inconsistent. Quinidine depresses myocardial contractility; failure may be precipitated in damaged hearts.

ECG: Quinidine increases P-R and Q-T intervals and tends to broaden QRS complex. Changes in the shape of T wave may be seen reflecting effect on repolarization.

Mechanism of action: Quinidine blocks myocardial Na^+ channels in the open state—reduces automaticity and rate of 0 phase depolarization in a frequency dependent manner.

Prolongation of APD is due to K^+ channel block, while lengthening of ERP is caused by its moderate effect on recovery of Na^+ and K^+ channels. At high concentrations it also inhibits L type Ca^{2+} channels. Quinidine decreases the availability of Na^+ channels as well as delays their reactivation.

The extracardiac actions of quinidine are fall in BP (due to weak α adrenergic blockade and direct cardiac depression), decreased skeletal muscle contractility, augmented uterine contractions, vomiting, diarrhoea and neurological effects like ringing in ears, vertigo, deafness, visual disturbances and mental changes (Cinchonism). Like its levo isomer, it has antimalarial action, and has been used as a parenteral alternative to quinine for falciparum malaria. The important drug interactions of quinidine are:

- Rise in blood levels and toxicity of digoxin due to displacement from tissue binding and inhibition of P-glycoprotein mediated renal and biliary clearance of digoxin.
- Exaggerated fall in BP in patients receiving vasodilators.
- Risk of *torsades de pointes* is increased by hypokalaemia caused by diuretics.
- Synergistic cardiac depression with β-blockers, verapamil, K^+ salts.
- Quinidine inhibits CYP2D6: prolongs t½ of propafenone and inhibits conversion of codeine to morphine.

Use: Though quinidine is effective in many atrial and ventricular arrhythmias, it is seldom used now, because of risk of adverse effects, including that of *torsades de pointes*, sudden cardiac arrest or VF; idiosyncratic angioedema, vascular collapse, thrombocytopenia, etc.

In a dose of 100–200 mg TDS quinidine may rarely be used to maintain sinus rhythm after termination of AF or AFl.

QUINIDINE SULPHATE 200 mg tab; NATCARDINE 100 mg tab.

Procainamide

It is orally active amide derivative of the local anaesthetic procaine, with cardiac electrophysiological actions almost identical to those of quinidine, *viz.* slowing of upstroke of AP and impulse conduction, prolongation of APD, ERP, QRS complex and Q-T interval. Significant differences between the two are:

- Procainamide is less effective in suppressing ectopic automaticity than quinidine.
- Procainamide is a weaker depressant of cardiac contractility and A-V conduction.
- Antivagal action is absent.
- Procainamide is not an α blocker: causes less fall in BP. At high doses, fall in BP is due to ganglionic blockade.

Pharmacokinetics Oral bioavailability of procainamide is about 75%, peak plasma concentration occurs in 1 hour. It is metabolized in liver, primarily by acetylation to N-acetylprocainamide (NAPA) which has no Na^+ channel blocking property but blocks K^+ channels and prolongs repolarization: APD is lengthened. This may be responsible for *torsades de pointes* occurring in procainamide toxicity. There are fast and slow acetylators of procainamide (as for isoniazid). Plasma t½ is relatively short (3–4 hours).

Dose: For abolition of arrhythmia—0.5–1 g oral or i.m. followed by 0.25–0.5 g every 2 hours; or 500 mg i.v. loading dose (25 mg/min injection) followed by 2 mg/kg/hour. Maintenance dose—0.5 g every 4–6 hours.
PRONESTYL 250 mg tab., 1 g/10 ml inj.

Adverse effects Gastrointestinal tolerance of procainamide is better than quinidine, but nausea and vomiting do occur.

Weakness, mental confusion and hallucinations are noted at higher doses.

Flushing and hypotension are seen on rapid i.v. injection. Cardiac toxicity, ability to cause *torsades de pointes* are similar to quinidine.

Hypersensitivity reactions are rashes, fever, angioedema. Agranulocytosis and aplastic anaemia is rare.

Long-term high dose procainamide therapy can cause systemic lupus erythematosus (SLE), especially in slow acetylators.

Use Procainamide (i.v.) is a second line drug to terminate monomorphic VT and some supraventricular arrhythmias. Many WPW reciprocal VTs respond and it has been used to prevent recurrences of VF. However, oral use of procainamide has been dropped due to poor efficacy and risk of proarrhythmia as well as lupus.

Disopyramide

It is a quinidine like Class IA drug that has prominent cardiac depressant and anticholinergic actions, but no α adrenergic blocking property. Disopyramide usually has no effect on sinus rate because of opposing direct depressant and antivagal actions. Prolongation of P-R interval and QRS broadening are less marked.

Pharmacokinetics Bioavailability of oral disopyramide is about 80%. It is partly metabolized in liver by dealkylation, nearly half is excreted unchanged in urine; plasma t½ is 6–8 hrs. The t½ is increased in patients of MI and in renal insufficiency.

Dose: 100–150 mg 6–8 hourly oral.
NORPACE 100, 150 mg cap, REGUBEAT 100 mg tab.

Adverse effects Disopyramide causes less g.i. effects. Anticholinergic side effects are prominent: dry mouth, constipation, urinary retention (especially in elderly males), and blurred vision; which limit its long term use. Risk of torsades de pointes is like other class IA drugs.

Depression of cardiac contractility is more prominent. Cardiac decompensation and hypotension may occur in patients with damaged hearts because it also increases peripheral resistance, so that cardiac output may be markedly decreased.

Contraindications are—sick sinus, cardiac failure and prostate hypertrophy.

Use The primary indication of disopyramide is as a second line drug for prevention of recurrences of ventricular arrhythmia, but its use has declined. It may also be used for maintenance therapy after cardioversion of AF or AFl and to treat vagally mediated AF. The negative inotropic property of disopyramide has been utilized to afford symptomatic relief in hypertrophic cardiomyopathy with left ventricular outflow obstruction.

SUBCLASS IB

These drugs block Na^+ channels more in the inactivated than in the open state, but do not delay channel recovery (channel recovery time < 1S). They do not depress A-V conduction or prolong (may even shorten) APD, ERP and Q-T.

Lidocaine (Lignocaine)

It is the most commonly used local anaesthetic (*see* Ch. 26). In addition, it is a popular antiarrhythmic in intensive care units.

The most prominent cardiac action of lidocaine is suppression of automaticity in ectopic foci. Enhanced phase-4 depolarization in partially depolarized or stretched PFs, and after-depolarizations are antagonized, but SA node automaticity is not depressed.

The rate of 0 phase depolarization and conduction velocity in A-V bundle or ventricles is not decreased. Lidocaine abbreviates (contrast quinidine which prolongs) APD in PF and ventricular muscle, but has practically no effect on APD and ERP of atrial fibres. Atrial reentry is not affected. However, it can suppress reentrant ventricular arrhythmias either by abolishing one-way block or by producing two way block.

Lidocaine is a blocker of inactivated Na^+ channels more than that of open state. As such, it is relatively selective for partially depolarized cells and those with longer APD (whose Na^+ channels remain inactivated for longer period). While normal ventricular and conducting fibres are minimally affected, depolarized/damaged fibres are significantly depressed. Brevity of atrial AP and lack of lidocaine effect on channel recovery might explain its inefficacy in atrial arrhythmias.

Lidocaine has minimal effect on normal ECG; QT interval may decrease. It causes little depression of cardiac contractility or arterial BP. There are no significant autonomic actions: all cardiac effects are direct actions.

Pharmacokinetics Lidocaine is inactive orally due to high first pass metabolism in liver. Action of an i.v. bolus lasts only 10–20 min because of rapid redistribution. It is hydrolysed, deethylated and conjugated; metabolites are excreted in urine. Metabolism of lidocaine is hepatic blood flow dependent.

The t½ of early distribution phase is 8 min while that of later elimination phase is nearly 2 hours. Its t½ is prolonged in CHF, because of decrease in volume of distribution and hepatic blood flow: rate of infusion should be reduced.

Dose and preparations Lidocaine is given only by i.v. route: 50–100 mg bolus followed by 20–40 mg every 10–20 min or 1–3 mg/min infusion.

XYLOCARD, GESICARD 20 mg/ml inj. (5, 50 ml vials). These preparations for cardiac use contain no preservative. The local anaesthetic preparations should not be used for this purpose.

Propranolol prolongs t½ of lidocaine by reducing hepatic blood flow. Cimetidine also increases plasma levels of lidocaine.

Adverse effects The main toxicity is dose related neurological effects:

Drowsiness, nausea, paresthesias, blurred vision, disorientation, nystagmus, twitchings and fits.

Lidocaine has practically no proarrhythmic potential and is the least cardiotoxic antiarrhythmic. Only excessive doses cause cardiac depression and hypotension.

Use Lidocaine is safe if given by slow i.v. injection; is used to suppress VT and prevent VF. It is ineffective in atrial arrhythmias. Because of rapidly developing and titratable action

it is a good drug in the emergency setting, e.g. arrhythmias following acute MI or during cardiac surgery. In acute MI, i.v. infusion of lidocaine can prevent VF, but a metaanalysis has shown that it fails to improve survival; may even increase short term mortality. Therefore, lidocaine is no longer administered prophylactically to all MI patients, but may be used in selected cases, and to treat ventricular arrhythmias when they occur.

Efficacy of lidocaine in chronic ventricular arrhythmia is poor, but it suppresses VT due to digitalis toxicity, for which it is used because it does not worsen A-V block.

Mexiletine

It is a local anaesthetic and an orally active antiarrhythmic; chemically and pharmacologically similar to lidocaine. Automaticity in PF is reduced both by decreasing phase-4 slope and by increasing threshold voltage. By reducing the rate of 0 phase depolarization in ischaemic PF it may convert one-way block to two-way block.

Mexiletine is almost completely absorbed orally, 90% metabolized in liver and excreted in urine; plasma t½ 9–12 hours.

Bradycardia, hypotension and accentuation of A-V block may attend i.v. injection of mexiletine.

Neurological side effects—tremor, nausea and vomiting are common; dizziness, confusion, blurred vision, ataxia can occur.

Dose: 100–250 mg i.v. over 10 min., 1 mg/min infusion. Oral: 150–200 mg TDS with meals.

MEXITIL 50, 150 mg caps, 250 mg/10 ml. inj.

Use Parenteral mexiletine may be used in post-infarction sinister ventricular arrhythmias as alternative to lidocaine. Survival is not improved in high risk patients. Oral use for long term suppression of VES/VT is of questionable merit; therefore, infrequently prescribed.

SUBCLASS IC

These are the most potent Na^+ channel blockers with more prominent action on open state and the longest recovery times (> 10S). They markedly delay conduction, prolong P-R interval, broaden QRS complex, but have variable effect on APD. Drugs of this subclass have high proarrhythmic potential when administered chronically; sudden deaths have occurred.

Propafenone By blocking Na^+ channels propafenone considerably depresses impulse transmission and has profound effect on His-Purkinje as well as accessory pathway conduction. Anterograde as well as retrograde conduction in the bypass tract of WPW syndrome is retarded. Propafenone prolongs APD and has β adrenergic blocking property—can precipitate CHF and bronchospasm. It is not suitable for patients with damaged hearts, and those with ischaemic heart disease.

Propafenone is absorbed orally and undergoes variable first pass metabolism; there being *extensive* or *poor* metabolizers because the major metabolic isoenzyme CYP2D6 is deficient in poor metabolizers. CYP2D6 inhibitors like fluoxetine increase its bioavailability and plasma concentration. Bioavailability and t½ differs considerably among individuals. Some metabolites are active. Side effects are nausea, vomiting, bitter taste, constipation and blurred vision. As mentioned above, it can worsen CHF, asthma and increase the risk of sudden death.

Propaphenone is used mainly for maintaining sinus rhythm in patients with peroxysmal or persistentAF. It has also been advocated for self-treatment of paroxysmal AF. It is useful for prophylaxis of PSVT involving A-V node or accessory pathway. It can occasionally increase ventricular rate in AFl by slowing atrial rate and allowing 1:1 A-V transmission, therefore, should be combined with an A-V node blocking drug. Propafenone has been used to treat VES and VT, but some reentrant VTs may be worsened.

Dose: 150 mg BD–300 mg TDS;
RHYTHMONORM, PRADIL 150 mg tab.

Flecainide It is the prototype class IC antiarrhythmic which markedly delays Na^+ channel recovery. In contrast to propafenone, flecainide has no consistent effect on APD and no β adrenergic blocking property. It suppresses VES, VT, WPW tachycardia and prevents recurrences of AF and PSVT. But in the CAST study it was found to increase mortality in patients recovering from MI; can itself provoke arrhythmias during chronic therapy. It is reserved for resistant cases of paroxysmal AF and for life-threatening sustained VT in patients not having associated CHF.

CLASS II

The primary action of class II drugs is to suppress adrenergically mediated ectopic activity.

Propranolol (*see* Ch. 10) It is the most commonly selected β blocker for treatment and prevention of cardiac arrhythmias. At high doses some quinidine like direct membrane stabilizing action is also evident. However, in the clinically used dose range—antiarrhythmic action is exerted primarily because of cardiac adrenergic blockade. In a normal resting individual propranolol has only mild depressant action on SA node automaticity, but marked decrease in the slope of phase-4 depolarization and automaticity occurs in SA node, PF and other ectopic foci when the same has been increased under adrenergic influence. The other most important action is to prolong the ERP of A-V node (an antiadrenergic action). This impedes A-V conduction so that no paradoxical tachycardia can occur when atrial rate is reduced in AF or AFl (as occurs with quinidine).

Slow channel responses and after-depolarizations that have been induced by catecholamines (CAs) are suppressed. Reentrant arrhythmias that involve A-V node (many PSVTs) or that are dependent on slow channel/depressed fast channel response may be abolished by its marked depressant action on these modalities.

The most prominent ECG change is prolongation of PR interval. Depression of cardiac contractility and BP are mild.

Administration For rapid action, propranolol may be injected i.v. 1 mg/min (max. 5 mg) under close monitoring. The usual oral antiarrhythmic dose is 40–80 mg 2–4 times a day.

Use Propranolol is very useful in treating inappropriate sinus tachycardia. Atrial and nodal ESs, especially those provoked by emotion or exercise are suppressed by propranolol, but these ESs need to be treated only when symptomatic and disturbing. Propranolol is less effective than adenosine and verapamil for termination of PSVT (success rate ~ 60%), but can be used to prevent recurrences.

Propranolol rarely abolishes AF or AFl, but is used to control ventricular rate in patients with these arrhythmias. It is highly effective in sympathetically mediated arrhythmias seen in pheochromocytoma and during anaesthesia with halothane. Digitalis induced and thyrotoxicosis associated tachyarrhythmias may be suppressed.

Propranolol is less effective than Class I and Class III drugs in suppressing VES and VT, but some nonsustained VTs may respond, and it may prevent recurrences of VT. Its antiischaemic action may also be protective. Prophylactic treatment with β blockers reduces mortality in post-MI patients. Propranolol or esmolol injected i.v. may terminate *torsades de pointes*. Along with a class IA or IC drug, it may be used for WPW reciprocal rhythms. Combination of β blocker with amiodarone has been found to afford additive protection against life-threatening arrhythmias in intensive care units.

Esmolol (*see* p. 163) This quick and short acting β_1 blocker administered i.v. is very useful for emergency control of ventricular rate in AF/AFl. It can terminate supraventricular tachycardia, and is mainly used for arrhythmias associated with anaesthesia where rapidly developing β adrenergic blockade is desired.
MINIBLOCK 100 mg/10 ml, 250 mg/10 ml inj.; 0.5 mg/kg in 1 min followed by 0.05–0.2 mg/kg/min i.v. infusion.

CLASS III

The characteristic action of this class is prolongation of repolarization (phase-3); AP is widened and ERP is increased. The tissue remains refractory even after full repolarization: reentrant arrhythmias are terminated.

Amiodarone

This unusual iodine containing highly lipophilic long-acting antiarrhythmic drug exerts multiple (Class I, II, III and IV) actions:

- Prolongs APD and Q-T interval attributable to block of myocardial delayed rectifier K^+ channels. This also appears to reduce nonuniformity of refractoriness among different fibres.
- Preferentially blocks inactivated Na^+ channels (like lidocaine) with relatively rapid rate of channel recovery: more effective in depressing conduction in cells that are partially depolarized or have longer APD.

- Partially inhibits myocardial Ca^{2+} channels.
- Has noncompetitive β adrenergic blocking property and alters thyroid function.

Thus, amiodarone is a multichannel blocker with some additional activities.

Conduction is slowed and ectopic automaticity is markedly depressed, but that of SA node is only slightly affected. Effect of oral doses on cardiac contractility and BP are minimal, but i.v. injection frequently causes myocardial depression and hypotension.

Despite prolongation of APD, the arrhythmia (*torsades de pointes*) provoking potential of amiodarone is low, probably because it does not exhibit 'reverse use-dependence' of APD prolongation and a uniform action on this modality, or because of its multiple antiarrhythmic mechanisms. The prolongation of APD by other class III drugs is more marked at slower rates of activation (encouraging EAD) than at higher rates (reverse use-dependence), while with amiodarone it is independent of rate of activation.

Pharmacokinetics Amiodarone is incompletely and slowly absorbed from the g.i.t. Oral bioavailability varies from 35–65%. On daily oral ingestion the action develops over several days, even weeks. However, on i.v. injection, action develops rapidly. It has a very large volume of distribution, accumulates in muscle and fat from which it is slowly released and then metabolized in liver primarily by CYP3A4; and excreted mainly into bile. One metabolite is active. The duration of action is exceptionally long; t½ 3–8 weeks.

Dose: Amiodarone is mainly used orally 400–600 mg/day for few weeks, followed by 100–200 mg OD for maintenance therapy. 100–300 mg (5 mg/kg) slow i.v. injection over 30–60 min.

CORDARONE, ALDARONE, EURYTHMIC 100, 200 mg tabs, 150 mg/3 ml inj.

Use Amiodarone is effective in a wide range of ventricular and supraventricular arrhythmias including PSVT, nodal and ventricular tachycardia, AF, AFl, etc. Resistant VT and recurrent VF are the most important indications. It is also used to maintain sinus rhythm in AF when other drugs have failed. Rapid termination of ventricular (VT and VF) and supraventricular arrhythmias can be obtained by i.v. injection. WPW tachyarrhythmia is terminated by suppression of both normal and aberrant pathways.

The long duration of action makes amiodarone suitable for chronic prophylactic therapy. Apart from propranolol, it is the only antiarrhythmic drug which in the long term has been found to reduce sudden cardiac death. Because of high and broad spectrum efficacy and relatively low proarrhythmic potential, amiodarone is a very commonly used antiarrhythmic, despite its organ toxicity.

Adverse effects These are dose-related and increase with duration of therapy. Fall in BP, bradycardia and myocardial depression occurs on i.v. injection and after drug cumulation.

Nausea, gastrointestinal upset may attend oral medication, especially during the loading phase.

Photosensitization and sun burn like skin pigmentation occurs in about 10% patients. Corneal microdeposits are common with long-term use, may cause headlight dazzle, but are reversible on discontinuation.

Pulmonary alveolitis and fibrosis is the most serious toxicity of prolonged use, but is infrequent if daily dose is kept below 200 mg.

Peripheral neuropathy generally manifests as weakness of shoulder and pelvic muscles. Liver damage is rare. Amiodarone interferes with thyroid function in many ways including inhibition of peripheral conversion of T_4 to T_3 and interaction with thyroid hormone receptor. It is a source of iodine as well. Goiter, hypothyroidism and rarely hyperthyroidism may develop on chronic use.

Interactions Amiodarone can increase digoxin and warfarin levels by reducing their renal clearance. Additive A-V block can occur in patients receiving β blockers or calcium channel blockers.

Inducers and inhibitors of CYP3A4 respectively decrease and increase amiodarone levels.

Amiodarone itself inhibits CYP3A4, CYP2C9 and P-glycoprotein, to interact with many drugs.

Dronedarone This is a recently introduced noniodinated congener of amiodarone, less toxic, but also less effective class III antiarrhythmic. Clinical utility of dronedarone is limited to supraventricular arrhythmias; primary indication being maintenance of sinus rhythm in

haemodynamically stable patients of paroxysmal/non-permanent AF, and to control ventricular rate during AF/AFl.

In clinical trials, recurrence time for AF was increased by 2–3 times in dronedarone recipients. Like amiodarone, dronedarone is a multichannel blocker, inhibits delayed rectifier and other types of cardiac K^+ channels, inward Na^+ channel and L-type Ca^{2+} channel. The noncompetitive β adrenergic blocking activity is more marked compared to amiodarone, but it does not interfere with thyroid function. It increases myocardial APD, ERP and slows A-V conduction.

Dronedarone is less lipophilic; its absorption is doubled when taken with meals. It is metabolized by CYP3A4 and CYP2D6; inhibitors of these isoenzymes (Ketoconazole, erythromycin, metoprolol, etc.) markedly increase its blood levels. The elimination t½ is 24 hours. Side effects are mainly gastrointestinal disturbances, bradycardia, weakness, cough and dermatological reactions. Though it prolongs Q-T interval, risk of *torsades de pointes* is very low. Hypothyroidism, pulmonary fibrosis and peripheral neuropathy does not occur. Dronedarone is contraindicated in moderate-to-severe CHF, 2nd/3rd degree A-V block and in permanent AF.

Dose: 400 mg BD oral; MULTAQ, DILSAVE 400 mg tab.

Note: On the basis of two clinical trials PALLAS and ATHENA, the US-FDA in Dec 2011 issued a safety alert that dronedarone should not be used in AF patients who cannot and will not be converted to sinus rhythm (permanent AF), because it doubles the rate of stroke, heart failure and cardiovascular death in such patients. If during dronedarone therapy the patient is found to have AF, he should either be cardioverted or dronedarone should be stopped. Another trial (ANDROMEDA) has demonstrated that dronedarone therapy to prevent recurrence of AF, increases mortality due to worsening of heart failure in patients with ejection fraction <35%. Thus, it is contraindicated in such patients. A recent meta-analysis has also noted unfavourable cardiovascular and mortality outcomes with dronedarone, especially in patients with cardiovascular risk factors.

Sotalol (*see* p. 162) It is a nonselective β blocker having prominent Class III action of prolonging repolarization by blocking cardiac inward rectifier K^+ channels. It is a racemic mixture; the d-isomer has pure class III property, while the l-isomer is a β blocker. Sotalol is not a Na^+ channel blocker—does not depress conduction in fast response tissue, but delays A-V conduction and prolongs its ERP. Sotalol is effective in polymorphic VT, some WPW arrhythmias and for maintaining sinus rhythm in AF/AFl. Due to prolongation of APD and Q-T, risk of dose-dependent *torsades de pointes* is the major limitation. It is contraindicated in patients with long Q-T interval.

SOTALAR 40 mg tab, SOTAGARD 40, 80 mg tabs.

Dofetilide This newer antiarrhythmic prolongs APD and ERP by selectively blocking rapid component of delayed rectifier K^+ current (I_{kr}) without affecting other channels or receptors; has no autonomic or peripheral actions. It is therefore labelled as *pure* class III antiarrhythmic.

Oral dofetilide can convert AF or AFl to sinus rhythm in ~30% cases, but is more effective in maintaining sinus rhythm in converted patients, which is its primary indication. It is noteworthy that chronic therapy with dofetilide in patients with high risk of sudden cardiac death/post MI cases has not increased mortality, despite provoking *torsades de pointes* in some recipients. Dofetilide is mainly excreted unchanged in urine and produces few side effects. It is contraindicated in the presence of hypokalaemia and bradycardia.

Ibutilide This is another new class III antiarrhythmic that blocks rapid inward rectifier K^+ current (I_{kr}) used i.v. for pharmacological conversion of AFl and AF to sinus rhythm. Efficacy is higher in recent onset cases and in AFl compared to AF. Patients who respond, generally convert within 20–30 min of the injection. Induction of *Torsades de pointes* is a risk.

CLASS IV

The primary action of this class of drugs is to inhibit Ca^{2+} mediated slow channel inward current.

Verapamil

Of the many Ca^{2+} channel blockers, verapamil has the most prominent cardiac electrophysiological action (Table 39.1). It blocks L type Ca^{2+} channels and delays their recovery. Its antiarrhythmic aspects are described here, while other aspects are covered in Ch. 40 and 41.

The basic action of verapamil is to depress Ca^{2+} mediated depolarization. This suppresses automaticity and reentry dependent on slow

Table 39.1: Electrophysiological actions of calcium channel blockers

				Verapamil	*Diltiazem*	*Nifedipine*
1.	SA node automaticity			↓	↓, –	—
2.	Ventricular automaticity			↓, –	—	—
3.	ERP	:	atrial	—	—	—
		:	A-V nodal	↑↑	↑	↑↓
		:	ventricular	—	—	—
		:	bypass tract	↑↓	↑↓	—
4.	ECG	:	R-R interval	↑	↑↓	↓
		:	P-R interval	↑	↑	—

↑ : increase; ↓ : decrease; — no change

channel response which is more likely in partially depolarized fibres. Phase-4 depolarization in SA node is reduced resulting in bradycardia. Reflex sympathetic stimulation due to vasodilatation partly counteracts the direct bradycardia producing action. Delayed after-depolarizations in PFs are dampened.

The most consistent action of verapamil is prolongation of A-V nodal ERP. As a result A-V conduction is markedly slowed (P-R interval increases) and reentry involving A-V node is terminated. Intraventricular conduction, however, is not affected. Verapamil has negative inotropic action due to interference with Ca^{2+} mediated excitation-contraction coupling in myocardium. This may precipitate failure in damaged hearts.

Uses and precautions

1. PSVT—Verapamil can terminate attacks of PSVT; 5 mg i.v. over 2–3 min is effective in ~ 80% cases. However, i.v. verapamil carries the risk of marked bradycardia, A-V block, cardiac arrest and hypotension. It should not be used if PSVT is accompanied with hypotension or CHF and in patients who have received β blockers. For preventing recurrences of PSVT, verapamil 60 to 120 mg TDS may be given orally.

2. To control ventricular rate in AF or AFl: Verapamil in a dose range of 40–120 mg TDS oral causes a dose dependent reduction in ventricular rate and is a first line drug for this purpose. In case of inadequate response, digoxin may be added to it. Verapamil can also be injected i.v. for emergency control of ventricular rate in AF and AFl.

Reentrant supraventricular and nodal arrhythmias are susceptible to verapamil, but it is contraindicated in broad QRS complex WPW tachycardia in which it may abbreviate the ERP of bypass tract. A class IA (procainamide) or IC (propafenone) drug which prolongs ERP of bypass tract and depresses conduction is to be combined with verapamil so as to concurrently depress A-V conduction.

Verapamil has poor efficacy in ventricular arrhythmias. In contrast to β blockers, verapamil prophylaxis does not reduce mortality in post-MI patients. In some patients of VT, i.v. injection of verapamil has precipitated VF: therefore contraindicated. It is also not recommended for digitalis toxicity, because additive A-V block may occur. It is contraindicated in partial heart block and sick sinus.

CALAPTIN 40, 80 mg tab; 120, 240 mg SR tab, 5 mg/2 ml inj.

Diltiazem The direct cardiac actions of diltiazem are similar to those of verapamil. However, bradycardia and depression of cardiac contractility are less marked. Diltiazem is an alternative to verapamil for termination as well as prophylaxis of PSVT.

For rapid control of ventricular rate in AF or AFl, i.v. diltiazem is preferred over verapamil, because it can be more easily titrated to the target heart rate, causes less hypotension or

myocardial depression and can be used even in the presence of mild-to-moderate CHF.
DILZEM 30, 60, 90 mg tabs, 25 mg/5 ml inj.

Drugs for PSVT

An attack of PSVT can be terminated by reflex vagal stimulation through Valsalva maneuver, splashing ice cold water on face, hyperflexion (head between knees), etc. Alternatively, or if it does not work, the drug of choice is adenosine (i.v.). Other alternatives are i.v. injection of verapamil/diltiazem/esmolol. To prevent recurrences, oral therapy with verapamil, diltiazem or propranolol alone or combined with digoxin may be prescribed.

Adenosine

Adenosine is an ultrashort acting endogenous purine signal molecule. Administered by rapid i.v. injection (over 1–3 sec) either as the free base (6–12 mg) or as ATP (10–20 mg), it terminates within 30 sec. more than 90% episodes of PSVT involving the A-V node. It activates ACh sensitive K^+ channels to accentuate inward rectifier K^+ current and causes membrane hyperpolarization through interaction with A1 type of adenosine GPCRs on SA node fibers (pacemaker depression → bradycardia), on A-V node fibres (prolongation of ERP → slowing of conduction) and in atrium (shortening of AP, reduced excitability). Adenosine indirectly reduces Ca^{2+} current in A-V node. Depression of the reentrant circuit through A-V node is responsible for termination of majority of PSVTs. Adrenergically induced DADs in ventricle are also suppressed. Coronary dilatation occurs transiently.

ADENOJECT, ADENOCOR 3 mg adenosine (base) per ml in 2 ml and 10 ml amp.

Adenosine has a very short t½ in blood (~10 sec) due to uptake into RBCs and endothelial cells where it is converted to 5-AMP and inosine. Almost complete elimination occurs in a single passage through coronary circulation. Injected ATP is rapidly converted to adenosine. Dipyridamole potentiates adenosine action by inhibiting uptake, while theophylline/caffeine antagonize its action by blocking A1 receptors. Higher doses may be required in heavy tea/coffee drinkers. Patients on carbamazepine are at greater risk of developing heart block. Advantages of adenosine for termination of PSVT are:

- Efficacy equivalent to or better than verapamil.
- Action lasts < 1 min; adverse effects (even cardiac arrest, if it occurs) are transient.
- No haemodynamic deterioration. It can be given to patients with hypotension, CHF or those receiving β blockers. Verapamil is contraindicated in these situations.
- Safe in wide QRS tachycardia (verapamil is unsafe).
- May be effective in patients not responding to verapamil.

However, adenosine produces transient dyspnoea, chest pain, fall in BP and flushing in 30–60% patients; ventricular standstill for few sec or VF occurs in some patients, but resolves quickly. Bronchospasm may be precipitated in asthmatics; verapamil is the drug of choice for such patients. Adenosine has to be rapidly injected in a large vein and has brief action. Therefore, it is not suitable for prophylaxis in recurrent cases.

Other uses of adenosine

(a) Diagnosis of tachycardias dependent on A-V node.
(b) To induce brief coronary vasodilatation during certain diagnostic/interventional procedures.
(c) To produce controlled hypotension during surgery.

Drugs for sinus tachycardia

Ivabradine

Inappropriate sinus tachycardia is a relatively uncommon disorder which may produce troublesome symptoms like palpation, dyspnoea, anxiety, dizziness, postural hypotension, and can precipitate angina. It is treated with drugs, only when symptomatic; and β blockers or verapamil are the first line drugs. *Ivabradine* is a pure bradycardic drug which lowers heart rate, but has no other significant cardiac action. It is primarily used as antianginal drug (*see* p. 600). Recently, it has been found clinically useful in symptomatic inappropriate sinus tachycardia as an alternative drug. Ivabradine lowers heart rate and relieves the symptoms, but should be used only when β blockers and verapamil are contraindicated or not tolerated.

Drugs for A-V Block

The definitive treatment of persistent heart block is pacing with an implanted cardiac pacemaker.

Drugs are of value only for acute/transient A-V block and as an interim measure.

Atropine: When A-V block is due to vagal overactivity, e.g. digitalis toxicity, some cases of MI; the block can be improved by atropine 0.6–1.2 mg i.m. Atropine abbreviates A-V node ERP and increases conduction velocity in bundle of His.

Sympathomimetics (Adr, isoprenaline): These drugs may overcome partial heart block by facilitating A-V conduction and shortening ERP of conducting tissues.

They may also be used in complete (3rd degree) heart block to maintain a sufficient idioventricular rate (by increasing automaticity of ventricular pacemakers) till external pacemaker can be implanted.

Choice and use of antiarrhythmic drugs

Mere detection of an arrhythmia does not necessitate treatment.

Asymptomatic arrhythmias and those which do not jeopardize haemodynamics, e.g. most AES and occasional VES, first degree A-V block, bundle branch block, etc. in an otherwise normal heart, do not require antiarrhythmic treatment; reassurance is enough. If a patient is particularly disturbed by AES, propranolol is the best option. Chronic prophylactic therapy with class I and class IV antiarrhythmics does not appear to afford survival benefit, except in few selected cases. The proarrhythmic potential of antiarrhythmic drugs and the increased risk of sudden cardiac death seems to offset any survival advantage that these drugs might afford over long-term. Only propranolol and to some extent amiodarone have been shown to reduce cardiovascular mortality in the long-term. On the other hand, vigorous therapy is indicated when:

- Arrhythmia is life-threatening, e.g. sustained VT, *torsades de pointes*, VF.
- Arrhythmia is causing hypotension, breathlessness, activity limitation or cardiac failure.
- Palpitation is marked, e.g. in PSVT, sustained VT, AF, *torsades de pointes*.
- When simple arrhythmia may lead to more serious ones, e.g. after MI (warning arrhythmias).

In the above situations antiarrhythmic drugs are mostly needed for short periods. Majority of antiarrhythmic drugs have narrow margin of safety. A simple clinical classification of antiarrhythmic drugs is presented in the box below.

The selection of an antiarrhythmic in a patient depends on:

(a) ECG diagnosis
(b) Possible mechanism underlying the arrhythmia
(c) Mechanism of action and range of antiarrhythmic activity of the drug
(d) Pharmacokinetic profile of the drug.
(e) Haemodynamic effects of the drug.

The aim is to improve cardiovascular function either by restoring sinus rhythm, or by controlling ventricular rate, or by conversion to a more desirable pattern of electrical and mechanical activity.

Despite extensive investigation, choice of an antiarrhythmic is still largely empirical. A practical guide to the choice and use of antiarrhythmic drugs is summarized in the box on next page.

Clinical classification of antiarrhythmic drugs

Supraventricular arrhythmias only	*Supraventricular and ventricular arrhythmias*		*Ventricular arrhythmias only*
Adenosine	Amiodarone	Procainamide	Lidocaine
Verapamil	β blockers	Disopyramide	Mexiletine
Diltiazem	Propranolol	Quinidine	
Dronedarone	Sotalol	Flecainide	
Digoxin	Esmolol	Propafenone	

Choice of antiarrhythmic drugs for cardiac arrhythmias

	Arrhythmia		*Clinical objective*	*Drug(s)*
1.	Atrial extrasystoles (Symptomatic)	:	Suppression, symptom relief	No drug if asymptomatic or non-disturbing Propranolol (only if disturbing)
2.	Paroxysmal supraventricular tachycardia (PSVT)	: :	Termination of PSVT Prevention of recurrence	i.v. adenosine / verapamil / diltiazem / esmolol Oral verapamil / diltiazem / propranolol / sotalol
3.	Atrial fibrillation (AF)	:	Reversal to SR (Rhythm control) (for paroxysmal / persistent AF)	Cardioversion i.v. amiodarone, catheter ablation
			Maintenance of SR	Sotalol / propafenone / amiodarone / dronedarone / dofetilide
		:	Ventricular rate control (for permanent AF / during recurrence of AF)	oral verapamil / diltiazem / propranolol ± digoxin
		:	Urgent vent. rate control	i.v. esmolol / verapamil / amiodarone
4.	Atrial flutter (AFl)	:	Reversal to SR	Cardioversion, radiofrequency ablation, Propafenone (after rate control with diltiazem / verapamil / propranolol)
		:	Ventricular rate control	Propranolol / verapamil / diltiazem ± digoxin or Amiodarone
5.	Wolff-Parkinson-White syndrome (WPW) tachycardia	: :	Termination Maintenance	Radiofrequency ablation, cardioversion
			- narrow QRS	Propafenone / procainamide
			- wide QRS	Propafenone + verapamil / propranolol or Amiodarone / sotalol
6.	Acute-MI arrhythmia			
	Bradycardia	:	Reversal to normal rate	Atropine (i.v.)—no effect—Pacing
	Vent. extrasystoles / tachycardia	:	Abolition to prevent serious arrhythmia	i.v. Lidocaine / procainamide / amiodarone Cardioversion (if haemodynamically unstable)
7.	Chronic vent. tachycardia			
	Nonsustained VT	:	Suppression	Propranolol / amiodarone (oral)
	Sustained VT	:	Abolition	i.v. Amiodarone ± propranolol or cardioversion or propafenone / lidocaine (i.v.)
		:	Maintenance therapy (prevention of VF / arrest)	Amiodarone / sotalol Implantable defibrillator
8.	Ventricular fibrillation (VF)	: :	Termination Recurrence prevention	Defibrillation ± amiodarone (i.v.) Amiodarone (oral) / propranolol

SR—Sinus rhythm

☞ PROBLEM DIRECTED STUDY

39.1 A sales executive aged 55 years presented with palpitation felt off-and-on, both during activity as well as at rest for the last one month or so. He also complained of tiredness and anxiety. The pulse was irregular in volume and frequency with average rate 104/min, respiration 20/min, BP 130/84 mm Hg, apex beat was irregular, with an average rate 120/min. Heart sounds were irregular, but there was no murmur. The ECG showed atrial fibrillation (AF) with no sign of ischaemia. A diagnosis of persistent AF was made, and it was decided to electrically cardiovert him. He was put on warfarin sod. 5 mg twice daily for 2 days followed by 5 mg once daily and dose to be adjusted to an INR between 2–2.5. This was to be maintained for 1 month before attempting cardioversion.

(a) Why the patient has been put on warfarin therapy before attempting cardioversion?
(b) Can some drugs be given to control and regularize his heart rate in the mean time? If so, which drug(s)?
(c) If electrical cardioversion does not succeed, can some drugs be given to revert him to sinus rhythm (SR)?
(d) After cardioversion, can some drugs be given to maintain SR and prevent recurrence of AF?

(see Appendix-1 for solution)

Chapter 40 Antianginal and Other Anti-ischaemic Drugs

ANTIANGINAL DRUGS

Antianginal drugs are those that prevent, abort or terminate attacks of angina pectoris.

Angina pectoris It is a pain syndrome due to induction of an adverse oxygen supply/demand situation in a portion of the myocardium. Metabolites that accumulate due to myocardial ischaemia elicit the pain. Two principal forms of angina are recognized:

(a) *Classical angina* (common form) Attacks are predictably provoked (stable angina) by exercise, emotion, eating or coitus and subside when the increased energy demand is withdrawn. The underlying pathology is—severe arteriosclerotic affliction of larger coronary arteries (conducting vessels) which run epicardially and send perforating branches to supply the deeper tissue (Fig. 40.1). The coronary obstruction is 'fixed'; blood flow fails to increase during increased demand despite local factors mediated dilatation of resistance vessels (Fig. 40.2) and ischaemic pain is felt. Due to inadequacy of ischaemic left ventricle, the end diastolic left ventricular pressure rises from 5 to about 25 mm Hg—produces subendocardial 'crunch' during diastole (blood flow to the subendocardial region occurs only during diastole) and aggravates the ischaemia in this region. Thus, a form of acutely developing and rapidly reversible left ventricular failure results which is relieved by taking rest and reducing the myocardial workload.

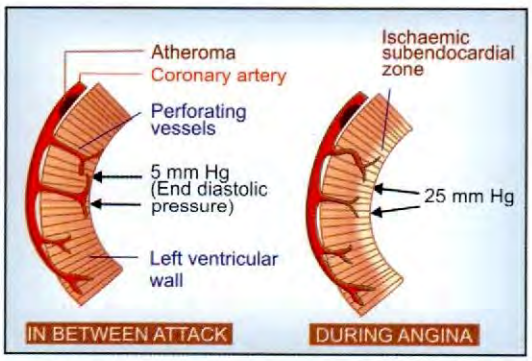


Fig. 40.1: Diagrammatic representation of subendocardial 'crunch' during an attack of angina

Drugs that are useful, primarily reduce cardiac work (directly by acting on heart or indirectly by reducing preload hence end diastolic pressure, and afterload). They may also cause favourable redistribution of blood flow to the ischaemic areas.

(b) *Variant/Prinzmetal/Vasospastic angina* (uncommon form) Attacks occur at rest or during sleep and are unpredictable. They are due to recurrent localized (occasionally diffuse) coronary vasospasm (Fig. 40.2) which may be superimposed on arteriosclerotic coronary artery disease. Abnormally reactive and hypertrophied segments in the coronary arteries have been demonstrated. Drugs are aimed at preventing and relieving the coronary vasospasm.

Unstable angina (UA) with rapid increase in duration and severity of attacks which may occur even during rest, is mostly due to rupture of an atheromatous plaque attracting platelet

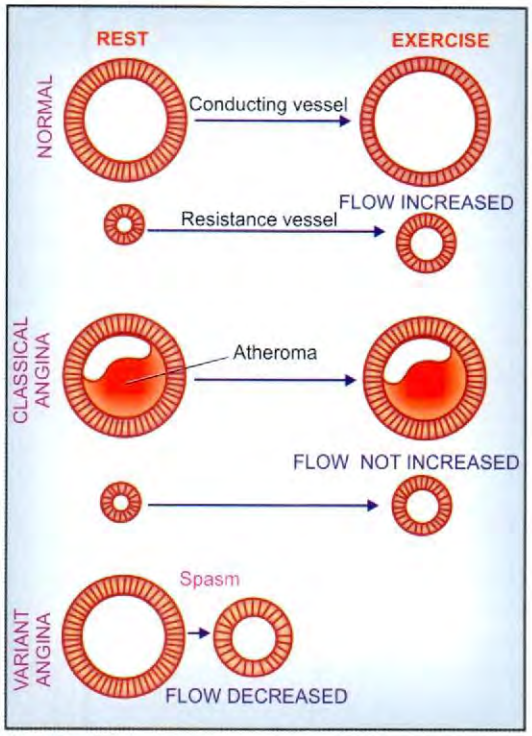


Fig. 40.2: Diagrammatic representation of coronary artery calibre changes in classical and variant angina

deposition and progressive occlusion of the coronary artery; occasionally with associated coronary vasospasm. Patients with UA are at high risk of myocardial infarction (MI).

Chronically reduced blood supply causes atrophy of cardiac muscle with fibrous replacement (reduced myocardial work capacity → CHF) and may damage conducting tissue to produce unstable cardiac rhythms. Antianginal drugs relieve cardiac ischaemia but do not alter the course of coronary artery disease (CAD); no permanent benefit is afforded. On the other hand, aspirin, ACE inhibitors and statins (hypocholesterolaemic) can modify coronary artery disease and improve prognosis.

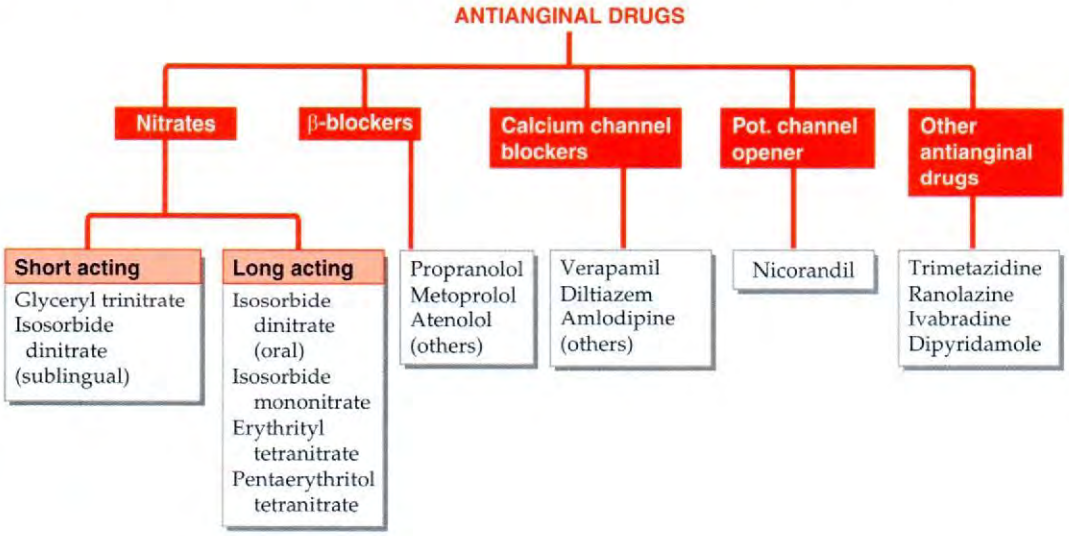
Glyceryl trinitrate, the drug unsurpassed in its ability to abort and terminate anginal attack, was introduced by Murrell in 1879. Other organic nitrates were added later, but a breakthrough was achieved in 1963 when propranolol was used for chronic prophylaxis. The calcium channel blockers have been a major contribution of the 1970s. A number of vasodilator and other drugs have been promoted from time to time, but none is uniformly effective. Some potassium channel openers (nicorandil), metabolic modulator (trimetazidine), late Na^+ current inhibitor (ranolazine) and heart rate lowering (ivabradine) have been introduced lately.

Clinical classification

A. *Used to abort or terminate attack* GTN, Isosorbide dinitrate (sublingually).
B. *Used for chronic prophylaxis* All other drugs.

NITRATES (GTN as prototype)

All organic nitrates share the same action; differ only in time course. The only major action is



direct nonspecific smooth muscle relaxation, particularly vascular smooth muscle.

Preload reduction Nitrates dilate veins more than arteries → peripheral pooling of blood → decreased venous return, i.e. preload on heart is reduced → end diastolic size and pressure are reduced. This decreases cardiac work according to *Laplace relationship* (*see p. 561*).

Reduction in ventricular radius decreases the tension that must be generated in the ventricular wall—hence decreased O_2 consumption. Reduction in cardiac output (c.o.) occurs at rest but is less marked during angina due to better ventricular emptying. The decrease in end diastolic pressure abolishes the subendocardial crunch by restoring the pressure gradient across ventricular wall due to which subendocardial perfusion occurs during diastole. It is through their action on peripheral veins that nitrates exert major beneficial effects in classical angina.

Afterload reduction Nitrates also produce some arteriolar dilatation → slightly decrease total peripheral resistance (t.p.r.) or afterload on heart; BP falls somewhat; systolic more than diastolic (reflex sympathetic activity tends to maintain diastolic BP). This action contributes to the reduction in cardiac work which is directly proportional to aortic impedance.

With usual doses, and if the patient does not stand still (which favours pooling of blood in the legs), tachycardia is not prominent. With large doses and if the mean BP falls significantly, reflex sympathetic stimulation occurs → tachycardia, increased cardiac contractility → increased cardiac work → angina may be precipitated. Fainting and cold sweat occur due to cerebral ischaemia. All these can be prevented by lying down and raising the foot end.

Redistribution of coronary flow In the arterial tree, nitrates preferentially relax bigger conducting (angiographically visible) coronary arteries than arterioles or resistance vessels. This pattern of action may cause favourable redistribution of blood flow to ischaemic areas in angina patients. Dilatation of conducting vessels all over by nitrate along with ischaemia-induced dilatation of autoregulatory resistance vessels restricted to the ischaemic zone increases blood flow to this area (*see* Fig. 40.5B), while in the non-ischaemic zones, resistance vessels maintain their tone → flow does not increase, or may decrease to compensate for increased flow to ischaemic zone. In fact, nitrates do not appreciably increase total coronary flow in angina patients.

Mechanism of relief of angina The relaxant effect on larger coronary vessels is the principal action of nitrates benefiting variant angina by counteracting coronary spasm. In classical angina undoubtedly the primary effect is to reduce cardiac work by action on peripheral vasculature, though increased blood supply to ischaemic area may contribute. Exercise tolerance of angina patients is improved because the same amount of exercise causes lesser augmentation of cardiac work.

Heart and peripheral blood flow Nitrates have no direct stimulant or depressant action on the heart. They dilate cutaneous vessels (especially over face and neck responsible for flushing) and meningeal vessels causing headache. Splanchnic and renal blood flow decreases to compensate for vasodilatation in other areas. Nitrates tend to decongest lungs by shifting blood to systemic circulation.

Other smooth muscles Bronchi, biliary tract and esophagus are mildly relaxed. Effect on intestine, ureter, uterus is variable and insignificant.

Mechanism of action Organic nitrates are rapidly denitrated enzymatically in the smooth muscle cell to release the reactive free radical *nitric oxide (NO)* which activates cytosolic soluble guanylyl cyclase → increased cGMP → causes dephosphorylation of myosin light chain kinase (MLCK) through a cGMP dependent protein kinase (PKG, Fig. 37.2, 40.3). Reduced availability of phosphorylated (active) MLCK interferes with activation of myosin → it fails to interact

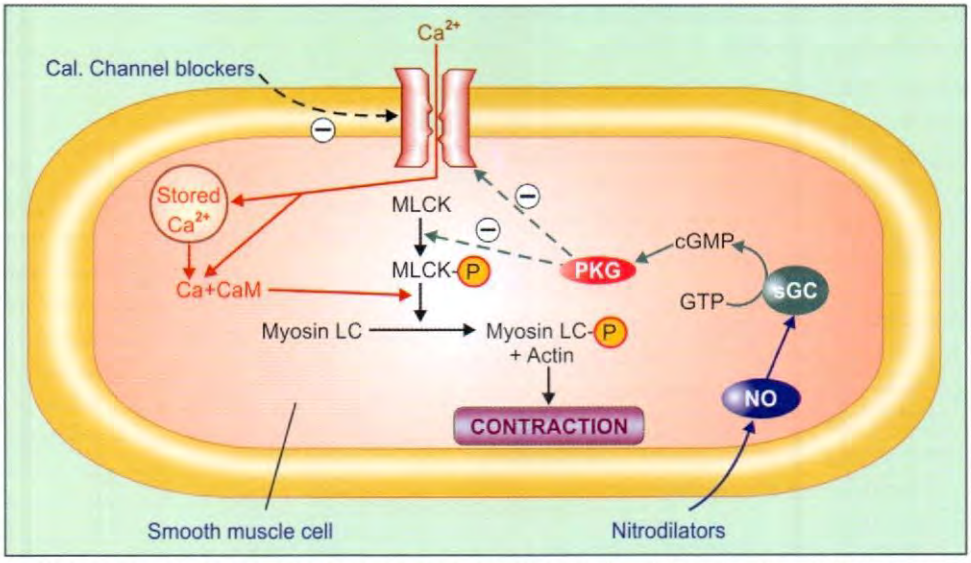


Fig. 40.3: Mechanism of vascular smooth muscle relaxant action of nitrodilators like glyceryl trinitrate and calcium channel blockers; (- - -→) Inhibition
CaM—Calmodulin; NO—Nitric oxide; MLCK—Myosin light chain kinase; MLCK-P—Phosphorylated MLCK; GTP—Guanosine triphosphate; cGMP—Cyclic guanosine monophosphate; Myosin LC—Myosic light chain; sGC—Soluble guanylyl cyclase; PKG—Protein kinase G

with actin to cause contraction. Consequently, relaxation occurs. Raised intracellular cGMP may also reduce Ca^{2+} entry—contributing to relaxation.

Veins express greater amount of mitochondrial aldehyde dehydrogenase, the enzyme that generates NO from GTN, than arteries. This may account for the predominant venodilator action. It has been suggested that preferential dilatation of epicardial conducting arteries over autoregulatory arterioles is also due to differential distribution of nitrate metabolizing enzymes in these vessels.

Platelets Though platelets are poor in mitochondrial aldehyde dehydrogenase, the NO generated from nitrates activates cGMP production in platelets as well, leading to a mild antiaggregatory effect. This action may be valuable in unstable angina.

Pharmacokinetics Organic nitrates are lipid-soluble: well absorbed from buccal mucosa, intestines and skin. Ingested orally, all except isosorbide mononitrate undergo extensive and variable first pass metabolism in liver. They are rapidly denitrated by a glutathione reductase and a mitochondrial aldehyde dehydrogenase. The partly denitrated metabolites are less active, but have longer t½. Though nitrates have been traditionally classified into short-acting and long-acting, it is the rate of absorption from the site of administration and the rate of metabolism that govern the duration of action of a particular nitrate. For example, GTN and isosorbide dinitrate are both short-acting from sublingual but longer-acting from oral route.

Adverse effects These are mostly due to vasodilatation.

- Fullness in head, throbbing headache; some degree of tolerance develops on continued use.
- Flushing, weakness, sweating, palpitation, dizziness and fainting; these are due to postural hypotension, and are mitigated by lying down. Standing still and alcohol accentuate these symptoms.
- Methemoglobinemia is not noticeable with clinically used doses; but can further reduce O_2 carrying capacity of blood in severe anaemia.

- Rashes are rare, though relatively more common with pentaerythritol tetranitrate.

Tolerance Attenuation of haemodynamic and antiischaemic effect of nitrates occurs in a dose and duration of exposure dependent manner if they are continuously present in the body. This tolerance weans off rapidly (within hours) when the body is free of the drug. Clinically, no significant tolerance develops on intermittent use of sublingual GTN for attacks of angina. However, it may become important when GTN is used orally, transdermally or by continuous i.v. infusion, as well as with the use of long acting agents, especially sustained release formulations. Cross tolerance occurs among all nitrates.

The mechanism of rapid nitrate tolerance is not well understood. It appears that the reactive oxygen species which are produced during denitration of organic nitrates themselves inhibit mitochondrial aldehyde dehydrogenase and related enzymes, so that further NO generation is interfered. Activation of compensatory mechanisms including volume expansion, sympathetic and renin-angiotensin system stimulation or other humoral pathways may contribute to nitrate tolerance.

The most practical way to prevent nitrate tolerance is to provide nitrate free intervals everyday.

Dependence On organic nitrates is now well recognized. Sudden withdrawal after prolonged exposure has resulted in spasm of coronary and peripheral blood vessels. MI and sudden deaths have been recorded. Angina threshold is lowered during the nitrate free interval in some patients: episodes of angina may increase. In such patients an antianginal drug of another class should be added. Withdrawal of nitrates should be gradual.

Interactions Sildenafil and other PDE-5 inhibitors cause dangerous potentiation of nitrate action: severe hypotension, MI and deaths are on record (*see* p. 328). Additive hypotension is possible when nitrate is given to a patient receiving other vasodilators.

Clinically used nitrates

1. Glyceryl trinitrate (GTN, Nitroglycerine)

It is a volatile liquid which is formulated by adsorbing on the inert matrix of the tablet and rendered nonexplosive. The tablets must be stored in a tightly closed glass (not plastic) container lest the drug should evaporate away. The sublingual route is used when terminating an attack or aborting an imminent one is the aim. The tablet may be crushed under the teeth and spread over buccal mucosa. It acts within 1–2 min (peak blood level in 3–6 min) because of direct absorption into systemic circulation (bypassing liver where almost 90% is metabolized).

Plasma t½ is 2 min, duration of action depends on the period it remains available for absorption from buccal mucosa. When anginal pain is relieved, the remaining part of tablet may be spit or swallowed. A sublingual spray formulation has been recently marketed—acts more rapidly and is more stable than sublingual tablet. Hepatic metabolizing capacity can be overwhelmed by administering a large dose (5–15 mg) orally. Sustained release oral capsules containing much larger amounts of GTN can be used for chronic prophylaxis.

Nitroglycerine is readily absorbed from the skin. A transdermal patch has been developed which provides steady delivery for 24 hours. The patch starts working within 60 min and has a bioavailability of 70–90%. However, tolerance to the haemodynamic effects develops. The effects start fading after 8–10 hours. It is advised that the patch be taken off for 8–10 hours daily. A transmucosal dosage form which has to be stuck to the gums under the upper lip has also been produced. It acts in 5 min and releases the drug for 4–6 hours.

Intravenous infusion of GTN provides rapid, steady, titratable plasma concentration for as long as desired. It has been successfully used

Table 40.1: Organic nitrates available for angina pectoris

	Drug	Preparations	Dose & route	Duration of action
1.	GTN (Nitroglycerine)	ANGISED 0.5 mg tab NITROLINGUAL, GTN SPRAY 0.4 mg per spray ANGISPAN-TR 2.5, 6.5 mg SR cap. NITROCONTIN, CORODIL 2.6, 6.4 mg tabs. NITRODERM-TTS 5 or 10 mg patch MYOVIN, MILLISROL, NITROJECT 5 mg/ml inj	0.5 mg sublingual 0.4–0.8 mg s.l. spray 5–15 mg SR oral One patch for 14–16 hr per day 5–20 µg/min i.v.	10–30 min 10–30 min 4–8 hr Till applied, max 24 hr. Till infused
2.	Isosorbide dinitrate	SORBITRATE 5, 10 mg tab, ISORDIL 5 mg sublingual & 10 mg oral tab. DITRATE 5, 10 mg tab; 20, 40 mg SR tab	5 mg sublingual 10–20 mg oral 10–40 mg SR oral	20–40 min 2–4 hr 6–10 hr
3.	Isosorbide-5-mononitrate	MONOTRATE 10, 20, 40 mg tab, 25, 50 mg SR tabs 5-MONO, MONOSORBITRATE 10, 20, 40 mg tab.	10–40 mg oral 10–40 mg SR oral	6–10 hr
4.	Erythrityl-tetranitrate	CARDILATE 5, 15 mg tab	15–60 mg oral	4–6 hr
5.	Pentaerythritol-tetranitrate	PERITRATE 10 mg tab PERITRATE-SA 80 mg SR tab	10–40 mg oral 80 mg SR oral	3–5 hr 8–12 hr

for unstable angina, coronary vasospasm, LVF accompanying MI, hypertension during cardiac surgery, etc. Begin with 5 µg/min, adjust according to need. Early institution of infusion may limit the size of infarct in MI.

2. Isosorbide dinitrate It is a solid but similar in properties to GTN; can be used sublingually at the time of attack (slightly slower in action than GTN, peak in 5–8 min) as well as orally for chronic prophylaxis. Presystemic metabolism on oral administration is pronounced and variable. The t½ is 40 min, but sustained release formulation may afford protection for 6–10 hours. Last dose should not be taken later than 6 PM to allow nitrate level to fall during sleep at night.

3. Isosorbide mononitrate This is an active metabolite of isosorbide dinitrate. When administered orally it undergoes little first pass metabolism: bioavailability is high, interindividual differences are minimal and it is longer acting (t½ 4–6 hr). Last dose is to be taken in the afternoon; SR tablet once a day in the morning.

4. Erythrityl tetranitrate and pentaerythritol tetranitrate These are longer-acting nitrates used only for chronic prophylaxis. Sustained release oral preparations are now available for 2–3 times a day dosing.

There has been considerable scepticism in the past about the efficacy of orally administered long-acting nitrates. Studies with high doses have shown that firstpass metabolism in liver can be saturated and haemodynamic effects lasting 4–6 hours do occur.

USES

1. *Angina pectoris* Nitrates are effective in classical as well as variant angina. For aborting or terminating an attack, sublingual GTN tablet or spray, or isosorbide dinitrate is taken on 'as and when required' basis. GTN produces relief within 3 min in 75% patients, the rest may require another dose

or take longer (upto 9 min). Nitrates increase exercise tolerance and postpone ECG changes of ischaemia. Longer-acting formulations (oral, transdermal) of GTN or other nitrates are used on regular schedule for chronic prophylaxis. However, development of tolerance and dependence may limit the usefulness of this approach: 6–8 drug free hours daily are advisable. Moreover, chronic nitrate therapy in angina does not decrease cardiac mortality. In terms of prognostic benefit chronic prophylactic therapy with CCBs is superior to long-acting nitrates in variant angina.

2. *Acute coronary syndromes (ACS)* These are characterized by rapid worsening of anginal status of the patient: include unstable angina (UA) and non-ST segment elevation myocardial infarction (NSTEMI). Aggressive therapy with a combination of drugs intended to prevent further coronary occlusion, increase coronary blood flow and decrease myocardial stress (oxygen demand) is needed. Nitrates are useful by decreasing preload (myocardial work) as well as by increasing coronary flow (dilatation and antagonism of coronary spasm, if present). Initially GTN is given sublingually, but if pain persists after 3 tablets 5 min apart, i.v. infusion of GTN is started. The role of nitrates appears to be limited to relief of pain, because no mortality benefit has been demonstrated in large randomized clinical trials such as GISSI-3 (1994) and ISIS-4 (1995).

Antiplatelet drugs like aspirin, clopidogrel, $GPII_b/III_a$ antagonists, with or without heparin are the primary measures in UA/NSTEMI. The weak antiaggregatory action of GTN is insufficient by itself, but may contribute to the benefit.The β blockers are indicated in all patients (if there are no contraindications) to reduce myocardial oxygen demand. A CCB is indicated only when coronary spasm is not effectively counteracted by the nitrate. Revascularization by thrombolytics/coronary angioplasty with stents/coronary bypass surgery is considered in high risk patients.

3. *Myocardial infarction (MI)* Administered by carefully titrated i.v. infusion to avoid hypotension and tachycardia, GTN is frequently used during evolving MI with the aim of relieving chest pain, pulmonary congestion and limiting the area of necrosis by favourably altering O_2 balance in the marginal partially ischaemic zone (a consequence of preload reduction). However, evidence that it decreases mortality is not robust; prognostic benefits appear marginal. Proper patient selection is important. GTN should not be administered if:

- Systolic BP is < 90 mm Hg
- Heart rate is < 50 or > 100 beats/min
- Right ventricular infarction is suspected
- Hypotension caused by nitrate limits the administration of β blockers which have more powerful salutary effects.
- Patient has taken sildenafil in the past 24 hours.

4. *CHF and acute LVF* The role of vasodilators in CHF is described in Ch. 38. Nitrates afford relief by venous pooling of blood (which can be aided by sitting posture while managing acute LVF or severe chronic CHF) → reduced venous return (preload) → decreased end diastolic volume → improvement in left ventricular function by *Laplace law* and regression of pulmonary congestion. Intravenous GTN is the preparation of choice for emergency use. Rate of infusion must be guided by continuous haemodynamic monitoring.

5. *Biliary colic* due to gall stone or morphine—responds to sublingual GTN or isosorbide dinitrate.

6. *Esophageal spasm* Sublingual GTN promptly relieves pain. Nitrates taken before a meal facilitate feeding in esophageal achalasia by reducing esophageal tone.

7. *Cyanide poisoning* Nitrates and nitrites generate methaemoglobin which has high affinity for cyanide radical (CN) and forms cyanomethaemoglobin. However, this may again dissociate to release cyanide. Therefore, sodium thiosulfate is given to form Sod. thiocyanate which is poorly dissociable and is excreted in urine.

Cytochrome and other oxidative enzymes are thus protected from cyanide; even the enzyme which has complexed CN is reactivated. However, early treatment is critical. The antidotes should be repeated as required.

Haemoglobin
↓ ← Sod. nitrite (10 ml of 3% solution i.v.)
Methaemoglobin
↓ ← Cyanide
Cyanomethaemoglobin
↓ ← Sod. thiosulfate (50 ml of 25% solution i.v.)
Methaemoglobin + Sod. thiocyanate
↓
Excreted in urine

Sodium nitrite is used for this purpose because it is a very weak vasodilator; large doses (>300 mg) sufficient to generate enough methaemoglobin can be injected i.v. without producing hypotension.

Alternative and probably safer antidotes that are being used in UK and USA are:

- *Hydroxocobalamin*: A form of vit B_{12} which has high affinity for CN, is injected i.v. in massive dose (5 g for adult or 70 mg/kg). It combines with CN to form cyanocobalamin (another form of vit B_{12}). It is particularly indicated in smoke inhalation during fire accidents (such smoke contains HCN).
- *Dicobalt edetate:* This cobalt compound also has high affinity for CN, and is indicated only in confirmed cases, because it can itself be toxic in non CN-poisoning cases. A dose of 300 mg (in 15 ml) is injected i.v. over 1 min, followed by 50 ml of 50% glucose solution.

β BLOCKERS (*see* Ch. 10)

These are very valuable antianginal drugs, but do not dilate coronaries or other blood vessels; total coronary flow is rather reduced due to blockade of dilator β_2 receptors. However, flow to the ischaemic subendocardial region is not reduced because of favourable redistribution and decrease in ventricular wall tension. β blockers act by reducing cardiac work and O_2 consumption as a consequence of decreased heart rate, inotropic state and mean BP. While these effects are marginal at rest, β blockers limit the increase in cardiac work that occurs during exercise or anxiety by their antiadrenergic action on heart. Reduction in heart rate indirectly improves coronary perfusion by prolonging diastole during which subendocardial perfusion occurs.

All β blockers, except those with intrinsic sympathomimetic activity (e.g. pindolol), are nearly equally effective in decreasing frequency and severity of attacks and in increasing exercise tolerance in classical angina, but the cardioselective agents (atenolol, metoprolol) are preferred over nonselective $\beta_1 + \beta_2$ blockers (e.g. propranolol). The latter are particularly prone to worsen variant angina due to unopposed α receptor mediated coronary constriction that may accentuate the coronary spasm. Long term β blocker therapy clearly lowers risk of sudden cardiac death among ischaemic heart disease patients. β blockers are the only antianginal drugs which prolong the life-expectancy of CAD patients. As per current guidelines, they should be the first line drugs in all stable angina patients, unless contraindicated.

The dose of β blockers has to be individualized. Abrupt discontinuation after chronic use may precipitate severe attacks, even MI.

Unstable angina (UA)/Non-ST-elevation MI (NSTEMI) Unless contraindicated, β blockers are routinely used in UA/NSTEMI. However, they should be given only after starting nitrate ± calcium channel blocker to counteract coronary vasospasm, if present (β blockers carry the risk of worsening coronary vasospasm). β blockers reduce myocardial O_2 demand and afford additional benefit by reducing risk of impending MI/sudden cardiac death.

CALCIUM CHANNEL BLOCKERS

Verapamil was developed in Germany in 1962 as a coronary dilator. It had additional cardiodepressant property, but its mechanism of action was not known. Fleckenstein (1967) showed that it interfered with Ca^{2+} movement into the cell. In the subsequent years, a large number of chemically diverse Ca^{2+} channel blockers have been produced.

The calcium channel blockers (CCBs) have been grouped into three chemical classes which have distinct pharmacodynamic profiles.

The dihydropyridines (DHPs) are lipophilic and are the most potent CCBs, while verapamil and diltiazem are relatively hydrophilic and less potent.

Calcium channels

Three types of Ca^{2+} channels have been described in smooth muscles (other excitable cells as well):

Voltage sensitive calcium channels

	L-type (Long lasting current)	T-type (Transient current)	N-type (Neuronal)
1. Conductance	25 pS	8 pS	12–20 pS
2. Activation threshold	High	Low	Medium
3. Inactivation rate	Slow	Fast	Medium
4. Location and function	• Excitation-contraction coupling in cardiac and smooth muscle • SA, A-V node—conductivity • Endocrine cells—hormone release • Neurones—transmitter release	• SA node—pace-maker activity • 'T' current and repetitive spikes in thalamic and other neurones • Endocrine cells—hormone release • Certain arteries—constriction	• Only on neurones in CNS, sympathetic and myenteric plexuses — transmitter release
5. Blocker	Nifedipine, diltiazem, verapamil	Mibefradil, flunarizine, ethosuximide	ω-Conotoxin

(a) *Voltage sensitive channel* Activated when membrane potential drops to around –40 mV or lower.

(b) *Receptor operated channel* Activated by Adr and other agonists—independent of membrane depolarization (NA contracts even depolarized aortic smooth muscle by promoting influx of Ca^{2+} through this channel and releasing Ca^{2+} from sarcoplasmic reticulum).

(c) *Leak channel* Small amounts of Ca^{2+} leak into the resting cell and are pumped out by Ca^{2+}ATPase. Mechanical stretch promotes inward movement of Ca^{2+}, through the leak channel or through separate *stretch sensitive channel.*

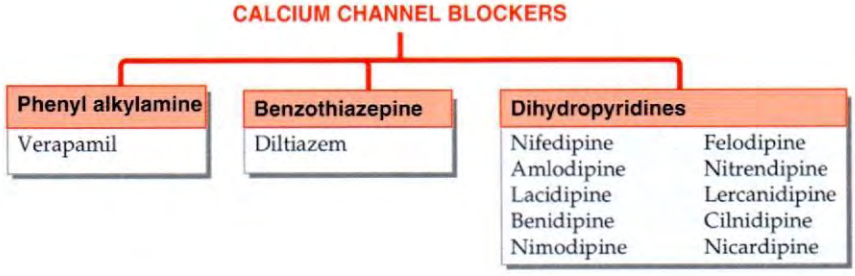
The *voltage sensitive Ca^{2+} channels* are heterogeneous: three major types have been identified (*see* box):

All voltage sensitive Ca^{2+} channels are membrane spanning funnel shaped glycoproteins that function as ion selective valves. They are composed of a major α_1 subunit which encloses the ion channel and other modulatory subunits like α_2,β, γ and δ. In L-type Ca^{2+} channels each subunit exists in multiple isoforms which may be site specific, e.g.

Skeletal muscle L-channels are: α_{1s} . α_2/δ_a . β_1 . γ
Cardiac muscle L-channels are: α_{1ca} . α_2/δ_c . β_2
Smooth muscle L-channels are: α_{1cb} . α_2/δ . β_3

Even smooth muscle L-channels differ between vascular and nonvascular. Moreover, distribution may be heterogeneous in different parts of the vascular bed.

Only the voltage sensitive L-type channels are blocked by the CCBs. All CCBs bind primarily to the open and inactivated states of the channel, and minimally to the resting state. The 3 groups of CCBs *viz.* phenylalkylamines (verapamil), benzothiazepine (diltiazem) and dihydropyridines (nifedipine) bind to their own specific binding sites on the α_1 subunit; all restricting Ca^{2+} entry, though characteristics of channel blockade differ. Further, different drugs may have differing affinities for various site specific isoforms of the L-channels. This may account for the differences in action exhibited by various CCBs. The vascular smooth muscle has a more depolarized membrane (RMP about –40 mV) than heart. This may contribute to the vascular selectivity of certain CCBs.



PHARMACOLOGICAL ACTIONS AND ADVERSE EFFECTS

The common property of all three classes of CCBs is to inhibit Ca^{2+} mediated slow channel component of action potential (AP) in smooth/cardiac muscle cell. The two most important actions of CCBs are:

(i) Smooth muscle (especially vascular) relaxation.

(ii) Negative chronotropic, inotropic and dromotropic action on heart.

Smooth muscle Smooth muscles depolarize primarily by inward Ca^{2+} movement through voltage sensitive L-type channel. These Ca^{2+} ions trigger release of more Ca^{2+} ions from intracellular stores and together bring about excitation-contraction coupling through phosphorylation of myosin light chain as depicted in Fig. 40.3. The CCBs cause relaxation by decreasing intracellular availability of Ca^{2+}. They markedly relax arterioles but have mild effect on veins. Extravascular smooth muscle (bronchial, biliary, intestinal, vesical, uterine) is also relaxed.

The dihydropyridines (DHPs) have the most marked smooth muscle relaxant and vasodilator action; verapamil is somewhat weaker followed by diltiazem.

Nitrendipine and few other DHPs have been shown to release NO from endothelium and inhibit cAMP-phosphodiesterase resulting in raised smooth muscle cAMP. These additional mechanisms may account for their predominant smooth muscle relaxant action. Released endothelial NO may exert antiatherosclerotic action as well.

Heart In the working atrial and ventricular fibres, Ca^{2+} moves in during the plateau phase of AP and releases more Ca^{2+} from sarcoplasmic reticulum. This Ca^{2+} surge causes contraction through binding to troponin—allowing interaction of myosin with actin (*see* Fig. 38.3). The CCBs would thus have negative inotropic action.

The 0 phase depolarization in SA and A-V nodes is largely Ca^{2+} mediated. Automaticity and conductivity of these cells appear to be dependent on the rate of recovery of the Ca^{2+} channel.

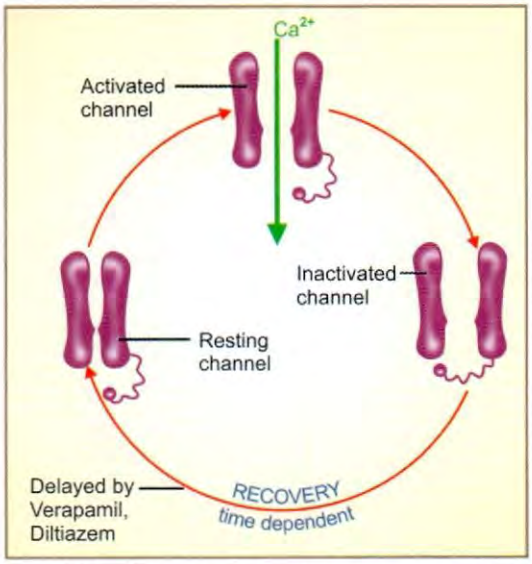


Fig. 40.4: Activation–inactivation–recovery cycle of cardiac Ca^{2+} channels

The L-type Ca^{2+} channels activate as well as inactivate at a slow rate. Consequently, Ca^{2+} depolarized cells (SA and A-V nodal) have a considerably less steep 0 phase and longer refractory period. The recovery process which restores the channel to the state from which it can again be activated (Fig. 40.4) by membrane depolarization is delayed by verapamil and diltiazem (resulting in depression of pacemaker activity and conduction), but not by DHPs (they have no negative chronotropic/dromotropic action). Moreover, channel blockade by verapamil is enhanced at higher rates of stimulation, that by nifedipine is independent of frequency, while diltiazem is intermediate. Thus, verapamil slows sinus rate and A-V conduction, but nifedipine does not. Effect of diltiazem on sinus node automaticity and A-V conduction is similar to that of verapamil.

The relative potencies to block slow channels in smooth muscle do not parallel those in the heart. The DHPs are more selective for smooth muscle L channels. At concentrations which cause vasodilatation they have negligible negative inotropic action which is most prominent

Table 40.2: Comparative properties of representative calcium channel blockers

		Verapamil	*Nifedipine*	*Diltiazem*
1.	Channel blocking potency	++	+++	+
2.	Frequency dependence of channel blockade	++	–	+
3.	Channel recovery rate	Much delayed	No effect	Delayed
4.	**Cardiac effects** (In vivo at usual clinical doses)			
	Heart rate	↓	↑	↓, –
	A-V conduction velocity	↓↓	–	↓↓
	Contractility	–, ↓	↑	↓,↑
	Output	–, ↓	↑	–, ↑
5.	Vascular smooth muscle relaxation	++	+++	+
6.	Clinical use in	Arrhythmia Angina (Hypertension)	Angina Hypertension Raynaud's	Angina Hypertension Arrhythmia

↑ increase; ↓ decrease; – no change

in verapamil. Diltiazem causes less depression of contractility than verapamil. Important differences between the three representative CCBs are summarized in Table 40.2. Their cardiac electrophysiological effects are compared in Table 39.1.

Verapamil It dilates arterioles and has some α adrenergic blocking activity, thereby decreases t.p.r. but BP is only modestly lowered. The pronounced direct cardiodepressant effect is partially offset *in vivo* by reflex effects of peripheral vasodilatation. The HR generally decreases, A-V conduction is slowed, but c.o. is maintained by reflex sympathetic stimulation and reduction in aortic impedance. However, ventricular contractility may be markedly impaired in CHF patients. Coronary flow is increased.

Dose: 40–160 mg TDS oral, 5 mg by slow i.v. injection. CALAPTIN 40, 80 mg tabs, 120, 240 mg SR tabs, 5 mg/2 ml inj. VASOPTEN 40, 80, 120 mg tab.

Adverse effects Constipation is the most common side effect. Bradycardia and nausea are more common than with DHPs, while flushing, headache and ankle edema are less common. Hypotension is occasional. It can accentuate conduction defects (contraindicated in 2nd and 3rd degree A-V block) and precipitate CHF in patients with preexisting disease. Cardiac arrest has occurred on i.v. injection and when it is given to patients with sick sinus.

Interactions Verapamil should not be given with β blockers—additive sinus depression, conduction defects or asystole may occur.

It increases plasma digoxin level by decreasing its excretion: toxicity can develop.

It should not be used along with other cardiac depressants like quinidine and disopyramide.

Diltiazem It is somewhat less potent vasodilator than nifedipine and verapamil, and has modest direct negative inotropic action, but direct depression of SA node and A-V conduction are equivalent to verapamil. A nonspecific antiadrenergic action has also been demonstrated. Usual clinical doses produce consistent fall in BP with little change or decrease in HR. Large dose or i.v. injection decreases t.p.r. markedly which may elicit reflex cardiac effects. Diltiazem dilates coronaries.

Dose: 30–60 mg TDS–QID oral; DILZEM, 30, 60 mg tabs, 90 mg SR tab; 25 mg/5 ml inj; ANGIZEM 30, 60, 90, 120, 180 mg tab, DILTIME 30, 60 mg tab; 90, 120 mg SR tab.

Adverse effects Side effects are milder, but the profile is similar to verapamil. Like verapamil, it increases plasma digoxin level.

Diltiazem should not be given to patients with preexisting sinus, A-V nodal or myocardial disease. Only low doses should be given to patients on β blockers.

Dihydropyridines (DHPs)

All DHPs have similar pharmacodynamic profile, but minor differences in organ selectivity and major differences in pharmacokinetic characteristics exist (Table 40.3). The slower and longer acting ones induce less reflex sympathetic stimulation. Tachycardia, propensity to increase cardiac work, flushing, headache, dizziness are subdued. They are the favoured DHPs because of milder side effects and because increased mortality among post-MI patients is reported with the regular short-acting nifedipine formulation.

Nifedipine It is the first and the prototype DHP, but infrequently used now. The overriding action is arteriolar dilatation → t.p.r. decreases, BP falls. The direct depressant action on heart is significant. As described above, it does not depress SA node or A-V conduction. Nifedipine acts rapidly, due to which reflex sympathetic stimulation of heart predominates producing tachycardia, increased contractility and c.o. No decrease in venous return along with lowering of afterload aids increase in c.o. Coronary flow is increased. The duration of action is short (3–6 hours).

Dose: 5–20 mg BD–TDS oral.

CALCIGARD, DEPIN, NIFELAT 5, 10 mg cap, also 10 mg, 20 mg S.R. (RETARD) tab; ADALAT RETARD 10, 20 mg SR tab.

Adverse effects Due to rapidly developing vasodilatation. Frequent side effects are palpitation, flushing, ankle edema, hypotension, headache, drowsiness and nausea. These are related to peaks of drug level in blood: can be minimized by low starting dose or use of retard formulation. Ankle edema is not due to fluid retention, but because of greater dilatation of precapillary than postcapillary vessels. Nifedipine has paradoxically increased the frequency of angina in some patients. Higher mortality among post MI patients has been confirmed. However, it has been safely administered with β blockers and digoxin.

By its relaxant effect on bladder nifedipine can increase urine voiding difficulty in elderly males. Gastroesophageal reflux may be worsened by all DHPs due to relaxation of lower esophageal sphincter.

Amlodipine Pharmacokinetically it is the most distinct DHP and the most popular. Oral absorption is slow, but complete; peak blood level occurs. after 6 to 9 hr—the early vasodilator side effects (palpitation, flushing, headache, postural dizziness) are largely avoided. Because of less extensive and less variable first pass metabolism, its oral bioavailability is higher and more consistent. Volume of distribution and t½ are exceptionally long: diurnal fluctuation in blood level is small and action extends over the next morning.

Dose: 5–10 mg OD; AMLOPRES, AMCARD, AMLOPIN, MYODURA 2.5, 5, 10 mg tabs.

S(–)Amlodipine The single enantiomer preparation is effective at half the dose and is claimed to cause less ankle edema.

Dose: 2.5–5 mg OD;

S-NUMLO, S-AMCARD, ASOMEX, ESAM 2.5, 5 mg tabs.

Felodipine It differs from nifedipine in having greater vascular selectivity, larger tissue distribution and longer t½. It is approved for symptomatic treatment of Raynaud's disease. The extended release preparation is suitable for once daily administration.

Dose: 5–10 mg OD, max. 10 mg BD.

FELOGARD, PLENDIL, RENDIL 2.5, 5, 10 mg ER tab.

Nitrendipine This DHP has an oral bioavailability of 10–30% and elimination t½ of 4–12 hours. Nitrendipine has been shown to release NO from the endothelium and inhibit cAMP phosphodiesterase. These may be the additional mechanisms of

vasodilator action. The endothelial NO may retard atherosclerosis. Ventricular contractility and A-V conduction are not depressed. Nitrendipine is indicated in hypertension and angina pectoris.

Dose: 5–20 mg OD; NITREPIN, CARDIF 10, 20 mg tabs.

Lacidipine A highly vasoselective DHP suitable for once daily administration. It is claimed to attain higher concentration in vascular smooth muscle membrane, and is approved only for use as antihypertensive.

Dose: 4 mg OD, increase to 6 mg OD if required.
LACIVAS, SINOPIL 2, 4 mg tabs.

Cilnidipine This DHP has been shown to inhibit N-type (neuronal) calcium channels in addition to the L-type channels, because of which it is claimed not to cause reflex tachycardia that occurs with other DHPs. Cilnidipine is approved for use in angina and in hypertension.

Dose: 5–20 mg OD; CILACAR, CILAGARD 5, 10 mg tabs.

Nimodipine It is a short-acting DHP which penetrates blood-brain barrier very efficiently due to high lipid solubility and has high affinity for the cerebral blood vessels. It is believed to selectively relax cerebral vasculature and is approved for prevention and treatment of neurological deficit due to cerebral vasospasm following subarachnoid haemorrhage or ruptured congenital intracranial aneurysms. Side effects are headache, flushing, dizziness, palpitation and nausea.

Dose: 30–60 mg 4–6 hourly for 3 weeks following subarachnoid haemorrhage; VASOTOP, NIMODIP, NIMOTIDE 30 mg tab; 10 mg/50 ml inj.

Nicardipine It is a highly vasoselective short acting DHP with more pronounced action on coronary and cerebral vessels. Direct effect on cardiac contractility and HR is minimal. Bioavailability of oral nicardipine is 35%; metabolism by CYP2C8, CYP2D6 and CYP3A4 is extensive and elimination t½ is 2–4 hours. The metabolites are excreted in both urine and faeces.

Nicardipine is water soluble, and is available as aqueous solution for i.v. use in hypertensive emergencies (*see* p. 618). Orally it is approved for use in chronic stable angina and Raynaud's disease.

Dose: 20–40 mg TDS or 30–60 mg BD as ER tab.
NICARDIPINE 25 mg/10 ml inj. 5–15 mg/hour i.v. infusion.

Lercanidipine Another DHP similar to nifedipine, but with longer duration of action. Peak plasma concentrations occur at 1.5–3 hrs; t½ is 5–10 hours. It is indicated in hypertension at a dose of 10–20 mg OD.
LEREZ, LERKA 10, 20 mg tabs.

Benidipine A long-acting DHP that owes its long duration of action to slow dissociation from the DHP receptor on the smooth muscle cell. Marketed only in India and Japan, it is indicated in hypertension and angina pectoris.

Dose: 4–8 mg OD; CARITEC 4, 8 mg tab.

PHARMACOKINETICS

The pharmacokinetic parameters of representative Ca^{2+} channel blockers are presented in Table 40.3. All CCBs are well absorbed orally, peak occurring at 1–3 hr (except amlodipine 6–9 hr), but the oral bioavailability is incomplete with marked inter- and intra-individual variations. This is due to high first pass metabolism (modest and less variable in case of amlodipine). All are highly plasma protein bound (min.: diltiazem 80%, max.: felodipine 99%).

The CCBs are high clearance drugs with extensive tissue distribution. All are > 90% metabolized in liver and excreted in urine. Some metabolites are active. The elimination t½ are in the range of 2–6 hr, but that of amlodipine is exceptionally long; followed by lacidipine, nitrendipine and felodipine.

On chronic use verapamil inhibits its own metabolism so that oral bioavailability is nearly doubled and t½ is prolonged.

Table 40.3: Pharmacokinetic characteristics of selected calcium channel blockers

	Drug	Bioavailability	Vd (L/Kg)	CL (L/hr/Kg)	Active metabolite	Elimin. t½ (hr)
1.	Verapamil	15–30%	5.0	0.9	Yes	4–6
2.	Diltiazem	40–60%	3.0	0.7	Yes	3–6
3.	Nifedipine	30–60%	0.8	0.42	Minor	2–5
4.	Felodipine	15–25%	10.0	1.0	None	12–18
5.	Amlodipine	60–75%	21.0	0.42	None	35–45

USES

Calcium channel blockers can be safely given to patients with obstructive lung disease and peripheral vascular disease in whom β blockers are contraindicated. The problem of rebound worsening of angina on withdrawal after chronic use is less marked with CCBs than with β blockers.

1. *Angina pectoris* All CCBs are effective in reducing frequency and severity of *classical as well as variant angina.* Benefit in classical angina appears to be primarily due to reduction in cardiac work, as a result of reduced afterload and the BP × HR product. Though, they can increase coronary flow in normal individuals, this is unlikely to be significant in patients with fixed arterial obstruction. Exercise tolerance is increased.

Many controlled studies and metaanalysis have concluded that myocardial ischaemia may be aggravated by short-acting DHPs. This may be due to decreased coronary flow secondary to fall in mean arterial pressure, reflex tachycardia and coronary steal. Trials using high dose regular short-acting nifedipine formulation have reported increased mortality among MI patients. The sudden rush of sympathetic activity evoked by each dose has been held responsible for the deleterious effect. The slow and long-acting DHPs do not share this disadvantage.

On the other hand, verapamil and diltiazem have a direct cardiodepressant effect which tends to reduce the O_2 demand. Vasodilatation and reflex sympathetic stimulation is also less marked. Thus, these CCBs are unlikely to aggravate myocardial ischaemia. However, they must be avoided in patients with heart failure or low EF. Amlodipine is the only CCB shown to be safe (not increase mortality) in CHF patients (PRAISE-2 trial, 2013).

Myocardial infarction: The concensus opinion is against use of CCBs in evolving MI as well as to prevent further attacks, but verapamil/diltiazem may be employed for the latter purpose when β blockers are contraindicated. There is no evidence that CCBs reduce mortality or improve outcome in post-MI patients.

The ability of CCBs to prevent arterial spasm is undoubtedly responsible for the beneficial effect in *variant angina.* Reduction of cardiac O_2 demand would also work in the same direction. No significant difference in efficacy among different CCBs has been noted in angina pectoris.

CCBs are not a first line treatment of *unstable angina,* but may be used as add-on therapy to nitrates when coronary vasospasm is prominent and is not counteracted by nitrate alone. Antiplatelet drugs and β blockers + a nitrate are the primary drugs which reduce infarction and mortality in UA. Use of DHPs in non-β blocked patients is to be avoided.

2. *Hypertension* The long acting DHPs, diltiazem and verapamil are among the first line drugs for hypertension (*see* Ch. 41).

3. *Cardiac arrhythmias* Verapamil and diltiazem are highly effective in PSVT and for control of ventricular rate in supraventricular arrhythmias (*see* Ch. 39).

4. *Hypertrophic cardiomyopathy* The negative inotropic action of verapamil can be salutary in this condition.

5. *Other uses* Nifedipine is an alternative drug for premature labour (*see* p. 359). The DHPs reduce severity of Raynaud's episodes by blocking vasospasm.

DRUG COMBINATIONS IN ANGINA

Along with any of the drugs used for chronic prophylaxis of angina, sublingual short-acting nitrate is allowed on 'as and when' required basis to abort and terminate anginal attacks when they occur. In addition to the symptomatic treatment with antianginal drugs, therapy aimed at modifying the course of coronary artery disease (CAD), and at cardioprotection with antiplatelet drugs, statins and ACE inhibitors is advised by professional guidelines. The β blockers ward-off attacks of angina as well as afford cardioprotection.

Of the three major classes of antianginal drugs described above, generally one agent is used initially; choice depends on the stage and severity of disease, associated cardiac/other medical conditions and individual acceptability of side effects. The antianginal efficacy and tolerability of long-acting nitrates (including transdermal GTN), β blockers and long-acting CCBs is similar. However, direct comparative studies have found β blockers to achieve greater reduction in the number of anginal attacks than CCBs. Moreover, they afford survival benefit. When monotherapy is unable to provide adequate relief in tolerated doses, concurrent use of 2 or 3 drugs may be required.

I. β blocker + long-acting nitrate combination is rational in classical angina because:

(a) Tachycardia due to nitrate is blocked by β blocker.

(b) The tendency of β blocker to cause ventricular dilatation is counteracted by nitrate.

(c) The tendency of β blocker to reduce total coronary flow is opposed by nitrate.

II. The above advantages may also be obtained by combining a slow acting DHP (in place of nitrate) with β blocker. The DHPs are particularly suitable if there is an element of coronary vasospasm in classical angina. However, verapamil or diltiazem should not be used with β blocker since their depressant effects on SA and A-V node may add up.

III. Nitrates primarily decrease preload, while CCBs have a greater effect on afterload and on coronary flow. Their concurrent use may decrease cardiac work and improve coronary perfusion to an extent not possible with either drug alone. This combination may be especially valuable in severe vasospastic angina, and when β blockers are contraindicated.

IV. In the more severe and resistant cases of classical angina, combined use of all the three classes is indicated. Since their primary mechanism of benefit is different, supraadditive results may be obtained.

- Nitrates primarily decrease preload.
- CCBs mainly reduce afterload + increase coronary flow.
- β blockers decrease cardiac work primarily by direct action on heart.

Verapamil/diltiazem should be avoided in such combinations.

POTASSIUM CHANNEL OPENER

Minoxidil and diazoxide are K^+ channel openers which were used earlier in severe hypertension and hypertensive emergencies. *Nicorandil* is a K^+ channel opener which was introduced as an antianginal drug in the 1990s, and is sporadically used as alternative to nitrates/CCBs. Multiple types of K^+ channels regulate movement of this ion across the cell membrane, out of which nicorandil opens the ATP-sensitive K^+ channels.

Nicorandil This dual mechanism antianginal drug activates ATP sensitive K^+ channels (K_{ATP}) in smooth muscle membrane thereby hyperpolarizing and relaxing it. The vasodilator action is partly antagonized by the K^+ channel blocker glibenclamide. Like nitrates it also acts as a NO donor—relaxes blood vessels by increasing cGMP. Thus, arterial dilatation is coupled with venodilatation, and both cardiac preload as well as afterload are reduced. Coronary flow is increased. No significant effects on cardiac contractility and conduction have been noted.

Beneficial effects on angina frequency and exercise tolerance comparable to nitrates and CCBs have been obtained in stable as well as vasospastic angina. Nicorandil is believed to exert cardioprotective action by simulating *'ischaemic preconditioning'* as a result of activation of mitochondrial K_{ATP} channels. Ischaemic preconditioning in a phenomenon in which brief periods of ischaemia and reperfusion exert a cardioprotective effect on subsequent total vascular occlusion, and involves opening of mito.K_{ATP} channels.

A large 'Impact of nicorandil in angina' (IONA, 2002) randomized trial found nicorandil to reduce acute coronary events in high risk stable angina patients.

Nicorandil is well absorbed orally, nearly completely metabolized in liver and is excreted in urine. It exhibits biphasic elimination; the

initial rapid phase t½ is 1 hour and later slow phase t½ is 12 hours.

Side effects of nicorandil are flushing, palpitation, weakness, headache, dizziness, nausea and vomiting. Large painful aphthous ulcers in the mouth, which heal on stopping nicorandil have been reported. Nitrate like tolerance does not occur with nicorandil, but it has the potential to interact with sildenafil.

Dose: 5–20 mg BD; NIKORAN, 5, 10 mg tabs, 2 mg/vial, 48 mg/vial inj; KORANDIL 5, 10 mg tabs.

Nicorandil is a 2nd line antianginal drug, whose efficacy and long term effects are less well established. It has failed to acquire wide acceptance, but may be useful in resistant angina when combined with other drugs. Administered i.v. during angioplasty for acute MI, it is claimed to improve outcome.

OTHER ANTIANGINAL DRUGS

1. Dipyridamole It is a powerful coronary dilator; increases total coronary flow by preventing uptake and degradation of adenosine which is a local mediator involved in autoregulation of coronary flow in response to ischaemia. It dilates resistance vessels and abolishes autoregulation, but has no effect on larger conducting coronary vessels. Cardiac work is not decreased because venous return is not reduced. Accordingly, it fails to relieve anginal symptoms or avert ECG changes.

The pharmacological success but therapeutic failure of dipyridamole has been explained on the basis of 'coronary steal' phenomenon (Fig. 40.5C). By dilating resistance vessels in nonischaemic zone as well, it diverts the already reduced blood flow away from the ischaemic zone.

Dipyridamole inhibits platelet aggregation. By potentiating PGI_2 and increasing cAMP in platelets, it enhances antiaggregatory influences. Though not useful as an antianginal drug, it is being employed as an adjuvant antiplatelet drug (*see* Ch. 45)

2. Trimetazidine This antianginal drug acts by nonhaemodynamic mechanisms. There is no effect on determinants of myocardial O_2 consumption, such as HR and BP, both at rest as well as during exercise, but angina frequency is reduced and exercise capacity is increased. In patients not adequately controlled by long-acting nitrate or β blocker or CCB, addition of trimetazidine further reduced anginal attacks and increased exercise duration.

The mechanism of action of trimetazidine is uncertain, but it may improve cellular tolerance to ischaemia by modulating myocardial metabolism. It has been shown to inhibit the mitochondrial *long chain 3-ketoacyl-CoA thiolase (LC3-KAT)*, a key enzyme in fatty acid oxidation. It thus reduces fatty acid oxidation and promotes glucose oxidation in myocardium. Ischaemic myocardium shifts to utilizing fatty acid as substrate, thereby increasing requirement of O_2 for the same amount of ATP generated. Since oxidation of fatty acid requires more O_2, shift back of substrate to glucose would reduce O_2 demand. Trimetazidine has been labelled as pFOX (fatty acid oxidation pathway) inhibitor.

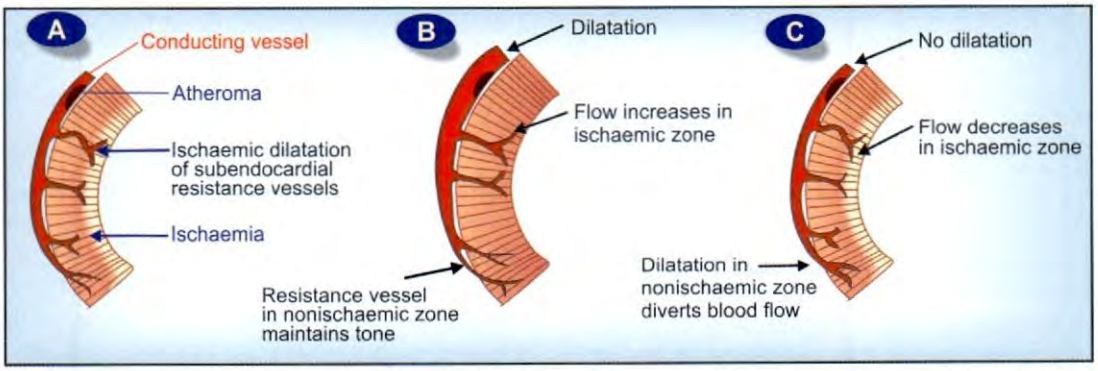


Fig. 40.5: Diagrammatic representation of coronary haemodynamics. A—in classical angina, B — Selective nitrate action on conducting vessels, which along with ischaemic dilatation of resistance vessels, increases flow to the subendocardial region → relief of angina. C—Dipyridamole action on all resistance vessels increases blood flow to nonischaemic zone to the detriment of ischaemic zone → coronary steal

Trimetazidine is absorbed orally, partly metabolized and largely excreted unchanged in urine; t½ is 6 hr. It is generally well tolerated; side effects are—gastric burning, dizziness, fatigue and muscle cramps. Reversible parkinsonism has been reported in the elderly.

For ischaemic heart disease, trimetazidine has been used in France, Spain, some other European countries and in India, but not in the UK or USA. It is mostly an add-on medication to conventional therapy in angina and post-MI patients.

Dose: 20 mg TDS.

FLAVEDON, CARVIDON, TRIVEDON 20 mg tabs, 35 mg modified release tab.

3. Ranolazine This novel antianginal drug primarily acts by inhibiting a late Na^+ current (late I_{Na}) in the myocardium which indirectly facilitates Ca^{2+} entry through Na^+/Ca^{2+} exchanger. Reduction in Ca^{2+} overload in the myocardium during ischaemia decreases contractility and has a cardioprotective effect. Sparing of fatty acid oxidation during ischaemia in favour of more O_2 efficient carbohydrate oxidation by inhibiting LC3KAT has also been demonstrated. This was earlier believed to be the main mechanism of antianginal action of ranolazine, but is now considered secondary. Ranolazine has no effect on HR and BP, but prolongs exercise duration in angina patient.

The efficacy of ranolazine in decreasing frequency of anginal attacks and in prolonging exercise duration has been demonstrated both as monotherapy as well as when added to conventional drugs in multicentric randomized trials: MARISA (monotherapy assessment of ranolazine in stable angina, 2004), CARISA (Combination assessment of ranolazine in stable angina, 2004), and ERICA (Efficacy of ranolazine in chronic angina, 2005). In the MERLIN-TIMI36 (2007) trial on non-ST-elevation acute coronary syndrome patients, ranolazine use was associated with a lower rate of ventricular arrhythmias. Incidence of AF was also decreased. However, ranolazine prolongs Q-T interval, and should not be used together with other Q-T prolonging drugs (class I and III antiarrhythmics, and other drugs listed on p. 572).

Oral absorption of ranolazine is slow taking 4–6 hours with a bioavailability of 30–50%. It is metabolized in liver mainly by CYP3A4 and excreted in urine, with an average t½ of 7 hours. Side effects reported are dizziness, weakness, constipation, postural hypotension, headache and dyspepsia. It should not be given to patients taking CYP3A4 inhibitors, but can be given to patients taking sildenafil.

Dose: 0.5–1.0 g BD as SR tab; RANOZEX, RANX, CARTINEX, REVULANT, RANOLAZ 0.5 g SR tab.

4. Ivabradine This 'pure' heart rate lowering antianginal drug has been introduced recently as an alternative to β blockers. The only significant action of ivabradine is blockade of cardiac pacemaker (sino-atrial) cell 'f' channels, which are *'funny'* cation channels that open during early part of slow diastolic (phase 4) depolarization. The 'f' channels are expressed primarily on the sino-atrial cells, and in some measure on retinal cells. The inward current (I_f) resulting from opening of 'f' channels determines the slope of phase 4 depolarization. Selective blockade of I_f current by ivabradine results in heart rate reduction without any other electro-physiological or negative inotropic or negative lucitropic (slowing of myocardial relaxation) effect. Heart rate reduction decreases cardiac O_2 demand and prolongation of diastole tends to improve myocardial perfusion (O_2 supply). Accordingly, in clinical trials, ivabradine has been found to improve exercise tolerance in stable angina and reduce angina frequency.

Ivabradine is well absorbed orally, 40% bioavailable due to first pass metabolism; degraded by CYP3A4 and excreted in urine with a t½ of 2 hours. Apart from excess bradycardia, the most important adverse effect is visual disturbance. Extrasystoles, prolongation of P-R interval, headache, dizziness and nausea are the other problems. It should not be used if heart rate is <60/min, in sick sinus and in AF. Concurrent use of drugs which prolong Q-T or which inhibit CYP3A4 is contraindicated.

Ivabradine is indicated in chronic stable angina in patients with sinus rhythm who are intolerant to β blockers or when the latter are contraindicated. It can also be used for inappropriate sinus tachycardia (*see* p. 581). Another indication is stable grade II to IV heart failure due to systolic dysfunction in patients with sinus rhythm >70/min (*see* p. 568).

Dose: Initially 5 mg BD, increase if needed to 7.5 mg BD, Elderly 2.5 mg BD.

IVABRAD, BRADIA, IVABEAT 5, 7.5 mg tab.

DRUGS FOR PERIPHERAL VASCULAR DISEASES

Peripheral vascular diseases (PVDs) are either primarily occlusive (Buerger's disease with intermittent claudication of legs), or mainly vasospastic (Raynaud's phenomenon with episodic blanching ± cyanosis of fingers followed by hyperaemia), or both as in arteriosclerotic/diabetic vascular insufficiency, ischaemic leg ulcers, frost bite, gangrene, cerebrovascular inadequacy, etc. Increased cardiovascular risk is associated with all PVDs. Measures that reduce cardiovascular risk (smoking cessation, BP normalization, antiplatelet drugs, diabetes control, statins, weight management, exercise training) have salutary effect on PVDs as well. In addition, vasodilators and many other types of drugs are used (*see* Chart). Most of these drugs have other primary indications and are described elsewhere in the book. The remaining are briefly considered below.

1. Cyclandelate It is a papaverine like general smooth muscle relaxant which increases cutaneous, skeletal muscle and cranial blood flow in normal individuals. However, benefits in PVD are minor and restricted to conditions with vasospasm. Side effects are flushing, palpitation and headache.

Dose: 200–400 mg TDS; CYCLOSPASMOL, CYCLASYN 200, 400 mg tab/cap.

2. Xanthinol nicotinate (Nicotinyl xanthinate) It is a compound of xanthine and nicotinic acid, both of which are vasodilators. It increases blood flow in many vascular beds and has been promoted for cerebrovascular disorders and PVDs, but therapeutic benefits are insignificant.

Dose: 300–600 mg TDS oral; 300 mg by i.m. or slow i.v. injection; COMPLAMINA 150 mg tab, 500 mg retard tab, 300 mg/2 ml inj.

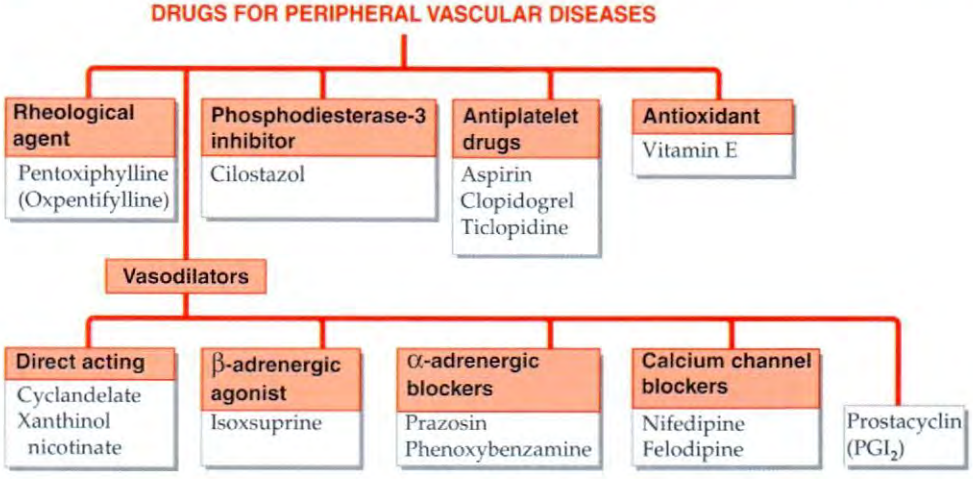
3. Pentoxiphylline (Oxpentifylline) An analogue of theophylline and a weak phosphodiesterase (PDE) inhibitor, which has been shown to increase blood flow in ischaemic areas by reducing whole blood viscosity and by improving flexibility of RBCs. The *rheological* (dealing with property of flow) action rather than vasodilatation is said to be responsible for improving passage of blood through microcirculation. Oral doses do not affect heart rate, t.p.r. or BP.

Pentoxiphylline is usually well tolerated: side effects are nausea, vomiting, dyspepsia and bloating which can be minimized by taking the drug after meals.

Dose: 400 mg BD–TDS; TRENTAL-400, FLEXITAL 400 mg SR tab, 300 mg/15 ml for slow i.v. injection.

Pentoxiphylline is mainly used in intermittent claudication (calf pain on walking) due to occlusive vascular disease (Buerger's disease). Other conditions claimed to be improved are: trophic leg ulcers, transient ischaemic attacks (TIAs), and chronic cerebrovascular insufficiency. However, overall benefits are minimal.

4. Cilostazol This is a PDE-3 inhibitor (like the inodilator inamrinone and milrinone, (*see* p. 568) which increases intracellular cAMP in platelets and vascular smooth muscle resulting in antiaggregatory and vasodilator effects. In clinical trials it has increased walking distance in patients with intermittent claudication and appears to be more effective than pentoxiphylline. Since long-term oral milrinone therapy for heart failure has increased cardiac mortality and has been discontinued, concern is expressed



about long-term safety of cilostazol. However, no increase in cardiovascular mortality has so far been observed with cilostazol, but a warning has been issued not to use it in patients with heart failure. It is also not to be used in patients who have pain even at rest, or in those with tissue necrosis.

The most common side effect is headache. Others are palpitation, dizziness, nausea, vomiting, weakness and increase in ventricular ectopics or nonsustained VT. Cilostazol is extensively metabolized by CYP3A4 and CYP2C19 into active and inactive metabolites, together having elimination t½ of ~ 12 hours. It should not be administered along with inhibitors of CYP3A4 and CYP2C19, which increase its toxicity.

Cilostazol is indicated exclusively for intermittent claudication in patients with no rest pain or heart failure.

Dose: 100 mg BD, 30 min before or 2 hours after food.

PLETOZ, CILODOC, STILOZ, ZILAST 50, 100 mg tabs.

Comment It is to be noted that no vasodilator can overcome organic obstruction. Because ischaemia itself is a potent vasodilator stimulus in skeletal muscle and cerebral beds, vasodilators can even divert the blood to nonischaemic areas (steal phenomenon). They obviously are more useful when vasospasm is wholely or partly involved, e.g. in Raynaud's phenomenon. Intravenous PGI_2 has been employed in severe cases with rest pain (p. 207).

DRUG THERAPY IN MYOCARDIAL INFARCTION

According to severity, the acute coronary syndromes (ACS) may be graded into:

- *Unstable angina (UA):* Vascular obstruction is incomplete, myocardial necrosis is absent—biochemical markers of ischaemia (raised myoglobin, CK-MB, troponin I) do not appear in blood, and ST segment is not elevated in ECG.
- *Non-ST segment elevation myocardial infarction (NSTEMI):* Vascular obstruction is incomplete, but is attended by partial thickness and relatively smaller area of myocardial necrosis; biochemical markers appear in blood, but ST segment is not elevated.
- *ST segment elevation myocardial infarction (STEMI):* Vascular obstruction is complete, full thickness of ventricular wall and larger area of myocardium is necrosed, biochemical markers are prominent and ST segment in ECG is elevated.

However, UA and NSTEMI may progress to STEMI.

Myocardial infarction (MI) is ischaemic necrosis of a portion of the myocardium due to sudden occlusion of a branch of coronary artery. An acute thrombus at the site of atherosclerotic obstruction is the usual cause. About ¼ patients die before therapy can be instituted. The remaining are best treated in specialized coronary care units with continuous monitoring of the haemodynamic parameters, biochemical markers and ECG to guide the selection of drugs and dosage. Those who receive such facility can be greatly benefitted by drug therapy, which according to needs of individual patients is directed to:

1. *Pain, anxiety and apprehension* After pain is not relieved by 3 doses of GTN given 5 min apart, an opioid analgesic (morphine) or diazepam is administered parenterally.
2. *Oxygenation* By O_2 inhalation and assisted respiration, if needed.
3. *Maintenance of blood volume, tissue perfusion and microcirculation* Slow i.v. infusion of saline/dextrose (avoid volume overload).
4. *Correction of acidosis* Acidosis occurs due to lactic acid production; can be corrected by i.v. sod. bicarbonate infusion.
5. *Prevention and treatment of arrhythmias* If there are no contraindications, prophylactic administration (i.v. or oral) of a β blocker (metoprolol, etc.) as soon as the MI patient is seen and its continuation orally for a few days has been shown to reduce the incidence of arrhythmias and mortality. β blockers used early in evolving MI can reduce the infarct size (myocardial salvage) and subsequent complications.

Tachyarrhythmias may be treated with i.v. lidocaine, procainamide or amiodarone. Routine prophylactic lidocaine infusion is not recommended now. Bradycardia and heart block may be managed with atropine or electrical pacing.

6. *Pump failure* The objective is to increase c.o. and/or decrease filling pressure without

unduly increasing cardiac work or lowering BP. Drugs used for this purpose are:

(a) *Furosemide*: indicated if pulmonary wedge pressure is > 20 mm Hg. It decreases cardiac preload.

(b) *Vasodilators*: Venodilator (GTN slow i.v. infusion) is mainly used. It may be supplemented by i.v. esmolol or labetolol.

(c) *Inotropic agents*: dopamine or dobutamine i.v. infusion may be needed to augment the pumping action of heart and tide over the crisis.

7. *Prevention of thrombus extension, embolism, venous thrombosis* Aspirin (162–325 mg) should be given for chewing and swallowing as soon as MI is suspected (if not already being taken on a regular basis). This is continued at 80–160 mg/day. Clopidogrel/prasugrel/ticagrelor may be given as alternative add-on antiplatelet drugs. Anticoagulants (heparin/fondaparinux followed by oral anticoagulants) are used primarily to prevent deep vein thrombosis (risk is increased due to bed rest) and pulmonary/systemic arterial embolism. The value of anticoagulants in checking coronary artery thrombus extension is uncertain. Any benefit is short-term; anticoagulants are not prescribed on long-term basis now (*see* Ch. 45).

8. *Thrombolysis and reperfusion* Fibrinolytic agents, i.e. plasminogen activators—alteplase/tenecteplase to achieve reperfusion of the infarcted area (*see* Ch. 45) are indicated only in STEMI or high risk NSTEMI. Unless thrombolysis can be started within 1–2 hours of MI symptom onset, primary percutaneous coronary intervention (PCI) with stenting is now the preferred revascularization procedure, wherever available.

9. *Prevention of remodeling and subsequent CHF* ACE inhibitors/ARBs are of proven efficacy and afford long-term survival benefit (*see* Ch. 36). They should be started as soon as the patient is haemodynamically stable.

10. *Prevention of future attacks*

(a) Platelet inhibitors—aspirin or clopidogrel or similar drug given on long-term basis is routinely prescribed (*see* Ch. 45).

(b) β blockers—These drugs reduce risk of reinfarction, CHF and mortality. All patients not having any contraindication are put on a suitable β blocker for at least 2 years.

(c) Control of hyperlipidaemia—dietary substitution with unsaturated fats, hypolipidemic drugs especially statins are routinely prescribed, irrespective of blood cholesterol level. They have been shown to reduce risk of cardiovascular events (*see* Ch. 46).

PROBLEM DIRECTED STUDY

40.1 A 55-year-old man presented with complaints of tightness and discomfort over middle part of chest felt episodically, particularly after walking briskly or climbing stairs or during sex. This is relieved within 5–10 minutes of rest. One or two episodes occur practically every day. He is a past smoker who quit smoking 5 years back when he was diagnosed to have chronic obstructive pulmonary disease (COPD), for which he regularly takes 2 inhalations of Ipratropium Br. 3 times a day and 2 puffs of salbutamol inhalation whenever he feels out of breath. The pulse was 90/min and BP 124/82 mm Hg. The resting ECG was normal, but stress test was positive. A diagnosis of exertional angina was made and he was prescribed—Tab glyceryl trinitrate 0.5 mg to be put under the tongue as soon as he begins to feel the chest discomfort, as well as before undertaking any physical exertion.

(a) Should he be prescribed another drug to be taken on a regular basis to prevent episodes of angina? If so, which drugs can be given to him and which cannot be given?

(b) Should additional medication be given to prevent long-term complications and improve survival?

(see Appendix-1 for solution)

Chapter 41 Antihypertensive Drugs

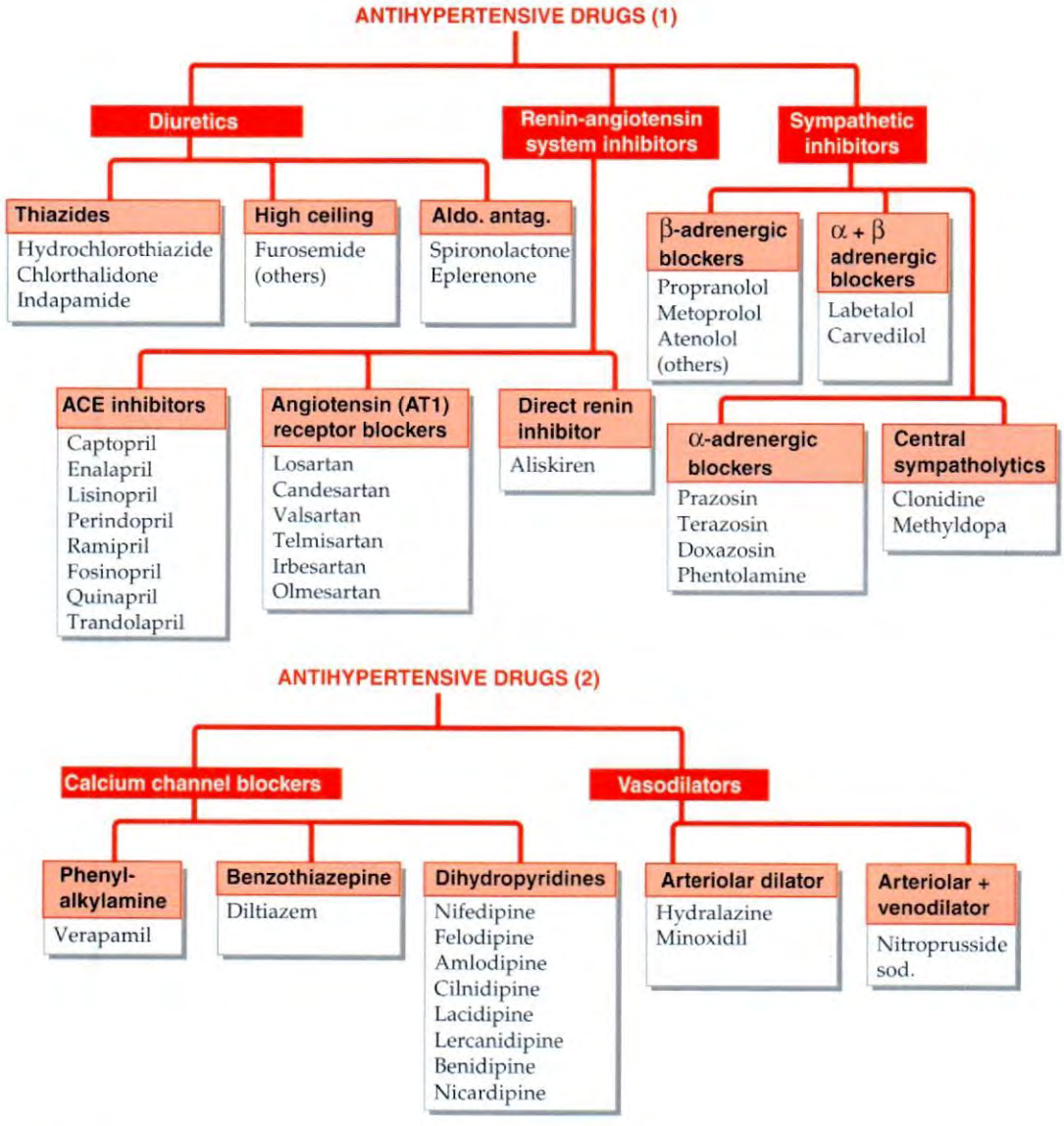
These are drugs used to lower BP in hypertension.

Hypertension (HT) is a very common disorder, particularly past middle age. It is not a disease in itself, but is an important risk factor for cardiovascular mortality and morbidity. The cutoff manometric reading between normotensives and hypertensives is arbitrary. For practical purposes 'hypertension' could be that level of BP at or above which long-term antihypertensive treatment will reduce cardiovascular mortality. Almost all HT management guidelines including NICE (2011), JNC8 (2014), WHO-ISH (2003), European Society of Hypertension (2007, 2013) define the cut-off level to be 140 mm Hg systolic and 90 mm Hg diastolic. However, the JNC8 have raised the defining level to 150/90 mm Hg for individuals above 60 years of age. Epidemiological studies have confirmed that higher the pressure (systolic or diastolic or both) greater is the risk of cardiovascular disease.

Majority of cases are of essential (primary) hypertension, i.e. the cause is not known. Sympathetic and renin-angiotensin systems (RAS) may or may not be overactive, but they do contribute to the tone of blood vessels and c.o. in hypertensives, as they do in normotensives. Many antihypertensive drugs interfere with these regulatory systems at one level or the other. Antihypertensive drugs, by chronically lowering BP, may reset the barostat to function at a lower level of BP.

Antihypertensive drug therapy has been remarkably improved in the last 60 years. Different classes of drugs have received prominence with passage of time in this period. Before 1950 hardly any effective and tolerated antihypertensive was available. *Veratrum* and *Sod. thiocyanate* could lower BP, but were toxic and difficult to use. The *ganglion blockers* developed in the 1950s were effective, but produced a variety of side effects. *Reserpine* was a breakthrough, but produced mental depression. The therapeutic potential of *hydralazine* could not be tapped fully because of marked side effects when it was used alone. *Guanethidine* introduced in 1961 was an improvement on ganglion blockers. The antihypertensives of the 1960–70s were *methyldopa, β blockers, thiazide* and *high ceiling diuretics* and *clonidine*. The status of β blockers and diuretics was consolidated in the 1970s and selective α_1 blocker *prazosin* broke new grounds. The antihypertensives introduced in the 1980–90s were angiotensin II converting enzyme *(ACE) inhibitors* and *calcium channel blockers*. Angiotensin receptor blockers (*losartan,* etc.) were added soon after, and the direct renin inhibitor *aliskiren* is the latest drug. With the development of many types of drugs, delineation of their long-term benefits and complications, and understanding of the principles on which to combine them, hypertension can now be controlled in most cases with minimum discomfort. Evidence-based guidelines for selection of antihypertensive drugs for different categories of patients have now been developed.

- JNC 7—The seventh report of Joint National Committee (of USA) on prevention, detection, evaluation and treatment of high blood pressure.
- JNC 8—Evidence-based guideline for the management of hgih blood pressure in adults; report from the panel members appointed to the JNC-8 (Joint National Committee (USA).
- NICE (2011)—National Institute for Health and Care Excellence (UK); Hypertension in adults: diagnosis and management (CG127).
- WHO-ISH—World Health Organization and International Society of Hypertension.



DIURETICS

Diuretics have been the standard antihypertensive drugs over the past nearly 5 decades, though they do not lower BP in normotensives. Their pharmacology is described in Ch. 42.

Thiazides Hydrochlorothiazide (HCZ) and chlorthalidone are the diuretic of choice for uncomplicated hypertension; have similar efficacy and are dose to dose equivalent. All megatrials have been carried out with these two only. Chlorthalidone is longer acting (~ 48 hours) than HCZ (< 24 hours) and may have better round-the-clock action; favoured by the NICE guidelines. Indapamide (*see* later) is also mainly used as antihypertensive, and is equally effective. Other members of the thiazide class should not be considered interchangeable with these as antihypertensive. The proposed mechanism of antihypertensive action is:

1. Initially, the diuresis reduces plasma and e.c.f. volume by 5–15%, and this decreases c.o.
2. Subsequently, compensatory mechanisms operate to almost regain Na^+ balance and plasma volume; c.o. is restored, but the fall in BP is maintained by a slowly developing reduction in t.p.r.
3. The reduction in t.p.r. is most probably an indirect consequence of a small (~5%) persisting Na^+ and volume deficit. Decrease in intracellular Na^+ concentration in the vascular smooth muscle may reduce stiffness of vessel wall, increase their compliance and dampen responsiveness to constrictor stimuli (NA, Ang II). Similar effects are produced by salt restriction; antihypertensive action of diuretics is lost when salt intake is high. A mild slowly developing vasodilator action of thiazides due to opening of smooth muscle K^+_{ATP} channels and hyperpolarization has been proposed, but does not appear to be real.

The fall in BP develops gradually over 2–4 weeks. During long-term treatment with thiazides, the heart rate and c.o. remain unaffected, while t.p.r. is reduced despite compensatory increase in plasma renin activity, which confirms persisting Na^+ deficit. Thiazides have no effect on capacitance vessels, sympathetic reflexes are not impaired: postural hypotension is rare. Thiazides are mild antihypertensives, average fall in mean arterial pressure is ~10 mm Hg. They are effective by themselves in only ~ 30% cases (mostly low grade hypertension) but they potentiate all other antihypertensives (except DHPs) and prevent development of tolerance to these drugs by not allowing expansion of plasma volume. Thus, in combination, they are useful in any grade of hypertension. They are more effective in the elderly. Maximal antihypertensive efficacy is reached at 25 mg/day HCZ, though higher doses produce greater diuresis. Their antihypertensive action is attenuated by NSAIDs.

High ceiling diuretics Furosemide is a strong diuretic, but a weaker antihypertensive than thiazides. The fall in BP is entirely dependent on reduction in plasma volume and c.o. The explanation to this paradox may lie in its brief duration of action. The natriuretic action lasting only 4–6 hr after the conventional morning dose is followed by compensatory increase in proximal tubular reabsorption of Na^+. The Na^+ deficient state in vascular smooth muscle may not be maintained round-the-clock. The t.p.r. and vascular responsiveness are not reduced. Moreover, the high ceiling diuretics are more liable to cause fluid and electrolyte imbalance, weakness and other side effects. They are indicated in hypertension only when it is complicated by chronic renal failure or coexisting refractory CHF, or when fluid retaining potent vasodilators are used.

Desirable properties of thiazide diuretics as antihypertensives are:

1. Once a day dosing and flat dose-response curve permitting simple standardized regimens.
2. No fluid retention, no tolerance.
3. Low incidence of postural hypotension and relative freedom from side effects, especially CNS, compared to sympatholytics.
4. More effective in elderly patients and in those with isolated systolic hypertension (ISH).
5. Thiazides decrease Ca^{2+} excretion; may lower risk of osteoporosis in older women.
6. Low cost.

Current status of diuretics as antihypertensives

In the 1960–70s thiazide diuretics were almost routinely prescribed alone or in combination, to nearly all hypertensive patients. The usual dose used was HCZ/chlorthalidone 50 mg/day. Soon a number of drawbacks were highlighted:

- Hypokalaemia—muscle pain, fatigue and loss of energy.
- Erectile dysfunction in males.
- Carbohydrate intolerance, precipitation of diabetes due to inhibition of insulin release (probably secondary to K^+ depletion).

- Dyslipidemia: rise in total and LDL cholesterol and triglycerides with lowering of HDL which could increase atherogenic risk.
- Hyperuricaemia: by inhibiting urate excretion—increased incidence of gout.
- Increased incidence of sudden cardiac death: attributed to episodes of *torsades de pointes* and ischaemic ventricular fibrillation precipitated by hypokalaemia.

Consequently, prescribing of diuretics decreased.

Subsequently, several dose-ranging studies and interventional trials demonstrated that the adverse consequences of thiazide use were dose-dependent, and that 25 mg/day HCZ dose yielded the best benefit-risk ratio. Favourable outcomes obtained at ≤25 mg/day HCZ in studies, including ALLHAT (2002) and a meta-analysis (2003) have reinstated thiazide diuretics as the first choice antihypertensive.

Findings with low dose (12.5–25 mg/day) thiazide therapy are:

- Though serum K^+ falls a little, significant hypokalaemia does not occur; K^+ sparing diuretics are usually not needed.
- Continuous ECG recording studies failed to document increased incidence of arrhythmias.
- Impairment of glucose tolerance or increase in serum cholesterol or hyperuricaemia over long-term are minimal. Benefits of low-dose thiazides outweigh its potential to worsen diabetes, and are not contraindicated in diabetics.
- Analysis of recent trials has found thiazides to reduce fatal and nonfatal MI by 27–44%. The incidence of stroke is reduced by 31–49%. Overall mortality and morbidity is reduced in long-term trials.
- Some recent trials in mild to moderate hypertension have found thiazides to reduce left ventricular hypertrophy.

The JNC 8, NICE (2011) and other guidelines recommend instituting 12.5–25 mg/day thiazide therapy, with or without added K^+ sparing diuretic, as a first choice treatment of essential hypertension, especially in the elderly. If the low dose (25 mg/day) fails to reduce BP to desired level, another antihypertensive should be added, rather than increasing dose of the diuretic. Thiazides are ineffective in patients with chronic kidney disease (CKD), and are not recommended. High-ceiling diuretes are effective in patients with CLcr 30 mg/ml or less, and may be used in place of HCZ.

Indapamide It is a mild diuretic, chemically related to chlorthalidone; reduces BP at doses which cause little diuresis. Electrolyte disturbances, K^+ loss and metabolic effects are minimal at antihypertensive doses. The NICE guidelines (2011) favour chlorthalidone and indapamide over hydrochlorthiazide.

Indapamide is well absorbed orally, has an elimination t½ of 16 hr. It is well tolerated: side effects are minor g.i. symptoms and fatigue. Hypokalaemia is infrequent.

LORVAS, NATRILIX 2.5 mg tab, NATRILIX-SR 1.5 mg SR tab

Aldosterone antagonists Spironolactone and eplerenone themselves lower BP slightly. Used in conjunction with a thiazide diuretic they prevent K^+ loss and augment the antihypertensive action. Spironolactone has hormonal side effects (gynaecomastia, impotence, menstrual irregularities). This problem is offset in the newer aldosterone antagonist eplerenone, which is increasingly used.

With the realization of the role of aldosterone in promoting hypertension related ventricular and vascular hypertrophy and renal fibrosis, it is considered that aldosterone antagonists will attenuate these complications. As such, there is resurgence in their use, especially in refractory hypertension.

The NICE and JNC 8 guidelines recommend adding an aldosterone antagonist to the ACE inhibitor/ARB + CCB + thiazide regimen, if the target level BP is not attained. Hyperkalemia should be watched when aldosterone antagonists are used, particularly in combination with ACE inhibitors/ARBs.

ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

The ACE inhibitors are one of the first choice drugs in all grades of essential as well as

renovascular hypertension (except those with bilateral renal artery stenosis). Most patients require relatively lower doses (enalapril 2.5–10 mg/day or equivalent) which are well tolerated. Used alone they control hypertension in ~50% patients, and addition of a diuretic/β blocker extends efficacy to ~90%. Because of supraadditive synergism, only a low dose of diuretic (12.5 mg of HCZ, rarely 25 mg) needs to be added. The pharmacology and use of ACE inhibitors in hypertension are described in Ch. 36. Of particular mention is their renal blood flow improving action, their potential to retard diabetic nephropathy and their capacity to regress left ventricular/vascular hypertrophy. They are the most appropriate antihypertensives in patients with diabetes, nephropathy (even nondiabetic CKD), left ventricular hypertrophy, CHF, angina and post MI cases. Several large prospective studies including AIRE (1993), HOPE (2000), ALLHAT (2002) have confirmed the antihypertensive and cardioprotective effects of ACE inhibitors. They appear to be more effective in younger (< 55 year) hypertensives than in the elderly, as well as in white races than in blacks. Dry persistent cough is the most common side effect requiring discontinuation of ACE inhibitors.

ANGIOTENSIN RECEPTOR BLOCKERS

The pharmacology of *losartan* and other ARBs is described on p. 535-37. In a dose of 50 mg/day losartan is an effective antihypertensive. Action manifests early and progresses to peak at 2–4 weeks. Addition of 12.5 mg/day HCZ further enhances the fall in BP. The newer ARBs—valsartan, candesartan, irbesartan and telmisartan have been shown to be as effective antihypertensives as ACE inhibitors, while losartan may be somewhat weaker than high doses of ACE inhibitors. ARBs are remarkably free of side effects. Because they do not increase kinin levels, the ACE inhibitor related cough is not encountered. Angioedema, urticaria and taste disturbance are also rare. Though effects of ACE inhibitors and ARBs are not identical, the latter have all the metabolic and prognostic advantages of ACE inhibitors.

Several interventional endpoint reduction trials like LIFE (2002), VALUE (outcomes in hypertensive patients with valsartan or amlodipine, 2004), SCOPE (study on cognition and prognosis in the elderly; stroke prevention with candesartan in elderly with isolated systolic hypertension, 2004), JLIGHT (Japanese losartan therapy intended for global renal protection in hypertensive patients, 2004) have attested to the favourable effects of ARBs on morbidity and mortality in hypertensive patients.

As antihypertensive, use of ARBs has outstripped that of ACE inhibitors. The NICE (2011) guidelines consider ARBs to be preferable over ACE inhibitors for black races. Both JNC8 and NICE recommend not to combine ACE inhibitors with ARBs for hypertension.

DIRECT RENIN INHIBITOR

Aliskiren the only available member of the latest class of RAS inhibitors which act by blocking catalytic activity of renin and inhibiting production of AngI and AngII. It is described in Ch. 36. Aliskiren is an equally effective antihypertensive as ACE inhibitors and ARBs, but experience with it so far is limited. However, no remarkable features have emerged and presently it is to be employed only when the more established ACE inhibitors or ARBs cannot be used.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (CCBs) are another class of first line antihypertensive drugs. Their pharmacology is described in Ch. 40. All 3 subgroups of CCBs, *viz.* dihydropyridines (DHPs, e.g. amlodipine), phenylalkylamine (verapamil) and benzothiazepine (diltiazem) are equally efficacious antihypertensives, but DHPs are mainly used. They lower BP by decreasing peripheral resistance without compromising c.o. Despite vasodilatation, fluid retention is insignificant.

Ankle edema that occurs in some patients is due to increased hydrostatic pressure across capillaries of the dependent parts as a result of reflex constriction of post capillary vessels in these vascular beds.

The onset of antihypertensive action is quick. With the availability of long acting preparations, most agents can be administered once a day. Short acting CCBs/formulations (nifedipine regular

formulation) are not used to treat hypertension. Monotherapy with CCBs is effective in ~ 60% hypertensives, and they may improve arterial compliance. Other advantages of CCBs are:

1. Do not compromise haemodynamics: no impairment of physical work capacity.
2. No sedation or other CNS effects; cerebral perfusion is maintained.
3. Not contraindicated in asthma, angina (especially variant) and PVD patients: may benefit these conditions.
4. Are particularly effective in elderly patients, black races and low renin hypertensives.
5. Do not affect male sexual function.
6. No deleterious effect on plasma lipid profile, uric acid level and electrolyte balance.
7. Shown to have no/minimal effect on quality of life.
8. No adverse foetal effects; can be used during pregnancy (but can weaken uterine contractions during labour).

The initial large controlled trials (HINT, TRENT, SPRINT I, II) and metaanalysis has consistently indicated increased mortality/reinfarction in patients treated with standard nifedipine (or other short-acting DHP) formulations. The increased mortality among coronary heart disease patients has been attributed to repeated surges of adrenergic discharge and marked swings of BP attending each dose of rapidly acting DHP. However, this risk cannot be extrapolated to verapamil/diltiazem as broughtout by DAVIT I, II and other controlled studies, as well as to slow acting DHPs (amlodipine type).

The Systolic hypertension in Europe (Syst-EUR) trial has shown that nitrendipine (long-acting DHP) reduces cardiovascular morbidity and mortality in elderly hypertensives. The Hypertension optimal treatment (HOT), and Sweedish trial in old patients with hypertension-2 (STOP-2) studies have also found CCBs equi-effective as diuretics/β blockers/ACE inhibitors in reducing major cardiovascular events as well as cardiovascular/total mortality. No excess mortality with the use of amlodipine in post MI and acute coronary syndrome patients has been noted in the ALLHAT (2002) study. On the other hand, CCBs do not afford survival benefit in post MI patients as β blockers, ACE inhibitors or low dose thiazides do. CCBs are also not as effective in suppressing left ventricular hypertrophy (a major risk factor in ischaemic heart disease) as ACE inhibitors.

Some large controlled trials including ASCOT-BPLA (2005) and ACCOMPLISH (2008) have testified to superior efficacy of amlodipine both as monotherapy and when combined with an ACE inhibitor for reducing cardiovascular events in high risk hypertensive patients. Thus, CCBs continue to be used as one of the first line monotherapy options (JNC8, 2014, NICE-2011 guidelines) because of their high efficacy and excellent tolerability. Also there is convincing evidence of their stroke preventing potential (syst EUR, ALLHAT studies). The long-acting DHPs are next to ACE inhibitors in reducing albuminuria and slowing disease progression in hypertensive/diabetic nephropathy. They are the most useful antihypertensives in cyclosporine induced hypertension in renal transplant recipients. However, the negative inotropic and dromotropic action of verapamil and diltiazem may worsen CHF and cardiac conduction defects, but DHPs are safe.

β-ADRENERGIC BLOCKERS

The pharmacology and mechanism of antihypertensive action of β blockers is described in Ch. 10. They are mild antihypertensives; do not significantly lower BP in normotensives. Used alone they suffice in 30–40% patients—mostly stage I cases. Additional BP lowering may be obtained when combined with other drugs.

The hypotensive response to β blockers develops over 1–3 weeks and is then well sustained. Despite short and differing plasma half lives, the antihypertensive action of most β blockers is maintained over 24 hr with a single daily dose.

All β blockers, irrespective of associated properties, exert equivalent antihypertensive effect. Drugs with intrinsic sympathomimetic activity (ISA) cause less/no reduction of HR and c.o. but decrease vascular resistance by β_2 agonism. Nebivolol lowers t.p.r. by enhancing endothelial NO production, and carvedilol does so by blocking α_1 receptors as well. These vasodilating β blockers are preferred by many experts on theoretical grounds.

There are several contraindications to β blockers, including cardiac, pulmonary and peripheral vascular disease. The nonselective β blockers have an unfavourable effect on lipid

profile (raise triglyceride level and LDL/HDL ratio). They have also fared less well on quality of life parameters like decreased work capacity, fatigue, loss of libido and subtle cognitive effects (forgetfulness, low drive), nightmares and increased incidence of antidepressant use. Many of these drawbacks are minimized in the β_1 selective agents and in those which penetrate brain poorly. However, some recent studies have pointed out that atenolol monotherapy may be less effective in preventing hypertension related stroke and coronary artery disease.

β blockers and ACE inhibitors are the most effective drugs for preventing sudden cardiac death in postinfarction patients. However, β blockers are less effective for primary prophylaxis of MI and for preventing left ventricular hypertrophy, but all-cause mortality has been decreased in long-term trials. Hypertensives with stable heart failure should be treated with one of the selected β blockers (metoprolol/bisoprolol/carvedilol/nebivolol) along with an ACE inhibitor/ARB (CIBIS, 1999; MERIT-HF, 1999, COPERNICUS, 2002 studies). Barring the above subsets of patients with compelling indications and suitability criteria, β blockers are not selected now as the initial antihypertensive. β blockers are considered less effective and less suitable for the older hypertensive. The LIFE (2002) and ALLHAT (2002) trials have found β blockers to be inferior to low-dose thiazide or ACE inhibitor/ARB or a combination of these in preventing stroke, as well as in diabetic patients. As monotherapy, ACE inhibitors/ARBs and CCBs appear to compromise quality of life less than β blockers. Rebound hypertension has occurred on sudden discontinuation of β blockers; myocardial ischaemia may be aggravated and angina or MI may be precipitated.

Mainly due to inferior efficacy in primary prevention of MI and stroke, as well as other drawbacks pointed out above, *β blockers are no longer considered first line antihypertensive drugs* for monotherapy, except in patients with other compelling indications (JNC 8, NICE guidelines 2011).

β+α ADRENERGIC BLOCKERS

Labetalol (*see* Ch. 10). It is a combined α and β blocker; reduces t.p.r. and acts faster than pure β blockers. It has been used i.v. for rapid BP reduction in hyperadrenergic states, cheese reaction, clonidine withdrawal, eclampsia, etc. (*see* p. 619). Oral labetalol therapy is restricted to moderately severe hypertension not responding to a pure β blocker, because side effects of both α blocker and β blocker occur with it. Labetalol is a preferred antihypertensive for rise in BP due to preeclampsia.

Carvedilol This nonselective β + weak selective α_1 blocker produces vasodilatation and has additional antioxidant/free radical scavenging properties. Whether these ancillary properties confer any superiority is not known. Carvedilol is a frequently selected drug for long-term treatment of CHF, and is approved as an antihypertensive as well. Side effects are similar to labetalol; liver enzymes may rise in some.

α-ADRENERGIC BLOCKERS

Prazosin (*see* Ch. 10)

This prototype selective α_1 antagonist dilates both resistance and capacitance vessels; effect on the former predominating. The haemodynamic effects, *viz* reduction in t.p.r. and mean BP accompanied by minor decrease in venous return and c.o. are similar to that produced by a direct acting vasodilator hydralazine. However, unlike hydralazine, there is little reflex cardiac stimulation and renin release during long-term therapy. Tachycardia does not compensate for the fall in BP, because release inhibitory α_2 (presynaptic) receptors are not blocked: autoregulation of NA release remains intact. Prazosin probably decreases central sympathetic tone as well.

Renal blood flow and g.f.r. are maintained but fluid retention may attend fall in B.P. Cardiovascular reflexes are not appreciably impaired during chronic therapy, but postural hypotension and fainting may occur in the beginning—called 'first dose effect', and with dose increments. This disappears with continued therapy, but may persist in the elderly. For this reason, prazosin is always started at low dose (0.5 mg) given at bedtime and gradually increased with twice daily administration till an adequate response is produced (max. dose 10 mg BD). An oral dose produces peak fall in BP after 4–5 hours

and the effect lasts for nearly 12 hours, though plasma t½ is only 3 hours. This may be due to generation of active metabolites.

Prazosin does not impair carbohydrate tolerance, and may have a small favourable effect on lipid profile. Symptomatic improvement may occur in males with urinary symptoms due to prostatic hypertrophy.

MINIPRESS XL: Prazosin GITS 2.5 mg, 5 mg tabs.; PRAZOPRESS 1, 2 mg tabs.

Adverse effects Prazosin is generally well tolerated at low doses. Apart from postural hypotension related symptoms (particularly in the beginning), other side effects are headache, drowsiness, dry mouth, weakness, palpitation, nasal blockade, blurred vision and rash. Ejaculation may be impaired in males: especially with higher doses. Fluid retention attending prazosin monotherapy may precipitate CHF.

Use Prazosin is a moderately potent antihypertensive, but is not used as a first line drug because fluid retention and tolerance gradually develops with monotherapy—necessitating dose increase—more side effects and risk of CHF. It may be added to a diuretic + β blocker in those not achieving target BP.

Terazosin, Doxazosin These are long-acting congeners of prazosin with similar properties but suitable for once daily dosing (*see* p. 155–56). In the ALLHAT (2002) study doxazosin monotherapy has doubled the incidence of CHF; but this can occur with any α_1 blocker. A higher incidence of stroke relative to patients receiving a thiazide diuretic was also noted.

Nonselective α blockers (Phentolamine, Phenoxybenzamine)

The nonselective α blockers have been disappointing for routine treatment of hypertension, because fall in t.p.r. is compensated by increased HR and c.o. They block both α_1 and α_2 receptors—NA release is accentuated. They are reserved for special situations like pheochromocytoma, clonidine withdrawal, cheese reaction, etc., where circulating CAs are responsible for the rise in BP.

CENTRAL SYMPATHOLYTICS

Clonidine It is an imidazoline derivative having complex actions. Clonidine is a partial agonist with high affinity and high intrinsic activity at α_2 receptors, especially α_{2A} subtype in brainstem. The major haemodynamic effects result from stimulation of α_{2A} receptors present mainly postjunctionally in medulla (vasomotor centre). This decreases sympathetic out flow resulting in fall in BP and bradycardia. Enhanced vagal tone contributes to bradycardia. Plasma NA declines. Though clonidine is capable of reducing NA release from peripheral adrenergic nerve endings (release inhibitory prejunctional α_2 action), this is not manifest at clinically used doses. Clonidine is a moderately potent antihypertensive.

Pharmacokinetics Clonidine is well absorbed orally; peak occurs in 2–4 hours; 1/2 to 2/3 of an oral dose is excreted unchanged in urine, the rest as metabolites. Plasma t½ is 8–12 hours. Effect of a single dose lasts for 6–24 hours.

Dose: Start with 100 µg OD or BD, max. 300 µg TDS, orally or i.m.

CATAPRES 150 µg tab, ARKAMIN 100 µg tab.

Adverse effects Side effects with clonidine are relatively common.

- Sedation, mental depression, disturbed sleep; dryness of mouth, nose and eyes (secretion is decreased by central action), constipation (antisecretory effect on the intestines).
- Impotence, salt and water retention, bradycardia.
- Postural hypotension occurs, but is mostly asymptomatic.
- Alarming rise in BP, in excess of pretreatment level, with tachycardia, restlessness, anxiety, sweating, headache, nausea and vomiting occur in some patients when doses of clonidine are missed for 1–2 days. The syndrome is very similar to that seen in pheochromocytoma: plasma catecholamine (CA) concentration is increased. This is due to:
  (a) Sudden removal of central sympathetic inhibition resulting in release of large quantities of stored CAs.
  (b) Supersensitivity of peripheral adrenergic structures to CAs that develops due to chronic reduction of sympathetic tone during clonidine therapy.

A combination of α blocker with a β blocker, or a potent vasodilator (nitroprusside) or clonidine itself can be used to treat the syndrome.

Interactions Tricyclic antidepressants and chlorpromazine abolish the antihypertensive action of clonidine, probably by blocking α receptors on which clonidine acts.

Use Clonidine was a popular antihypertensive in the late 1960s and 1970s, but frequent side effects, risk of withdrawal hypertension and development of tolerance have

relegated it to a 3rd or 4th choice drug. There is no data on prognostic benefits, if any, of clonidine. At present, it is occasionally used in combination with a diuretic.

Other indications

1. Opioid withdrawal: Opioid and α_2 adrenergic systems converge on the same effectors in many systems; both activate the Gi regulatory protein. Clonidine suppresses sympathetic overactivity of opioid withdrawal syndrome and reduces craving to some extent.

Clonidine has also facilitated alcohol withdrawal and smoking cessation.

2. Clonidine has analgesic activity. It has been used to substitute morphine for intrathecal/epidural surgical and postoperative analgesia.
3. Clonidine attenuates vasomotor symptoms of menopausal syndrome.
4. Clonidine has been used to control loose motions due to diabetic neuropathy. It may be acting by α_2 receptor mediated enhancement of salt absorption in gut mucosa.

Methyldopa This α-methyl analogue of dopa is converted in the body to α methyl NA, which is a selective α_2 agonist. In the brain, the α methyl NA generated from methyldopa acts on central α_2 receptors to decrease efferent sympathetic activity. However, in contrast to clonidine, methyldopa decreases t.p.r. more than HR or c.o. In large doses, methyldopa inhibits the enzyme dopa decarboxylase. It was initially believed that methyldopa acted as antihypertensive by depressing synthesis of NA in peripheral sympathetic neurones, and by generating α methyl NA which acted as a *false* (weak) *transmitter*. Subsequently α methyl NA was found to be as potent vasoconstrictor as NA. Many other findings have later confirmed the primary central site of action of methyldopa.

Methyldopa is a moderate efficacy antihypertensive. Circulating levels of NA and renin tend to fall due to reduction in sympathetic tone. Inhibition of postural reflexes is mild.

Pharmacokinetics Though methyldopa is transported actively by intestinal amino acid carrier, less than 1/3 of an oral dose is absorbed. It is partly metabolized and partly excreted unchanged in urine. Antihypertensive effect develops over 4–6 hours and lasts for 12–24 hours.

Dose: 0.25–0.5 g BD–QID oral.

EMDOPA, ALPHADOPA 250 mg tab.

Adverse effects Sedation, lethargy and reduced mental capacity are common side effects. Cognitive impairment may develop. Dryness of mouth, nasal stuffiness, headache, fluid retention, weight gain and impotence are the other side effects.

Postural hypotension is generally mild.

Positive Coomb's test occurs in 1/6 patients, few develop haemolytic anaemia. Fever, rash, hepatitis, 'flu' like illness, thrombocytopenia and rarely lupus syndrome occur.

Rebound hypertension on sudden withdrawal of methyldopa is mild and less common.

Interactions Tricyclic antidepressants reverse its action by blocking its active transport into the adrenergic neurones.

Use Methyldopa was a widely used antihypertensive in the 1960s and 1970s, especially in combination with a diuretic. However, it is rarely used now, except to treat hypertension during pregnancy wherein it has a long track record of safety, both for the mother as well as the foetus.

VASODILATORS

Hydralazine/Dihydralazine Introduced in the 1950s, it is a directly acting arteriolar vasodilator with little action on venous capacitance vessels. Hydralazine reduces t.p.r. and causes greater decrease in diastolic than in systolic BP. Reflex compensatory mechanisms are evoked which cause tachycardia, increase in c.o. and renin release → increased aldosterone → Na^+ and water retention. Thus, a hyperdynamic circulatory state is induced—angina may be precipitated due to increased cardiac work. There is no reduction in renal blood flow despite fall in BP. However, fluid retention and edema may occur by the above mechanism. Tolerance to the hypotensive action of hydralazine develops unless a diuretic or a β blocker or both are given together to block the compensatory mechanisms.

The mechanism of vascular smooth muscle relaxant action of hydralazine is not clearly known. Interference with Ca^{2+} release, opening of certain K^+ channels and/or NO generation may be involved.

Pharmacokinetics Hydralazine is well absorbed orally, and is subjected to first pass metabolism in liver. The chief metabolic pathway is acetylation which exhibits a bimodal distribution in the population: there are slow and fast acetylators.

Hydralazine is completely metabolized both in liver and plasma; the metabolites are excreted in urine, $t_{1/2}$ is 1–2

hours. However, hypotensive effect lasts longer (12 hours), probably because of its persistence in the vessel wall.

Dose: 25–50 mg OD–TDS; NEPRESOL 25 mg tab.

Adverse effects are frequent and mainly due to vasodilatation.

- Facial flushing, conjunctival injection, throbbing headache, dizziness, palpitation, nasal stuffiness, fluid retention, edema, CHF.
- Angina and MI may be precipitated in patients with coronary artery disease.
- Postural hypotension is not prominent because of little action on veins.
- Paresthesias, tremor, muscle cramps, rarely peripheral neuritis. Gastrointestinal disturbances are frequent.
- Lupus erythematosus or rheumatoid arthritis like symptoms develop on prolonged use of doses above 100 mg/day. This is more common in women and in slow acetylators.

Use Hydralazine is now rarely used as a second line alternative only in combination with a diuretic and/or β blocker for patients not achieving target BP with first line drugs. It is one of the antihypertensives that has been used during pregnancy, especially for preeclampsia. Injected hydralazine is occasionally employed in hypertensive emergencies. It is contraindicated in older patients and in those with ischaemic heart disease.

The arteriolar dilator action of hydralazine can be employed in the management of CHF particularly in combination with isosorbide dinitrate (*see* p. 566).

Minoxidil It is a powerful vasodilator, the pattern of action resembling hydralazine. Vasodilator side effects are more marked; risk of cardiac ischaemia and heart failure is high. It is not used orally now.

The active metabolite of minoxidil is an opener of ATP sensitive K^+ channels; causes vasodilatation by hyperpolarizing smooth muscle.

Use in alopecia Hirsutism was observed as a side effect of oral minoxidil. Applied topically (2% twice daily) it promotes hair growth in *male pattern baldness* and in *alopecia areata*. The response is slow (takes 2–6 months) and incomplete, but upto 60% subjects derive some benefit, albeit for short periods. Baldness recurs when therapy is discontinued. The mechanism of increased hair growth is not known; may involve:

(a) Opening of K^+ channels and enhanced microcirculation around hair follicles.

(b) Direct stimulation of resting hair follicles.

(c) Alteration of androgen effect on genetically programmed hair follicles.

Local irritation, itching and burning sensation are frequent. Dermatological reaction and systemic side effects (headache, dizziness, palpitation) occur in 1–3% cases.

MINTOP, GROMANE 2% scalp lotion, MULTIGAIN 2% topical solution and metered spray, MANEXIL 5% gel; apply twice a day.

Sodium nitroprusside It is a rapidly (within seconds) and consistently acting vasodilator with brief duration of action (2–5 min) so that vascular tone can be titrated with the rate of i.v. infusion. Nitroprusside relaxes both resistance and capacitance vessels: reduces t.p.r. as well as c.o. (by decreasing venous return). Myocardial work is reduced, but ischaemia may be accentuated due to coronary steal. Only mild reflex tachycardia is produced in supine posture. Plasma renin is increased.

In patients with heart failure and ventricular dilatation, nitroprusside improves ventricular function and c.o. mainly by reducing aortic impedance (afterload), but also by lowering atrial filling pressure (preload).

Endothelial cells, RBCs (and may be other cells) split nitroprusside to generate NO which relaxes vascular smooth muscle (also *see* p. 544). This occurs both enzymatically and nonenzymatically. The enzymes involved are different from those that produce NO from glyceryl trinitrate. Nonenzymatically it is converted to NO (and CN) by glutathione. This may be responsible for the different pattern of vasodilator action compared to nitrates, as well as for the fact that no nitrate like tolerance develops to nitroprusside action.

Nitroprusside is now a second line drug for certain hypertensive emergencies (*see* p. 619). 50 mg is added to a 500 ml bottle of saline/glucose solution. The infusion is started at 0.02 mg/min and titrated upward with the response: 0.1–0.3 mg/min is often needed. It decomposes at alkaline pH and on exposure to light: the infusion bottle should be covered with black paper.

Nitroprusside is split to release cyanide. The latter is converted in liver to thiocyanate which is excreted slowly. If larger doses are infused, excess thiocyanate may accumulate and produce toxicity, including psychosis and other CNS effects. Intracranial pressure may rise.

Side effects mainly due to vasodilatation are—palpitation, nervousness, vomiting, perspiration, pain in abdomen, weakness, disorientation, and lactic acidosis (caused by the released cyanide).

Nitroprusside has also been used to produce controlled hypotension, in refractory CHF (*see* p. 566) and in acute mitral regurgitation.

SONIDE, PRUSIDE, NIPRESS 50 mg in 5 ml inj.

ADRENERGIC NEURONE BLOCKERS

Reserpine It is an alkaloid from the roots of *Rauwolfia serpentina* (sarpgandha) indigenous to India which has been used in 'Ayurvedic' medicine for centuries. The pure alkaloid was isolated in 1955 and later found to act by causing CA and 5-HT depletion. It was a popular antihypertensive of the late 1950s and early 1960s, but is now used only as a pharmacological tool.

Reserpine acts at the membrane of intraneuronal vesicles which store monoamines (NA, DA, 5-HT) and irreversibly inhibits the vesicular monoamine transporter (VMAT2). The monoamines are gradually depleted and degraded by MAO. The effects last long after the drug is eliminated (hit and run drug) because tissue CA stores are restored only gradually.

Higher doses deplete CAs and 5-HT in the brain as well; cause sedation and mental depression. Antipsychotic effect (mild) and extrapyramidal symptoms are produced due to DA depletion.

Guanethidine It is a polar guanidine compound which is taken up into the adrenergic nerve endings by active amine transport, where it inhibits nerve impulse-coupled release of NA.

Guanethidine has gone out of use now due to marked side effects.

TREATMENT OF HYPERTENSION

The aim of antihypertensive therapy is to prevent morbidity and mortality associated with persistently raised BP by lowering it to the target level, with minimum inconvenience to the patient. Both systolic and diastolic BP predict the likelihood of target organ damage (TOD) and complications such as:

- Cerebrovascular disease, transient ischaemic attacks, stroke, encephalopathy.
- Hypertensive heart disease—left ventricular hypertrophy, heart failure.
- Coronary artery disease (CAD), angina, myocardial infarction (MI), sudden cardiac death.
- Arteriosclerotic peripheral vascular disease, retinopathy.
- Dissecting aneurysm of aorta.
- Glomerulopathy, renal failure.

Patients who have already suffered some TOD have greater risk of further organ damage and death at any level of raised BP, than those without TOD.

The current NICE guidelines (2011) have graded hypertension as:

BP		
Hypertension	*Systolic*	*Diastolic*
Stage I	140–159	90–99
Stage II	160–179	100–109
Severe	≥ 180	≥ 110

Since the risk of complications depends not only on the level of BP, but also on other risk factors (*see* box) and existing TOD, these have also to be considered in selection of drugs and in devising therapeutic regimens.

Cardiovascular risk factors

1. Age > 55 years (men), > 65 years (women)
2. Family h/o premature CV disease
3. Smoking
4. Dyslipidemia (↑LDL, ↓HDL, ↑TG)
5. Diabetes mellitus
6. Hypertension
7. Obesity (BMI ≥ 30)
8. CKD (Microalbuminuria or g.f.r. < 60 ml/min)
9. Sedentary life style

CKD–Chronic kidney disease.

The JNC7 have also identified compelling indications (*see* box) which may mandate use of specific antihypertensive drugs even in patients with BP values lower than 140/90 mm Hg. Moreover, presence of compelling indications may suggest fixing a lower target BP value to be attained by drug therapy.

Compelling indications for specific antihypertensive drug classes	
Diuretics	
1.	Heart failure
2.	High coronary artery disease risk
3.	Recurrent stroke prevention
ACE inhibitors/ARBs	
1.	Heart failure
2.	Post-myocardial infarction
3.	High coronary artery disease risk
4.	Diabetes
5.	Chronic kidney disease
6.	Recurrent stroke prevention
Calcium channel blockers	
1.	Diabetes
2.	Stroke prevention
β-Adrenergic blockers	
1.	Stable heart failure
2.	Post-myocardial infarction
3.	High coronary artery disease risk

Beneficial effects of lowering BP has been established in all patients having BP above 140/90 mm Hg, and even in the 120–139 (systolic) or 80–89 mm Hg (diastolic) range in those with compelling indications or cardiovascular risk factors; e.g. in diabetics, lowering diastolic BP to 80 mm Hg was found to reduce cardiovascular events to a greater extent than on reducing it upto 90 mm Hg.

However, for patients aged ≥60 years the JNC 8 (2014) has suggested threshold systolic BP value of 150 mm Hg for initiating treatment, as well as to be the treatment goal (< 150 mm Hg). The threshold and goal distolic BP value of 90 mm Hg is the same as for patients <60 years age.

Data from several large studies has shown that effective use of antihypertensive drugs reduces occurrence of stroke by 30–50%, heart failure by 40–50% and coronary artery disease (CAD) by ~15%.

If the cause of hypertension can be identified (hormonal, vascular abnormality, tumour, renal disease, drugs) all efforts should be made to remove it. Nonpharmacological measures (life style modification—diet, Na^+ restriction, aerobic activity or exercise, weight reduction, moderation in alcohol intake, mental relaxation, etc.) should be tried first and concurrently with drugs. When significant cardiovascular and/or renal damage has already occurred, lowering BP to normotensive level may not be tolerated: edema, CHF, angina, rise in blood urea and syncope may be precipitated. Therefore, BP reduction should be gradual and only to the level tolerated.

Selection of antihypertensive drug/ combination

In the past, evaluation of thiazide diuretics, β blockers, ACE inhibitors/ARBs and CCBs in large randomized trials with morbidity and mortality end points, established these drugs as first line antihypertensive drugs. However, the latest hypertension treatment guidelines (JNC 8, NICE 2011) have excluded β blockers from the list of first line drugs due to their lower efficacy in primary prevention of MI and stroke as well as other drawbacks described on p. 610.

A *stepped care approach*, initially using a single drug and progressively adding one or more drugs from different groups according to need, is recommended by most experts and therapeutic guidelines.

Step 1 The drug to initiate therapy is selected on the basis of compelling indications (if present); but for the majority of hypertensive patients who have no compelling indication, *age* and *race* has been recognized as valid basis for selecting the initial medication. Because young (< 55 years) non-black subjects generally have higher plasma renin activity, they respond better to ACE inhibitors/ARBs, while older patients and blacks of any age have lower renin status and show a weaker response to ACE inhibitors/ARBs. Accordingly, JNC8 recommend initiating antihypertensive therapy with any one of thiazide diuretic, or ACE inhibitor/ARBs or CCB for young (< 55 years) non-blacks, but the options for blacks of any age and older non-blacks are either thiazide

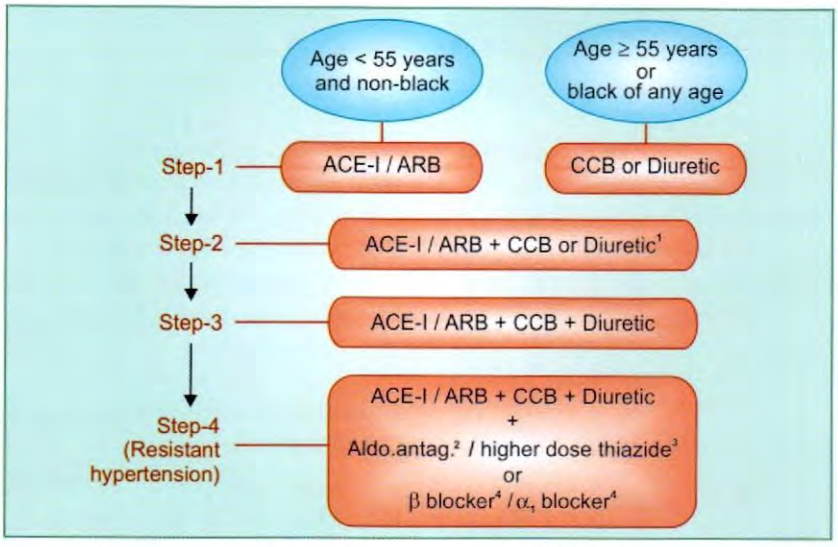


Fig. 41.1: Schematic depiction of stepwise drug treatment guideline for hypertension recommended by National Institute for Health and Care Excellence (UK) 2011

1. A thiazide diuretic to be considered only if calcium channel blocker (CCB) cannot be used, e.g. patient has edema/heart failure/high risk of heart failure.
2. Aldosterone antagonist (Aldo. antag.) to be used only when serum K^+ is <4.5 mmol/L.
3. Higher dose of thiazide to be used only when serum K^+ is > 4.5 mmol/L.
4. β blocker or α, blocker to be considered only if aldosterone antagonist or higher dose thiazide is ineffective or not tolerated or contraindicated.

ACE-I—Angiotensin converting enzyme inhibitor, ARB—Angiotensin receptor blocker.
https//www. nice.org.UK/guidance/cg127 (last updated Nov 2016).

or CCB. Since thiazide diuretics, even in low doses (12.5–25 mg/day), have an adverse (though minimal) metabolic profile, the NICE guidelines recommend only ACE inhibitor/ARB for young patients and CCB for older patients as well as for all blacks (*see* Fig. 41.1). Diuretics may be used as alternatives to CCBs in patients not tolerating CCBs and in those with edema or heart failure. In women with child bearing potential and in those young hypertensives who have another contraindication to ACE inhibitor/ARB or are intolerant to these drugs, a β blocker may be used as the initial drug.

Step 2 When the target BP is not attained by a single drug a combination of two drugs, i.e. ACE inhibitor/ARB + CCB or diuretic if CCB not suitable, is recommended irrespective of the age or race of the patient. In selected cases where therapy has been initiated with a β blocker, the second drug should be a CCB. Combination of β blocker with diuretic is to be avoided, because this increases the risk of developing diabetes.

Initiating antihypertensive therapy with two drugs is advised by JNC8 in case the BP at diagnosis is >20 mm Hg systolic and/or >10 mm Hg diastolic higher than the goal BP.

Step 3 The step 3 treatment includes all 3 first line drug classes, *viz.* ACE inhibitor/ARB + CCB + diuretic. However, before adding the third drug, the dose of existing medication should be titrated to the optimal or the best tolerated.

Step 4 Patients who do not achieve target BP even when taking optimal doses of 3 drugs are regarded as having resistant hypertension. Many patients having diabetes and/or CKD fall in this category. In such cases the NICE recommend adding a fourth drug, which can either be an aldosterone antagonist (if serum K^+ is <4.5

mmol/L) or higher dose of the thiazide (if serum K^+ is >4.5 mmol/L) or a β blocker (especially β blocker with vasodilating property, *viz.* carvedilol, nebivolol) or a selective α_1 blocker.

Only few patients are likely to still remain uncontrolled. They require further evaluation and possible use of reserve drugs.

Antihypertensive combinations to be avoided

1. An α or β adrenergic blocker with clonidine: apparent antagonism of clonidine action has been observed.
2. Hydralazine with a DHP or prazosin; because of similar pattern of haemodynamic action.
3. ACE inhibitor with an ARB.
4. Verapamil or diltiazem with β blocker, because marked bradycardia, A-V block can occur.
5. Methyldopa with clonidine or any two drugs of the same class.
6. β blocker with diuretic, because of increased risk of developing diabetes.

Some antihypertensive combinations

1. Amlodipine 5 mg + Lisinopril 5 mg—AMLOPRES-L, LISTRIL-AM
2. Amlodipine 5 mg + Atenolol 50 mg—AMCARD-AT, AMLOPIN-AT, AMLOPRES-AT
3. Amlodipine 5 mg + Enalapril 5 mg—AMACE, AMTAS-E
4. Atenolol 25 mg or 50 mg + chlorthalidone 12.5 mg—TENOCLOR, TENORIC
5. Enalapril 10 mg + Hydrochlorothiazide 25 mg—ENACE-D, VASONORM-H
6. Ramipril 2.5 mg + Hydrochlorothiazide 12.5 mg—CARDACE-H
7. Losartan 50 mg + Hydrochlorothiazide 12.5 mg—LOSAR-H, TOZAAR-H, LOSACAR-H
8. Lisinopril 5 mg + Hydrochlorothiazide 12.5 mg—LISTRIL PULS, LISORIL-HT
9. Losartan 50 mg + Ramipril 2.5 mg or 5 mg—TOZAAR-R, LAPIDO-R
10. Losartan 50 mg + Amlodipine 5 mg—AMCARD-LP, AMLOPRESS-Z, LOSACAR-A
11. Losartan 50 mg + Ramipril 2.5 mg + Hydrochlorothiazide 12.5 mg—LOSANORM-HR
12. Irbesartan 150 mg + Hydrochlorothiazide 12.5 mg—IROVEL-H, XARB-H.

When the BP has been well controlled for > 1 year, stepwise reduction in dose and/or withdrawal of one or more components of a combination may be attempted to workout a minimal regimen that will maintain the target BP. However, in most patients of essential hypertension, drug therapy is usually life-long.

Hypertension in pregnancy A sustained BP reading above 140/90 mm Hg during pregnancy has implications both for the mother and the foetus. Reduction of BP clearly reduces risks. Two types of situations are possible:

(a) A woman with preexisting chronic hypertension becomes pregnant.
(b) Pregnancy related hypertension: as in toxaemia of pregnancy—preeclampsia: BP rises after 20 weeks of gestation.

Toxaemic hypertension is associated with a hyperadrenergic state, decrease in plasma volume (despite edema) and increase in vascular resistance.

In the first category the same therapy instituted before pregnancy may be continued. However, one of the 'safer' drugs listed below may be substituted if one of the 'drugs to be avoided' was being used. The BP should be gradually reduced to a target level of <150 mm Hg systolic and 80–100 mm Hg diastolic, but drastic reduction should be avoided, because this may impair uteroplacental blood flow.

Women with diabetes, CKD, chronic hypertension and history of rise in BP during earlier pregnancy are at higher risk of developing preeclampsia. To reduce the risk *aspirin* (80–100 mg/day) should be given from the 12th week of gestation till the baby is born. Aspirin is believed to prevent toxaemia by inhibiting TXA_2 synthesis, which presumably plays a causative role.

Antihypertensives to be avoided during pregnancy

ACE inhibitors, ARBs: Risk of foetal damage, growth retardation.

Diuretics: There is some evidence that by reducing blood volume, diuretics tend to accentuate uteroplacental perfusion deficit (of toxaemia)—increase risk of foetal wastage, placental infarcts, miscarriage, stillbirth.

Nonselective β blockers: Propranolol has been implicated to cause low birth weight, decreased placental size, neonatal bradycardia and hypoglycaemia.

Sod. nitroprusside: Contraindicated in eclampsia.

Antihypertensives for use during pregnancy

Labetalol This combined α + β adrenergic blocker (*see* p. 165) given orally is effective in majority of cases, and is most widely used now.

Nifedipine (sustained release) This dihydropyridine CCB is a vasodilator that has been used in preeclampsia with good results. However, it should be stopped before labour begins, because it may weaken uterine contractions.

Methyldopa It has the longest record of use during pregnancy with safety, and is still used. A positive Coomb's test may occur, but has no adverse implication.

Hydralazine This old vasodilator has been safely used during pregnancy, but is not favoured now.

Hypertensive emergencies and urgencies

Systolic BP > 220 or diastolic BP > 120 mm Hg with evidence of active target organ damage (TOD) is labelled '*hypertensive emergency*', while the same elevation of BP with symptoms, but no signs of acute TOD is termed '*hypertensive urgency*'. Severity and rate of progress of TOD determines the seriousness of the condition.

Controlled reduction of BP over minutes (in emergencies) or hours (in urgencies) is required to counter threat to organ function and life in the following situations:

1. Cerebrovascular accident (haemorrhagic or ischaemic stroke) or head injury with high BP.
2. Hypertensive encephalopathy (headache, confusion, irritability, disorientation, mental deterioration).
3. Hypertensive acute LVF and pulmonary edema.
4. Acute coronary syndrome (ACS) or MI with raised BP.
5. Dissecting aortic aneurysm.
6. Acute renal failure with raised BP.
7. Eclampsia.
8. Hypertensive episodes in pheochromocytoma, cheese reaction or clonidine withdrawal.

Parenteral drugs

Hypertensive emergencies require aggressive parenteral (preferably i.v.) therapy. Mean BP should be lowered by upto 25% over a period of minutes or may be 1–2 hours, and then more gradually to not lower than 160/100 mm Hg. If the BP is reduced too quickly or too drastically perfusion of vital organs may suffer leading to impairment of kidney function, myocardial ischaemia, cerebral infarction, blindness, etc. Intravenous drugs with fast, predictable, titratable and short lasting action are therefore required. Vasodilators acting directly on vascular smooth muscle (dihydropyridine CCBs, nitrodilators) and adrenergic blockers meet these requirements best.

1. Nicardipine This is one of the few DHPs available for parenteral (i.v.) use, and has lately become the most popular drug for a variety of hypertensive emergencies, replacing nitroprusside. Nicardipine is highly vasoselective; primarily dilates arterioles. As such reflex tachycardia may attend the fall in BP, to offset which a β blocker like esmolol or labetalol should be coadministered when it is used in hypertensive emergencies attending MI or ACS.

Nicardipine is a short acting DHP with rapid onset and offset of hypotensive effect after i.v. infusion. The fall in BP is predictable and dose related. The elimination t½ on i.v. infusion is 45 min and action lasts for 3–4 hours. In clinical trials, i.v. nicardipine was as effective as nitroprusside in lowering BP in severe hypertension. The target BP level was reached within 1 hour in >90% cases with both the drugs. Nicardipine has been found beneficial in both ischaemic as well as haemorrhagic stroke with raised BP. Its usefulness has been demonstrated in aortic

dissection, acute heart failure and acute renal failure due to markedly raised BP, as well as in preeclampsia.

Nicardipine infused i.v. is better tolerated and less toxic than nitroprusside. Adverse effects of nicardipine are mostly due to vasodilatation, and are nonserious.

Dose: Initially 5 mg/hour i.v. infusion, increase rate of infusion as needed upto 15 mg/hour.

NICARDIPINE HCl 25 mg/10 ml inj.

Nicardipine has also been used in hypertension attending cardiac surgery and neurosurgery as well as to facilitate percutaneous coronary intervention.

2. Sodium nitroprusside (see p. 613) Because of instantaneous, potent and combined arteriovenous vasodilatory action, nitroprusside has been a commonly used drug for hypertensive emergencies. However, availability of less toxic and more manageable drugs has restricted its use. The major indication now is in cases of aortic dissection, where it is combined with the short acting β_1 blocker esmolol. It may also be used along with a loop diuretic in selected cases of acute hypertensive heart failure.

Due to its potency and rapidity of action, nitroprusside needs a precise infusion pump and intra-arterial BP monitoring. Nitroprusside generates cyanide and thiocyanate which can produce CNS and other toxicities. In ischaemic stroke, it may further compromise cerebral blood flow, while intracranial pressure may be further raised in haemorrhagic stroke. Nitroprusside is better avoided in these conditions.

3. Glyceryl trinitrate (GTN) Infused i.v. (5–20 µg/min) GTN acts within 2–5 min, but is not a potent hypotensive. Due to its predominant venodilator action, it is particularly suitable for use in MI or other ACS and in acute heart failure accompanied by rise in BP. However, for any substantial lowering of BP, it needs to be combined with i.v. labetalol or i.v. nicardipine. Tolerance tends to develop to GTN action if it is continuously infused for >12 hours. GTN needs to be avoided in severe hypertension with ischaemic or haemorrhagic stroke.

4. Labetalol Unlike pure β blockers, this combined β and α adrenergic blocker is an efficacious hypotensive when injected i.v. (*see* p. 165), and carries low risk of causing excessive hypotension. It is particularly useful in lowering BP during episodes of rise in BP in pheochromocytoma and other hyperadrenergic states, e.g. cheese reaction, cocaine abuse, etc. Labetalol has been safely used in severe hypertension complicating aortic dissection, MI and other ACS, ischaemic stroke, intracranial haemorrhage and preeclampsia. It is good for patients with altered mental function, because it does not cause sedation or increase intracranial pressure. However, heart failure and asthma preclude its use.

Dose: 20–40 mg i.v. every 10 min till response or 20 mg/hour i.v. infusion, increased up to 120 mg/hour.

LABESOL, LABETA 20 mg/amp. and 100 mg/amp. inj.

5. Esmolol This short acting selective β_1 blocker (*see* p.163) given as 0.5 mg/kg bolus i.v. injection followed by 50–200 µg/kg/min i.v. infusion acts in 1–2 min, and the action lasts till 10–20 min after infusion is terminated. Esmolol is particularly useful when cardiac contractility and work is to be reduced, such as in aortic dissection. Nicardipine or nitroprusside is given concurrently because its BP lowering action is weak. In MI/ACS complicated by raised BP and tachycardia, esmolol can be usefully combined with nicardipine or GTN. It needs to be avoided in presence of systolic heart failure or asthma.

MINIBLOCK 100 mg/10 and 250 mg/10 ml inj.

6. Phentolamine This non-selective $\alpha_1 + \alpha_2$ adrenergic blocker (*see* p.155) is an alternative drug to labetalol for hyperadrenergic states, e.g. hypertensive episodes in pheochromocytoma. Injected i.v. (5–10 mg) it acts in 2 min and action lasts 5–15 min. Tachycardia and myocardial ischaemia may complicate its use, for which a β blocker may be added.

7. Hydralazine Injected i.m. or i.v. slowly, hydralazine (*see* p. 612–13) acts in 20–30 min, and keeps BP low for 4–6 hours, but is less predictable. It is an alternative drug that has been particulary used for preeclampsia/eclampsia. It causes tachycardia, and should be avoided in patients with myocardial ischaemia or aortic dissection. A β blocker may be combined.

8. Furosemide (20–80 mg slow i.v.) This high ceiling diuretic (*see* Ch. 42) is not a hypotensive, but may be given as a useful adjunct with any of the above drugs, particularly vasodilators, if there is volume overload (in acute LVF, pulmonary edema) or cerebral edema (in encephalopathy). It needs to be avoided when patient may be hypovolemic due to pressure induced natriuresis (especially in eclampsia, pheochromocytoma).

Fenoldopam (dopamine agonist), *Clevidipine* (ultrashort acting DHP) and *enalaprilat* (a parenteral ACE inhibitor) are the other drugs that are used in hypertensive emergencies, but are not available in India.

Oral drugs

Oral hypotensive drugs that lower BP over a period of 2–48 hours may be more appropriate and safer in hypertensive urgencies, when there is no immediate threat to life or of organ damage. The following oral drugs have been used:

1. Labetalol In a dose of 100–200 mg BD, it is a moderately potent hypotensive (*see* p.165), that starts acting after 2–4 hours and is satisfactory in many cases of severe hypertension without TOD. Labetalol is particularly suitable in preeclampsia, pheochromocytoma, stroke and ischaemic heart disease, but is contraindicated in the presence of heart failure.

2. Amlodipine This slow and long acting DHP (*see* p.595) has been effectively and safely employed in many cases of severe hypertension, when raised BP is the only finding and there is no impending TOD or threat to life. In a dose of 10 mg oral repeated after 12 hours and then once daily, it starts acting in 6–8 hours and may take 2–4 days to lower BP to target level. It is particularly suitable for elderly patients and those prone to postural hypotension.

3. Captopril This non-prodrug, rapidly acting ACE inhibitor (*see* p. 530–31), has also been used orally (25 mg repeated as required) in hypertensive urgencies. Though it may lower BP in 30 min, the response is unpredictable both in intensity as well as in latency. It is not favoured now.

4. Clonidine (see p. 611) Oral clonidine (100 µg every 1–2 hours) lowers BP within a few hours, but produces sedation, dry mouth and rebound rise in BP on stopping. It is not suitable for the elderly, and seldom used.

Oral or sublingual use of *immediate release nifedipine* capsules in hypertensive urgencies has been abandoned.

SECTION 8

PROBLEM DIRECTED STUDY

41.1 A 70-year-old male presented with complaint of dull headache, giddiness, weakness and occasional breathlessness. He gave history of left sided paralytic stroke about 2 years back, from which he has recovered nearly completely, but is taking Aspirin 75 mg per day. The pulse was 66/min. The BP was found to range between 152–160 mm Hg systolic and 82–86 mm Hg diastolic, when measured on 3 occasions over one week. The ECG showed signs of left ventricular hypertrophy, but no ischaemia. Fundus examination revealed mild age related changes. Fasting blood sugar was 96 mg/dl; kidney function, liver function tests and lipid profile were within normal range.

(a) Should he be prescribed antihypertensive medication? If so, whether one, or more than one, antihypertensive should be prescribed concurrently, and which drug/drugs will be more suitable for him?

(see Appendix-1 for solution)

SECTION 9

DRUGS ACTING ON KIDNEY

Relevant Physiology of Urine Formation

Urine formation starts from glomerular filtration (g.f.) in a prodigal way. Normally, about 180 L of fluid is filtered everyday: all soluble constituents of blood minus the plasma proteins (along with substances bound to them) and lipids, are filtered at the glomerulus. More than 99% of the glomerular filtrate is reabsorbed in the tubules; about 1.5 L urine is produced

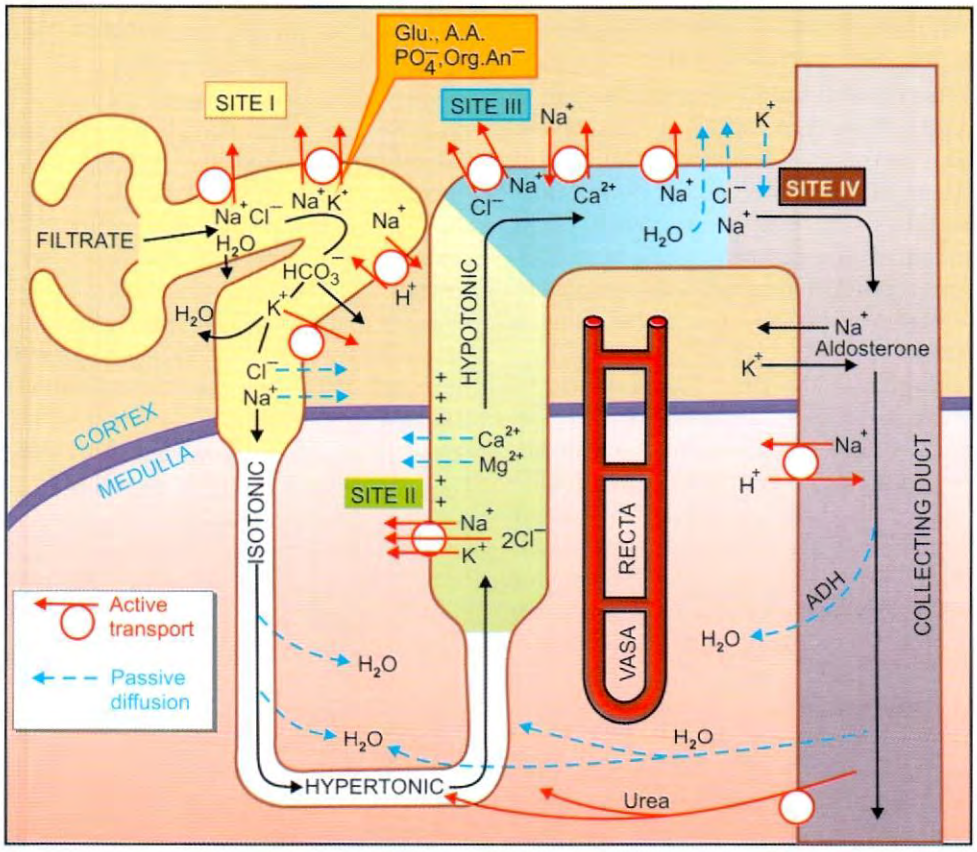


Fig. IX.1: Diagrammatic representation of nephron showing the four sites of solute reabsorption. The thick ascending limb of loop of Henle (TAL) is impermeable to water
Glu.—Glucose; A.A.—Amino acid; Org. An.—Organic anions.

in 24 hours. The diuretics act primarily by inhibiting tubular reabsorption: just 1% decrease in tubular reabsorption would more than double urine output.

The mechanisms that carryout ion movement across tubular cells are complex and involve a variety of energy dependent transmembrane pumps as well as channels in between the loose fitting cells of the proximal tubule (PT). All the Na^+ that enters tubular cells through the luminal membrane is pumped out of it into the renal interstitium at the basolateral membrane by Na^+K^+ATPase energised Na^+-K^+ antiporter (*see* Figs 42.1 and 42.2). Because there is a large intracellular to extracellular gradient for K^+, it diffuses out through K^+ channels to be recirculated by the Na^+-K^+ antiporter. For simplification, tubular reabsorption can be divided into four sites (Fig. IX.1).

Site I: Proximal tubule Four mechanisms of Na^+ transport have been defined in this segment.

(a) Direct entry of Na^+ along a favourable electrochemical gradient. This is electrogenic.

(b) Transport of Na^+ and K^+ coupled to active reabsorption of glucose, amino acids, other organic anions and PO_4^{3-} through specific symporters. Only the glucose coupled Na^+ reabsorption is electrogenic.

(c) Exchange with H^+: The PT cells secrete H^+ with the help of a Na^+-H^+ antiporter (Na^+-H^+ exchanger-3) located at the luminal membrane. This exchange moves Na^+ from tubular fluid to inside the cell. The secreted H^+ combines with HCO_3^- in the tubular fluid to form carbonic acid (Fig. IX.2). This H_2CO_3 is broken into $H_2O + CO_2$ by membrane bound brush border CAse (Type IV enzyme), because spotaneous dissociation of H_2CO_3 is very slow. Both CO_2 and H_2O diffuse inside the cell and recombine to form H_2CO_3 (intracellular soluble type II CAse catalysed reaction) which is the source of H^+. The dissociated HCO_3^- in the cell is transported to cortical e.c.f. by basolateral membrane Na^+-HCO_3^- symporter resulting in net reabsorption of $NaHCO_3$. Practically all HCO_3^- ion present in glomerular filtrate is reabsorbed in PT by

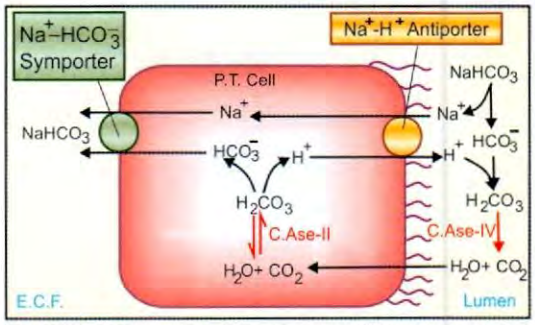


Fig. IX.2: The carbonic anhydrase (C.Ase) mediated bicarbonate absorption in proximal tubule (P.T.)

this mechanism, because tubular membrane, as such, is relatively impermeable to HCO_3^-.

(d) The disproportionately large HCO_3^-, acetate, PO_4^{3-}, amino acid and other anion reabsorption create passive driving forces for Cl^- to diffuse through the paracellular pathway (in between tubular cells), particularly in the later PT. This takes Na^+ and water along to maintain electrical neutrality and isotonicity.

Major part of filtered K^+ is reabsorbed in the PT *via* the paracellular pathway. Solute reabsorption creates osmotic forces for water to move in through transcellular aquaporin-1 channels and paracellular spaces. Because water permeability of PT is high, an isotonic tubular fluid with major changes in composition enters the thin descending limb of loop of Henle.

Site II: Thick ascending limb (TAL) of loop of Henle The TAL can be distinguished into two distinct portions:

(1) Medullary part lined by cuboidal cells.

(2) Cortical part lined by flattened cells.

Both portions are relatively impermeable to water but absorb salt actively and thus dilute the tubular fluid.

In the *medullary portion* a distinct luminal membrane carrier transports ions in the stoichiometric ratio of Na^+-K^+-$2Cl^-$ (*see* Fig. 42.1), and is nonelectrogenic. The Na^+ that enters the cell is pumped to e.c.f. by Na^+ K^+ AT-Pase at the basolateral membrane, while the excess intracellular K^+ back diffuses through K^+ channels. This creates a lumen positive

transepithelial potential at this site which drives reabsorption of other cations, such as Ca^{2+} and Mg^{2+} through the paracellular spaces. A Na^+-Cl^- symporter moves Cl^- down its electrochemical gradient into e.c.f. and carries Na^+ along. As the tubular fluid traverses TAL it progressively becomes hypotonic. Accumulation of NaCl in the medullary interstitium without accompanying water makes it hypertonic: a corticomedullary osmotic gradient is set up. This draws in water from the descending limb of loop of Henle (this thin segment has high osmotic water permeability but lacks active NaCl transport) so that the fluid that enters TAL becomes hypertonic. A 4 times higher osmolarity of medullary tip (papilla) is maintained by the hairpin structure of the loop of Henle acting as passive *counter current multiplier* and the arrangement of blood vessels as *vasa recti* which have shunts that prevents washing away of the osmotic gradient by progressively reducing blood flow to the inner medulla. Because of meagre blood supply, renal papilla is so prone to necrosis and suffers maximum damage when a toxic substance is being excreted.

Site III: Cortical diluting segment of loop of Henle This segment, also impermeable to water, continues to absorb salt, but here it is through a Na^+-Cl^- symporter (*see* Fig. 42.2). Tubular fluid gets further diluted.

Since no excess K^+ entry or back diffusion occurs in this segment, lumen positive transepithelial potential does not develop, and no electric potential driven reabsorption of Ca^{2+} and Mg^{2+} occurs. Rather, at this site Ca^{2+} reabsorption is an active process energized by a Na^+/Ca^{2+} exchanger which is regulated by PTH.

Site IV: Distal tubule (DT) and collecting duct (CD) Unlike cells in the other segments, the principal cells in the late DT and CD do not express any transporter for Na^+ or K^+ in their apical membranes. Rather, Na^+ enters these cells under its electrochemical gradient through specific amiloride sensitive *renal epithelial Na^+ channels*. This entry excludes Cl^- or any other anion so that a 10–15 mV lumen negative electric potential is created, which drives passive paracellular Cl^- diffusion into the interstitium, as well as K^+ efflux from the principal cell. Na^+ absorption at this site is controlled to a large extent by aldosterone (*see* Fig. 42.3). Since this is the final site of salt reabsorption, it provides fine tuning to electrolyte excretion according to body needs.

In common with other cells, the principal cells of DT and CD are rich in K^+; a chemical gradient exists for its diffusion into tubular lumen. This is aided by the lumen negative transepithelial potential difference at this site, and is therefore indirectly governed by the amount of Na^+ entering the cell.

The luminal membrane of collecting duct intercalated cells possess an active secretory pump for H^+ which is again governed by movement of Na^+ in the reverse direction. Any diuretic acting proximal to the aldosterone sensitive ion exchange site causes an increased delivery of Na^+ to the distal nephron—more exchange with K^+ takes place. Thus, K^+ is reabsorbed in the PT and TAL, but is secreted in the DT and CD. The net K^+ loss is regulated by variations in the secretory process and depends on:

- The Na^+ load delivered to distal segment
- Presence or absence of aldosterone
- Availability of H^+
- Intracellular K^+ stores

The characteristic feature of the principal CD cells is their responsiveness to antidiuretic hormone (ADH). If ADH is absent, the hypotonic fluid entering CD is passed as such, and dilute urine is produced during water loading. If ADH levels are high, CD cells become fully permeable to water due to insertion of aquaporin 2 water channels in their apical membrane (*see* Fig. 43.1) and equilibrate with hyperosmotic medulla so that concentrated urine is passed, as occurs during water deprivation or hypertonic saline infusion.

The CD and thin ascending limb of loop of Henle are the only segments permeable to urea. ADH promotes insertion of urea transporter (UT_1 or VRUT) into the luminal membrane of CD cells

(Fig. 43.1) and more urea is accumulated in the medullary interstitium, reinforcing the medullary hypertonicity during water deprivation.

Free water clearance It is defined as the volume of urine excreted per unit time in excess of that required to excrete the contained solute isoosmotically with plasma. It is positive when dilute urine is passed in the absence of ADH and negative when concentrated urine is passed in the presence of ADH. If isotonic urine is passed, regardless of its volume, free water clearance is zero.

Both positive and negative free water clearance are dependent on the production of a corticomedullary osmotic gradient; diuretics acting on medullary TAL depress both.

Organic ion transport The PT has nonspecific bidirectional active transport mechanism, separately for organic acids and organic bases. However, the magnitude of transport in the two directions may vary from compound to compound, e.g. reabsorption of uric acid is generally more than its secretion, while in case of penicillin the converse is true. Important diuretics like furosemide, thiazides and amiloride utilize this transport to approach their site of action from the luminal side of the tubule in the TAL/DT/CD.

Regulation of renal function

Glomerular filtration rate (g.f.r.) is dependent on the pumping action of heart, the magnitude of renal blood flow and the relative dimensions of afferent and efferent glomerular vessels. Thus, systemic and intrarenal haemodynamic changes can reflect in g.f.r.

About 80% nephrons lie in the outer cortex, have short loops of Henle and low Na^+ reabsorptive capacity; while 20% or so are juxtamedullary, possess long loops of Henle and are largely responsible for creating the corticomedullary osmotic gradient. Redistribution of blood flow between these two types of nephrons can alter salt and water excretion. Further, haemodynamic changes within different segments of renal vasculature can alter pressure relationships which govern flow of solute and water.

The *renin-angiotensin-aldosterone system* (RAAS) has a profound bearing on the distal tubular reabsorption of Na^+ and secretion of K^+/H^+. Angiotensin II produced locally in the kidney has direct effects on intrarenal vascular beds as well as on salt and water reabsorption (*see* Ch. 36).

Sympathetic stimulation of kidney results in renin release which would indirectly affect tubular transport. In addition, adrenergic drugs can directly enhance reabsorption of salt and water.

Prostaglandins (PGs) are produced locally in kidney; act as modulators of renal circulation and renin release. PGE_2 inhibits the action of ADH and has direct effects on tubular reabsorption.

Atrial natriuretic peptide (ANP) and related peptides produced from other sites (*see* Ch. 37) play important role in inducing natriuresis in response to salt and volume overload. ANP also mediates 'escape' from long-term aldosterone action.

All nephrons are so arranged that the ascending limb of loop of Henle passes close to the early PT of the same nephron. The macula densa cells are thus in close contact with afferent and efferent arterioles. This provides opportunity for feedback regulation of single unit function.

Relation to diuretic action

The relative magnitudes of Na^+ reabsorption at different tubular sites are:

PT 65–70%;	TAL 20–25%;
DT 8–9%;	CD 2–3%.

The maximal natriuretic response to a diuretic can give a clue to its site of action. It may appear that diuretics acting on PT should be the most efficacious. However, these agents are either too weak or cause distortion of acid-base balance (CAse inhibitors). Moreover, their effect is largely obscured by compensatory increase in reabsorption further down the nephron, because the reserve reabsorptive capacity of diluting segments is considerable and can overshadow more proximal actions.

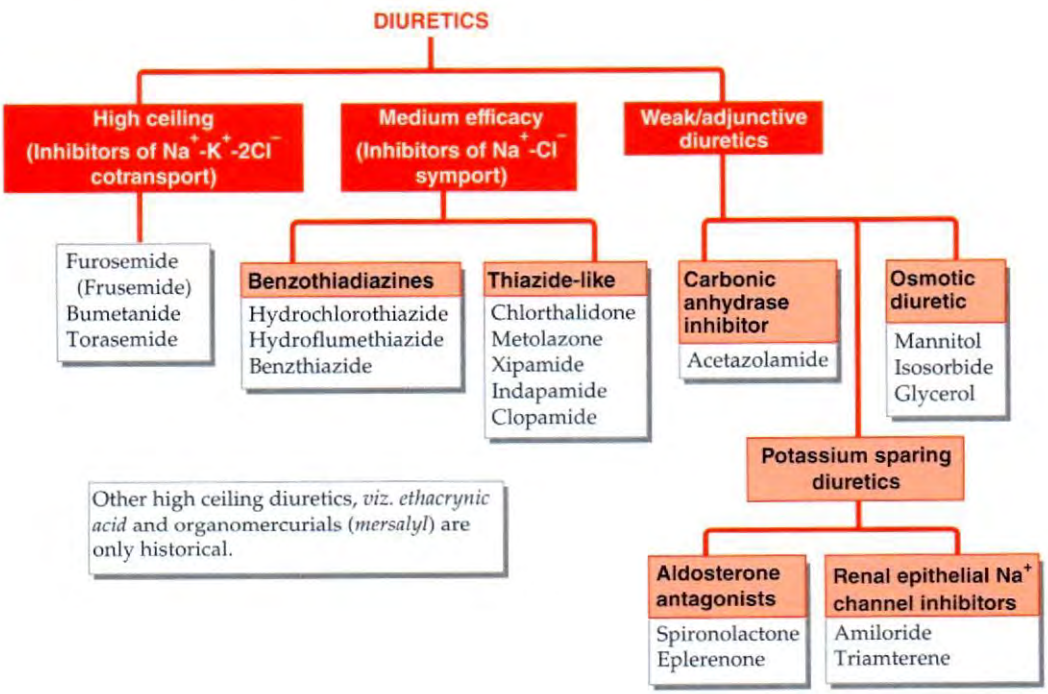
A diuretic having primary action on medullary TAL (furosemide) can produce substantial natriuresis because of limited capacity for salt absorption in DT and CD. This also explains why agents acting on DT and CD (K^+ sparing diuretics) evoke only mild saluretic effect. Diuretics acting on cortical diluting segment (thiazides) are intermediate between these two.

Chapter 42 | Diuretics

Diuretics (natriuretics) are drugs which cause a net loss of Na^+ and water in urine. However, when a diuretic is given regularly, Na^+ balance is soon restored by compensatory homeostatic mechanisms of the body, albeit with a certain degree of persisting Na^+ deficit and reduction in extracellular fluid volume.

Based on the diuretic action of calomel, organomercurials given by injection were introduced in the 1920s and dominated for nearly 40 years. The CAse inhibitors were developed in the 1950s from the observation that early sulfonamides caused acidosis and mild diuresis. The first modern orally active diuretic *chlorothiazide* was produced in 1957, and by early 1960s its congeners (thiazide diuretics) were already in common use. Availability of *furosemide* and *ethacrynic acid* by mid 1960s revolutionized the pattern of diuretic use. The aldosterone antagonist (*spironolactone*) and other K^- sparing diuretics *(triamterene/amiloride)* were developed in parallel to these.

Diuretics are among the most widely prescribed drugs. Application of diuretics in the management of hypertension has outstripped their use in edema. Availability of diuretics has also had a major impact on the understanding of renal physiology.



HIGH CEILING (LOOP) DIURETICS
(Inhibitors of Na^+-K^+-$2Cl^-$ Cotransport)

Furosemide (Frusemide) It is the first and the prototype drug of this class. The introduction of this rapidly acting highly efficacious oral diuretic was a breakthrough. Its maximal natriuretic effect is much greater than diuretics of other classes. The diuretic response goes on increasing with increasing dose: upto 10 L of urine may be produced in a day. It works even in patients with relatively severe renal failure. The onset of action is prompt (i.v. 2–5 min., i.m. 10–20 min., oral 20–40 min.) and duration short (3–6 hours).

The major site of action is the thick ascending limb of loop of Henle (TAL), therefore, called *loop diuretics*. Furosemide inhibits Na^+- K^+-$2Cl^-$ cotransport (site II, Fig. 42.1). A minor component of action on PT has also been demonstrated. It is secreted in PT by organic anion transport and reaches TAL where it acts from luminal side of the membrane. The corticomedullary osmotic gradient is abolished and positive as well as negative free water clearance is blocked. K^+ excretion is increased mainly due to high Na^+ load reaching DT.

Furosemide has weak CAse inhibitory action; increases HCO_3^- excretion as well; urinary pH may rise but the predominant urinary anion is Cl^-. Therefore, acidosis does not develop. The diuretic action is independent of acid-base balance of the body and it causes little distortion of the same; mild alkalosis due to Cl^- loss occurs at high doses.

In addition to its prominent tubular action, furosemide causes acute changes in renal and systemic haemodynamics. After 5 min of i.v. injection, renal blood flow is transiently increased and there is redistribution of blood flow from outer to midcortical zone; g.f.r. generally remains unaltered due to compensatory mechanisms despite increased total renal blood flow. Pressure relationship between vascular, interstitial and tubular compartments is altered, the net result of which is decreased PT reabsorption. The intrarenal haemodynamic changes are brought about by increased local PG synthesis.

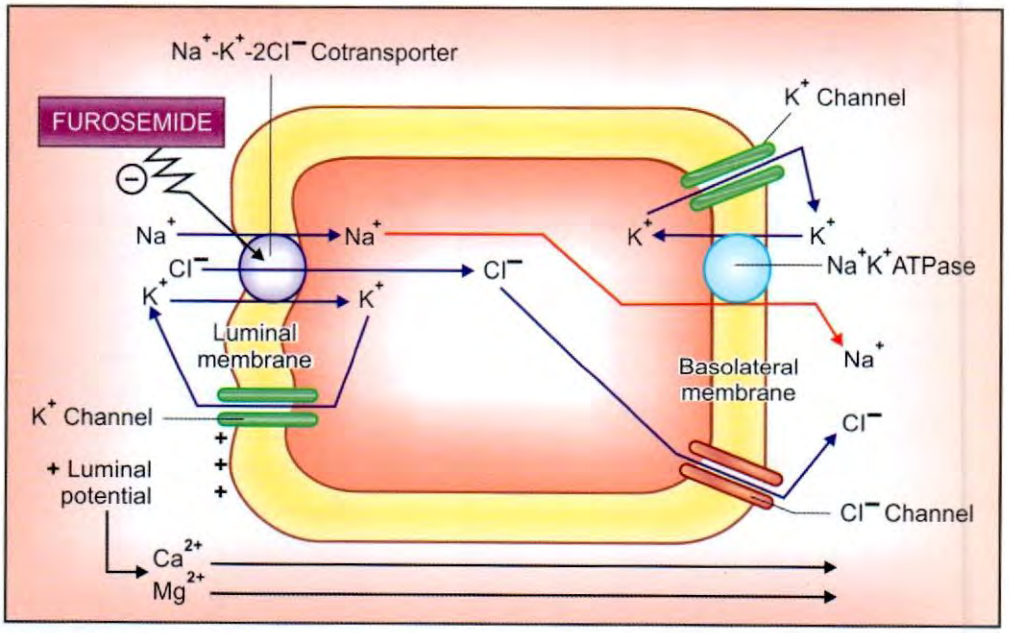


Fig. 42.1: Mechanism of salt reabsorption in the thick ascending limb of loop of Henle (TAL) cell, and site of action of furosemide on the Na^+-K^+-$2Cl^-$ cotransporter

Furosemide also sets in motion compensatory mechanisms which tend to limit its diuretic action. Interference with Na^+ entry into maculadensa causes marked renin release. Activation of the renin-angiotensin-aldosterone system is the major compensatory mechanism. Reflex sympathetic stimulation of the kidney reinforces renin release. These mechanisms restore Na^+ balance after termination of the diuretic action. Because of this phenomenon and short t½ of furosemide, its once daily administration may have less marked overall effect on Na^+ status of the body.

Intravenous furosemide causes prompt increase in systemic venous capacitance which decreases left ventricular filling pressure, even before the saluretic response is apparent. This action also appears to be PG mediated and is responsible for the quick relief it affords in LVF and pulmonary edema.

Furosemide increases Ca^{2+} excretion (contrast thiazides which reduce it) as well as Mg^{2+} excretion by abolishing the lumen positive transepithelial potential difference in the TAL which drives reabsorption of these divalent cations (*see* p 623). Furosemide tends to raise blood uric acid level by competing with its proximal tubular secretion as well as by increasing reabsorption in PT that occurs as a consequence of reduced e.c.f. volume. The magnitude of hyperuricaemia is lower than that with thiazides. A small rise in blood sugar level may be noted after regular use of furosemide, but this is again less marked compared to thiazides.

Molecular mechanism of action: A glycoprotein with 12 membrane spanning domains has been found to function as the Na^+-K^+-$2Cl^-$ cotransporter in many epithelia performing secretory/absorbing function, including TAL. Recently, distinct *absorptive* and *secretory* isoforms of Na^+-K^+-$2Cl^-$ cotransporter have been isolated. The former is exclusively expressed at the luminal membrane of TAL. Furosemide attaches to the Cl^- binding site of this protein to inhibit its transport function. The secretory form is expressed on the basolateral membrane of most glandular and epithelial cells.

Pharmacokinetics Furosemide is absorbed orally over 2–3 hours, and bioavailability is about 60%. In severe CHF oral bioavailability may be markedly reduced necessitating parenteral administration. Lipid-solubility is low, and it is highly bound to plasma proteins. It is partly conjugated with glucuronic acid and mainly excreted unchanged by glomerular filtration as well as tubular secretion. Some excretion in bile and directly in intestine also occurs. Plasma t½ averages 1–2 hour but is prolonged in patients with pulmonary edema, renal and hepatic insufficiency. Single oral dose acts for 3–4 hours.

Dose Usually 20–80 mg once daily in the morning. In renal insufficiency, upto 200 mg 6 hourly has been given by i.m./i.v. route. In pulmonary edema 40–80 mg may be injected i.v.

LASIX 40 mg tab., 20 mg/2 ml inj. LASIX HIGH DOSE 500 mg tab, 250 mg/25 ml inj; (solution degrades spontaneously on exposure to light), SALINEX 40 mg tab, FRUSENEX 40, 100 mg tab.

Bumetanide It is similar to furosemide in all respects, but is 40 times more potent. It induces very rapid diuresis and is highly effective in pulmonary edema. The site of action, ceiling effect, renal haemodynamic changes and duration of action are similar to furosemide. A secondary action in PT has also been demonstrated. Bumetanide may act in some cases not responding to furosemide, and may be tolerated by patients allergic to furosemide. Hyperuricaemia, K^+ loss, glucose intolerance and ototoxicity are claimed to be less marked, but bumetanide may rarely cause myopathy.

Bumetanide is more lipid-soluble; oral bioavailability is 80–100%. It is preferred for oral use in severe CHF, because its oral absorption is relatively unaffected by edema of the bowels. Bumetanide is extensively bound to plasma proteins, partly metabolized and partly excreted unchanged in urine. Its accumulation in tubular fluid is less dependent on active secretion. Plasma t½ is 60 min, but gets prolonged in renal and hepatic insufficiency.

Dose: 1–5 mg oral OD in the morning, 2–4 mg i.m./i.v., (max. 15 mg/day in renal failure).

BUMET, 1 mg tab., 0.25 mg/ml inj.

Torasemide (Torsemide) Another high ceiling diuretic with properties similar to furosemide, but 2–3 times more potent. Oral absorption is

more rapid and more complete even in patients with edema of the bowels due to CHF. The elimination t½ (3.5 hours) and duration of action (4–8 hours) are longer. Torasemide has been used in edema and in hypertension.

Dose: 2.5–5 mg OD in hypertension; 5–20 mg/day in edema; upto 100 mg BD in renal failure.

DIURETOR 10, 20 mg tabs, DYTOR, TIDE 5, 10, 20, 100 mg tabs, 10 mg/2 ml inj.

Use of high ceiling diuretics

1. *Edema* Diuretics are used irrespective of etiology of edema—cardiac, hepatic or renal. The high ceiling diuretics are preferred in CHF for rapid mobilization of edema fluid (*see* Ch. 38). Thiazides may be used for maintenance, but often prove ineffective and high ceiling diuretics are called in. For nephrotic and other forms of resistant edema, only the high ceiling diuretics are effective, and are the drugs of choice. In chronic renal failure massive doses have to be used, but they continue to be effective while thiazides just do not produce any action. In impending acute renal failure, loop diuretics may decrease the need for dialysis.

2. *Acute pulmonary edema (acute LVF, following MI):* Intravenous administration of furosemide or its congeners produces prompt relief. This is due to venodilator action that precedes the saluretic action. Subsequently, decrease in blood volume and venous return is responsible for the improvement.

3. *Cerebral edema* Though osmotic diuretics are primarily used to lower intracranial pressure by withdrawing water, furosemide may be combined to improve efficacy.

4. *Hypertension* High ceiling diuretics are indicated in hypertension only in the presence of renal insufficiency, heart failure, or in resistant cases and in hypertensive emergencies; otherwise thiazides are preferred (*see* Ch. 41).

5. Furosemide may be infused along with blood transfusion, to prevent volume overload in severely anaemic patients. Infused with hypertonic saline, it may be helpful in hyponatraemia.

6. *Hypercalcaemia of malignancy* This condition may present as a medical emergency with severe volume depletion. Rapid and large volume i.v. saline infusion is the most important measure (*see* p. 370). Addition of furosemide (10–20 mg/hour) to the i.v. drip after volume replacement, augments Ca^{2+} excretion and prevents volume overload.

Forced diuresis with saline and furosemide infusion is no longer recommended to treat poisonings.

THIAZIDE AND RELATED DIURETICS
(Inhibitors of Na^+-Cl^- symport)

Chlorothiazide was synthesized as a CAse inhibitor variant which (unlike acetazolamide) produced urine that was rich in Cl^-, and diuresis occurred in alkalosis as well as in acidosis. A large number of congeners were developed subsequently and the thiadiazine ring was replaced by other heterocyclic rings, but the type of activity remained the same. The important features of the available thiazide and thiazide-like diuretics are presented in Table 42.1.

Thiazides are medium efficacy diuretics with primary site of action in the cortical diluting segment or the early DT (Site III). Here they inhibit Na^+–Cl^- symport at the luminal membrane. They do not affect the corticomedullary osmotic gradient indicating lack of action at the medullary TAL. Positive free water clearance is reduced, because tubular fluid is not maximally diluted (very dilute urine cannot be passed in the absence of ADH), but negative free water clearance (in the presence of ADH) is not affected. This strengthens the view that the site of action is inbetween TAL and late DT. These drugs gain access to their site of action *via* organic acid secretory pathway in PT and then along the tubular fluid to the early DT, where they bind to specific receptors located on the luminal membrane. Like the Na^+-K^+-$2Cl^-$ cotransporter, the Na^+-Cl^- symporter is also a glycoprotein with 12 membrane spanning domains that binds thiazides but not furosemide or any other class of diuretics. This glycoprotein has been cloned and shown to be selectively

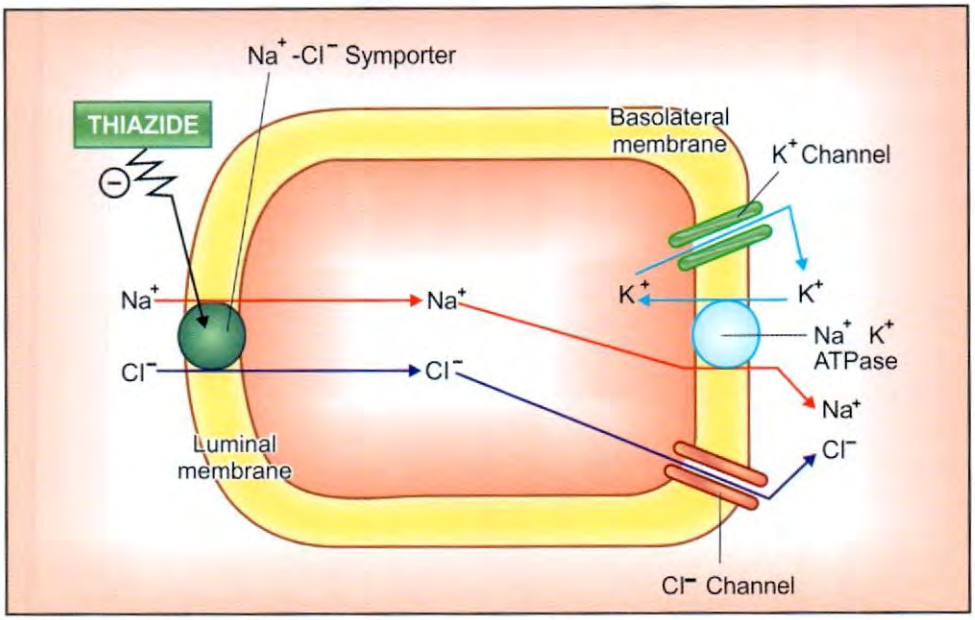


Fig. 42.2: Mechanism of salt reabsorption in early distal tubular cell and site of action of thiazide diuretics on Na^+Cl^- symporter

expressed on the luminal membrane in the DT. The site of action of thiazide diuretics is shown in Fig. 42.2.

Some of the thiazides and related drugs have additional CAse inhibitory action in PT; intensity of this action differs among different compounds (Table 42.1), but it is generally weak. However, it may confer some proximal tubular action to the compounds, and accounts for the increase in HCO_3^- and PO_4^{3-} excretion.

Under thiazide action, increased amount of Na^+ is presented to the distal nephron, more of it exchanges with K^+, so that urinary K^+ excretion is increased in parallel to the natriuretic response. The maximal diuresis induced by different agents falls in a narrow range; though potency (reflected in daily dose) differs markedly. Nevertheless, they are moderately efficacious diuretics, because nearly 90% of the glomerular filtrate has already been reabsorbed before it reaches their site of action. Thiazides have a flat dose response curve; little additional diuresis occurs when the dose is increased beyond 100 mg of hydrochlorothiazide or equivalent. Thiazides do not cause significant alteration in acid-base balance of the body.

By their action to reduce blood volume, as well as intrarenal haemodynamic changes, thiazides tend to reduce g.f.r. This is one reason why thiazides are not effective in patients with low g.f.r. As already explained (*see* p. 623), thiazides decrease renal Ca^{2+} excretion and increase Mg^{2+} excretion by a direct distal tubular action. Thiazides cause greater reduction in urate excretion than furosemide, but the mechanism is the same (*see* p. 627).

The *extrarenal actions* of thiazides consist of a slowly developing fall in BP in hypertensives (*see* p. 606), and elevation of blood sugar in some patients due to decreased insulin release which probably is a consequence of hypokalaemia.

Pharmacokinetics All thiazides and related drugs are well absorbed orally. There are no injectable preparations of these drugs. Their action starts within 1 hour, but the duration of action varies from 6–48 hours (Table 42.1). The more lipid-soluble agents have larger volumes

Table 42.1: Thiazides and related diuretics

Drug	*Trade name (Tab. strength) (mg)*	*Daily dose (mg)*	*CAse inhibition*	*Duration of action (Hr)*
1. Hydrochlorothiazide	AQUAZIDE, HYDRIDE THIAZIDE (12.5, 25, 50) ESIDREX (50)	12.5–100	+	6–12
2. Chlorthalidone	HYTHALTON (50,100) HYDRAZIDE, THALIZIDE (12.5, 25)	12.5–50	++	48
3. Metolazone	XAROXOLYN (5, 10) DIUREM, METORAL (2.5, 5, 10)	5–20	+	12–24
4. Xipamide	XIPAMID (20)	20–40	+	12
5. Indapamide	LORVAS (2.5)	2.5–5	–	16
6. Clopamide	BRINALDIX (20)	10–60	±	12–18

of distribution (some are also bound in tissues), lower rates of renal clearance and are longer acting. The protein binding is also variable. Most of the agents undergo little hepatic metabolism and are excreted unchanged. They are filtered at the glomerulus as well as secreted in the PT by organic anion transport. Tubular reabsorption depends on lipid solubility: the more lipid soluble ones are highly reabsorbed—prolonging duration of action.

The elimination t½ of hydrochlorothiazide is 3–4 hours, but action persists longer (6–12 hours).

Chlorthalidone It is a particularly long acting compound with a t½ 40–50 hours, used exclusively as antihypertensive.

Metolazone In common with loop diuretics, it is able to evoke a clinically useful response even in severe renal failure (g.f.r. ~15 ml/min), and has marked additive action when combined with furosemide. An additional proximal tubular action has been demonstrated; PO_4 reabsorption that occurs in PT, is inhibited. It is excreted unchanged in urine. Metolazone has been used mainly for edema (5–10 mg/day, rarely 20 mg), and occasionally for hypertension (2.5–5 mg/day).

Xipamide It has more pronounced diuretic action similar to low doses of furosemide. Though overall reduction in plasma K^+ level is similar to thiazides, several instances of severe hypokalemia with ventricular arrhythmias have been reported. It is used mainly for treatment of edema (40 mg/day, max. 80 mg/day).

Indapamide It has little diuretic action in the usual doses, probably because it is highly lipid-soluble, is extensively metabolized and only small quantity of unchanged drug is present in the tubular fluid. However, it retains antihypertensive action and is one of the favoured diuretics by NICE guidelines (2011) for hypertension (*see* p. 607).

Uses

Thiazides are typically administered once in the morning, so that diuresis does not disturb sleep.

1. *Edema* Thiazides may be used for mild-to-moderate cases. For mobilization of edema fluid more efficacious diuretics are preferred, but thiazides may be considered for maintenance therapy. They act best in cardiac edema; are less effective in hepatic or renal edema. Thiazides are powerless in the presence of renal failure, but metolazone may still act. Cirrhotics often develop refractoriness to thiazides due to development of secondary hyperaldosteronism.

2. *Hypertension* Thiazides and related diuretics, especially chlorthalidone and indapamide are one of the first line drugs (Ch. 41).

3. *Diabetes insipidus* Thiazides decrease positive free water clearance (*see* p. 624) and are the only drugs effective in nephrogenic diabetes insipidus. Modest reduction in urine volume occurs in pituitary-origin cases as well (*see* Ch. 43)

4. *Hypercalciuria* with recurrent calcium stones in the kidney. Thiazides act by reducing Ca^{2+} excretion.

Complications of high ceiling and thiazide type diuretic therapy

Most of the adverse effects of these drugs are related to fluid and electrolyte changes caused by them. Usual side effects are weakness and tiredness, but they are remarkably safe in low doses used over short periods. Many subtle metabolic effects have been reported in their long-term use as antihypertensives at the relatively higher doses used in the past (*see* p. 606-07).

1. *Hypokalaemia* This is the most significant problem. It is rare at low doses used for hypertension but may be of grave consequence when brisk diuresis is induced or on prolonged therapy, especially if dietary K^+ intake is low. Degree of hypokalaemia appears to be related to the duration of action of the diuretic; longer acting drugs cause more K^+ loss. The usual manifestations are weakness, fatigue, muscle cramps; cardiac arrhythmias are the serious complications. Hypokalaemia is less common with standard doses of high ceiling diuretics than with thiazides, possibly because of shorter duration of action of the former which permits intermittent operation of compensatory repletion mechanisms. Hypokalaemia can be prevented and treated by:

(a) High dietary K^+ intake or
(b) Supplements of KCl (24–72 mEq/day) or
(c) Concurrent use of K^+ sparing diuretics.

Measures (b) and (c) are not routinely indicated, but only when hypokalaemia has been documented or in special risk situations, e.g. cirrhotics, cardiac patients—especially post MI, those receiving digoxin, antiarrhythmics, or tricyclic antidepressants and elderly patients. Serum K^+ levels are only a rough guide to K^+ depletion, because K^+ is primarily an intracellular ion. Nevertheless, an attempt to maintain serum K^+ at or above 3.5 mEq/L should be made.

Combined tablets of diuretics and KCl are not recommended, because they may cause gut ulceration by releasing KCl at one spot.

K^+ sparing diuretics are more efficacious and more convenient in correcting hypokalaemia than are K^+ supplements. ACE inhibitors/AT_1 antagonists given with thiazides tend to prevent development of hypokalaemia.

Alkalosis may occur with hypokalaemia, because more H^+ exchanges with Na^+ in DT when less K^+ is available for exchange.

2. *Acute saline depletion* Overenthusiastic use of diuretics, particularly high ceiling ones, may cause dehydration and marked fall in BP, especially on standing up. The diuretic induced haemoconcentration increases risk of peripheral venous thrombosis. Serum Na^+ and Cl^- levels remain normal because isotonic saline is lost. This complication should be treated by saline infusion.

3. *Dilutional hyponatraemia* When vigorous diuresis with high ceiling diuretics is induced, especially in patients with heart failure, the kidney tends to retain water, though it is unable to retain salt due to the diuretic; e.c.f. gets diluted, hyponatraemia develops and edema persists despite natriuresis. Patients feel very thirsty. This occurs rarely with thiazides. Treatment of this distortion of fluid-electrolyte balance is difficult, but consists of withholding the diuretic, restricting water intake and giving glucocorticoid which enhances excretion of the water load. If hypokalaemia is present, its correction helps.

4. *GIT and CNS disturbances* Nausea, vomiting and diarrhoea may occur with any diuretic. Headache, giddiness, weakness, paresthesias, impotence are occasional complaints with thiazides as well as loop diuretics.

5. *Hearing loss* This occurs only with high ceiling diuretics, but is infrequent. The risk increases when these drugs are used in the presence of renal insufficiency. Increased salt content of the endolymph and a direct toxic action on the hair cells in internal ear appear to be causative.

6. *Allergic manifestations* Rashes, photosensitivity occur, especially in patients hypersensitive to sulfonamides. Blood dyscrasias are rare; any diuretic may be causative.

7. *Hyperuricaemia* Long-term use of higher dose thiazides in hypertension has caused rise in blood urate level. This is uncommon now due to use of lower doses (*see* Ch. 41). Furosemide produces a lower incidence of hyperuricaemia. This effect can be counteracted by allopurinol. Probenecid is better avoided, because it may interfere with the diuretic response, particularly of loop diuretics.

8. *Hyperglycaemia and dyslipidemia* These complications have occurred in the use of diuretics as antihypertensive (*see* p. 606). These metabolic changes are minimal with low dose thiazides now utilized.

9. *Hypocalcaemia* It can develop on regular use of high ceiling diuretics when these are administered chronically. Thiazides, on the otherhand, tend to raise serum Ca^{2+}.

10. *Magnesium depletion* It may develop after prolonged use of thiazides or loop diuretics, and may increase the risk of ventricular arrhythmias, especially after MI or when patients are digitalized. K^+ sparing diuretics given concurrently minimise Mg^{2+} loss.

11. Thiazides have occasionally *aggravated renal insufficiency*, probably by reducing g.f.r.

12. Brisk diuresis induced in cirrhotics may precipitate *mental disturbances* and hepatic coma. It may be due to hypokalaemia, alkalosis and increased blood NH_3 levels.

13. Diuretics should be avoided in *toxaemia of pregnancy* in which blood volume is low despite edema. Diuretics may further compromise placental circulation increasing the risk of miscarriage, foetal death.

Interactions

1. Thiazides and high ceiling diuretics potentiate all other antihypertensives. This interaction is intentionally employed in therapeutics.
2. Hypokalaemia induced by diuretics:
   - Enhances digoxin toxicity.
   - Increases risk of polymorphic ventricular tachycardia due to drugs which prolong Q-T interval (*see* p. 572).
   - Reduces sulfonylurea action.
3. High ceiling diuretics and aminoglycoside antibiotics are both ototoxic and nephrotoxic; their concurrent use requires caution.
4. Indomethacin and other NSAIDs diminish the action of high ceiling diuretics by inhibiting PG synthesis in the kidney, through which furosemide and related drugs induce intrarenal haemodynamic changes which secondarily affect salt output. This interference is more marked in cirrhotic and nephrotic patients. Antihypertensive action of thiazides and furosemide is also diminished by NSAIDs.
5. Probenecid competitively inhibits tubular secretion of furosemide and thiazides: decreases their diuretic action by lowering concentration in the tubular fluid. On the other hand diuretics diminish the uricosuric action of probenecid.
6. Serum lithium level rises due to enhanced reabsorption of Li^+ (and Na^+) in the PT.

Resistance to diuretics Refractoriness (progressive edema despite escalating diuretic therapy) is more common with thiazides, but occurs under certain circumstances with high ceiling diuretics as well. The causes and mechanism of such resistance include:

1. *Renal insufficiency:* Due to low g.f.r. and less secretion in PT, smaller quantity of the diuretic reaches its site of action.
2. *CHF:* Impaired oral absorption (especially of furosemide and thiazides) due to congestion of bowels. Decreased renal blood flow due to CHF also limits diuretic action.

3. *Cirrhosis of liver:* Raised aldosterone levels.
4. *Nephrotic syndrome:* Binding of the diuretic to the urinary protein, raised aldosterone.

Long-term use of loop diuretics causes distal nephron hypertrophy leading to resistance. Addition of a diuretic which acts on the distal tubule, i.e. a thiazide overcomes the refractoriness and restores diuresis. Metolazone is particularly effective for this purpose. Combination of these two types of diuretics can produce a marked response which needs close monitoring.

CARBONIC ANHYDRASE INHIBITORS

Carbonic anhydrase (CAse) is an enzyme which catalyses the reversible reaction $H_2O + CO_2 \rightleftarrows H_2CO_3$. Carbonic acid spontaneously ionizes $H_2CO_3 \rightleftarrows H^+ + HCO_3^-$ (Fig. IX.2). Carbonic anhydrase thus functions in CO_2 and HCO_3^- transport and in H^+ ion secretion. The enzyme is present in renal tubular cell (especially PT) gastric mucosa, exocrine pancreas, ciliary body of eye, brain and RBC. In these tissues a gross excess of CAse is present, more than 99% inhibition is required to produce effects.

Acetazolamide

It is a sulfonamide derivative which noncompetitively but reversibly inhibits CAse (type II) in PT cells resulting in slowing of hydration of CO_2. This decreases availability of H^+ to exchange with luminal Na^+ through the Na^+-H^+ antiporter. Inhibition of brush border CAse (type IV) retards dehydration of H_2CO_3 in the tubular fluid so that less CO_2 diffuses back into the cells. The net effect is inhibition of HCO_3^- (and accompanying Na^+) reabsorption in PT. However, the resulting alkaline diuresis is only mild (maximal fractional Na^+ loss 5%), because part of the Na^+ (but not HCO_3^-) rejected in the PT is reabsorbed at the high capacity TAL segment.

Secretion of H^+ by the intercalated cells of DT and CD is also interfered. Though H^+ is secreted at this site by a H^+-ATPase, it is generated in the cell by CAse mediated reaction. As such, this is a subsidiary site of action of CAse inhibitors. When CAse inhibitors are given, the distal Na^+ exchange takes place only with K^+ which is lost in excess. For the same degree of natriuresis CAse inhibitors cause the most marked kaliuresis compared to other diuretics. The urine produced under acetazolamide action is alkaline and rich in HCO_3^- which is matched by both Na^+ and K^+. Continued action of acetazolamide depletes body HCO_3^- and causes acidosis; less HCO_3^- (on which its diuretic action depends) is filtered at the glomerulus → less diuresis occurs (self-limiting diuretic action).

The extrarenal actions of acetazolamide are:

- Lowering of intraocular tension due to decreased formation of aqueous humour (aqueous is rich in HCO_3^-).
- Decreased gastric HCl and pancreatic $NaHCO_3$ secretion: This action requires very high doses—not significant at clinically used doses.
- Raised level of CO_2 in brain and lowering of pH → sedation and elevation of seizure threshold.
- Alteration of CO_2 transport in lungs and tissues. These actions are masked by compensatory mechanisms.

Pharmacokinetics Acetazolamide is well absorbed orally and excreted unchanged in urine. Action of a single dose lasts 8–12 hours.

Uses Because of self-limiting action, production of acidosis and hypokalaemia, acetazolamide is not used as diuretic. Its current clinical uses are:

1. *Glaucoma:* as adjuvant to other ocular hypotensives (*see* Ch. 10).
2. *To alkalinise urine:* for urinary tract infection or to promote excretion of certain acidic drugs.
3. *Epilepsy:* as adjuvant in absence seizures when primary drugs are not fully effective; but tolerance to antiepileptic action develops.
4. *Mountain sickness:* Rapid ascend to high altitude may produce symptoms like headache, nausea, giddiness, weakness and insomnia lasting 1–2 days. Few subjects develop an acute sickness due to production of pulmonary and cerebral edema. Acetazolamide affords

prophylaxis as well as symptomatic relief; should be started 1–2 days before travel. It probably works by altering CO_2 transport in lungs, tissues and brain, as well as by decreasing formation of CSF and lowering its pH.

5. Periodic paralysis.

Dose: 250 mg OD–BD; DIAMOX, SYNOMAX 250 mg tab. IOPAR-SR 250 mg SR cap.

Adverse effects are frequent.

Acidosis, hypokalaemia, drowsiness, paresthesias, fatigue, abdominal discomfort.

Hypersensitivity reactions—fever, rashes.

Bone marrow depression is rare but serious.

It is contraindicated in liver disease: may precipitate hepatic coma by interfering with urinary elimination of NH_3 (due to alkaline urine).

Acidosis is more likely to occur in patients of COPD.

Methazolamide and *Dichlorphenamide* are the other systemic CAse inhibitors, while *Dorzolamide* and *Brinzolamide* are topical CAse inhibitors used in glaucoma (*see* Ch.10).

POTASSIUM SPARING DIURETICS

Aldosterone antagonists and renal epithelial Na^+ channel inhibitors indirectly conserve K^+ while inducing mild natriuresis, and are called 'potassium sparing diuretics'.

Aldosterone antagonist

Spironolactone

It is a steroid, chemically related to the mineralocorticoid aldosterone. Aldosterone penetrates the late DT and CD cells (Fig. 42.3) and acts by combining with an intracellular mineralocorticoid receptor (MR) → induces the formation of *'aldosterone-induced proteins' (AIPs)*. The AIPs promote Na^+ reabsorption by a number of mechanisms (*see* legend to Fig. 42.3) and K^+ secretion. Spironolactone acts from the interstitial side of the tubular cell, combines with MR and inhibits the formation of AIPs to act as a competitive antagonist. It has no effect on Na^+ and K^+ transport in the absence of aldosterone, while under normal circumstances, it increases Na^+ and decreases K^+ excretion.

Spironolactone is a mild saluretic because majority of Na^+ has already been reabsorbed proximal to its site of action. However, it antagonises K^+ loss induced by other diuretics and adds to their natriuretic effect. Resistance to other diuretics that develops due to secondary hyperaldosteronism is reversed. The K^+ retaining action develops over 3–4 days. Spironolactone increases Ca^{2+} excretion by a direct action on renal tubules.

Pharmacokinetics The oral bioavailability of spironolactone from microfine powder tablet is 75%. It is highly bound to plasma proteins and completely metabolized in liver to generate active metabolites, the most important of which is *Canrenone* that is responsible for 1/2–2/3 of its action *in vivo*. The t½ of spironolactone is 1–2 hours, while that canrenone is ~18 hours. Some enterohepatic circulation occurs.

Dose: 25–50 mg BD–QID; max 400 mg/day

ALDACTONE 25, 50, 100 mg tabs.

ALDACTIDE: Spironolactone 25 mg + hydroflumethiazide 25 mg tab. LACILACTONE, SPIROMIDE: Spironolactone 50 mg + furosemide 20 mg tab, TORLACTONE Spironolactone 50 mg + torasemide 10 mg tab.

Use Spironolactone is a weak diuretic in its own right and is used mostly in combination with other more efficacious diuretics.

1. To counteract K^+ loss due to thiazide and loop diuretics.
2. *Edema:* Spironolactone is more useful in cirrhotic and nephrotic edema in which aldosterone levels are generally high. It potentiates thiazides and loop diuretics and is frequently added to them in the treatment of ascitis due to cirrhosis of liver. It breaks resistance to the thiazide/loop diuretic that develops due to secondary hyperaldosteronism and reestablishes the response. Thus, spironolactone is particularly employed in refractory edema.
3. *Hypertension:* Spironolactone is used to augment a thiazide in the treatment of resistant hypertension (*see* p. 607). It also serves to prevent thiazide-induced hypokalaemia. Further, it has the potential to attenuate hypertension related renal fibrosis and ventricular/vascular hypertrophy.

4. *Heart failure:* As additional drug to conventional therapy in moderate to severe CHF; it serves to retard disease progression and lower mortality (*see* p. 567).
5. *Primary hyperaldosteronism* (Conn's syndrome).

Interactions

1. Spironolactone and K^+ supplements given together can produce dangerous hyperkalaemia.
2. Aspirin blocks spironolactone action by inhibiting tubular secretion of its active metabolite canrenone.
3. More pronounced hyperkalaemia can occur in patients receiving ACE inhibitors/ARBs.
4. Spironolactone increases plasma digoxin concentration.

Adverse effects The side effects are drowsiness, ataxia, mental confusion, epigastric distress and loose motions. Being a steroid spironolactone interacts with progestin and androgen receptors as well. In addition, it may hasten testosterone clearance or its peripheral conversion to estradiol, producing dose and duration of treatment related hormonal side effects like gynaecomastia, erectile dysfunction or loss of libido in men, and breast tenderness or menstrual irregularities in women.

Most serious problem with spironolactone is risk of hyperkalaemia, especially if renal function is inadequate. Acidosis is a risk, particularly in cirrhotics. Peptic ulcer may be aggravated; it is contraindicated in ulcer patients.

Eplerenone

It is a newer and more selective aldosterone antagonist which has much lower affinity for androgen and progesterone receptors; therefore much less likely to produce hormonal disturbances like gynaecomastia, impotence, menstrual irregularities, etc. This feature makes it particularly suitable for long-term use in the therapy of hypertension and chronic heart failure. However, the risk of hyperkalaemia and g.i. side effects are like spironolactone. Other side effects have an incidence similar to placebo, and it has a better tolerability profile.

Eplerenone is well absorbed orally, inactivated in liver by CYP3A4, and excreted in urine ($2/3^{rd}$) as well as faeces ($1/3^{rd}$). The t½ is 4–6 hours. Inhibitors of CYP3A4 (clarithromycin, itraconazole, etc.) increase its blood levels, while inducers like carbamazepine, rifampin, etc. may decrease its efficacy.

Eplerenone is indicated specifically in moderate to severe CHF, post-infarction left ventricular dysfunction and hypertension. It affords prognostic benefit in these conditions, and can also be used as alternative to spironolactone.
Dose: 25–50 mg BD;
EPLERAN, EPTUS, ALRISTA 25, 50 mg tabs.

Renal epithelial Na^+ channel inhibitors

Triamterene and *amiloride* are two nonsteroidal organic bases with identical actions. Their most important effect is to decrease K^+ excretion, particularly when it is high due to large K^+ intake or use of a diuretic that enhances K^+ loss. This is accompanied by a small increase in Na^+ excretion. The excess urinary Na^+ is matched by Cl^- and variable amounts of HCO_3^-; urine is slightly alkalinized. The effect on urinary electrolyte pattern is superficially similar to spironolactone, but their action is independent of aldosterone. Ca^{2+} and Mg^{2+} excretion is also reduced, but there is no effect on renal haemodynamics.

Mechanism of action The luminal membrane of late DT and CD cells expresses a distinct *'renal epithelial'* or *'amiloride sensitive' Na^+ channel* through which Na^+ enters the cell down its electrochemical gradient which is generated by Na^+K^+ ATPase operating at the basolateral membrane (Fig. 42.3). This Na^+ entry partially depolarizes the luminal membrane because it is not accompanied by Cl^- or HCO_3^-, creating a –15 mV transepithelial potential difference which promotes secretion of K^+ into the lumen through K^+ channels. Though there is no direct coupling between Na^+ and K^+ channels, more the delivery of Na^+ to the distal nephron—greater

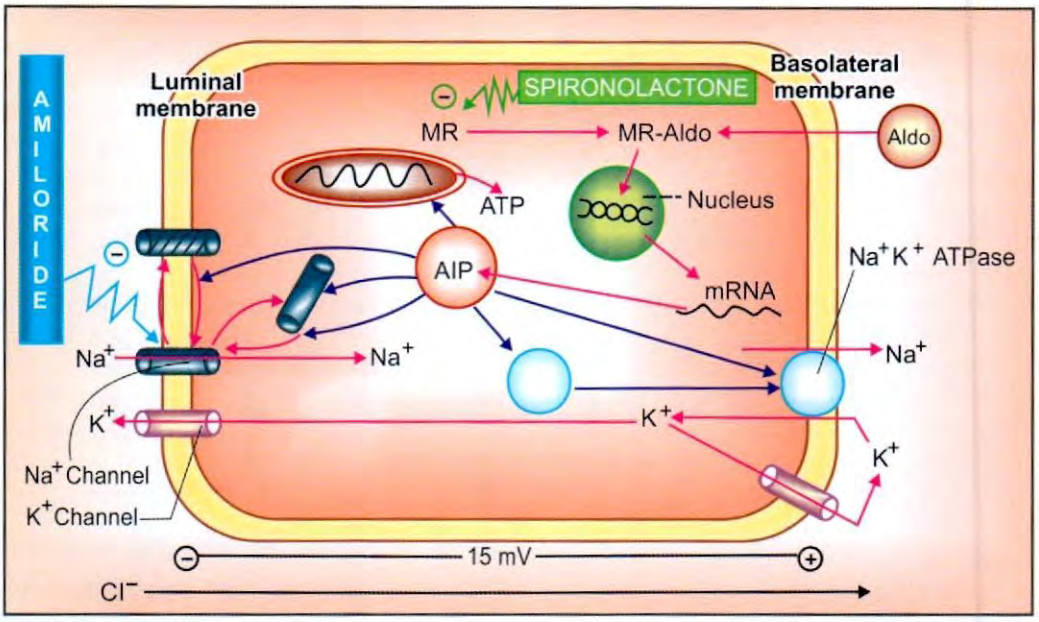


Fig. 42.3: Site and mechanism of action of potassium sparing diuretics on the late distal tubule/collecting duct principal cell.

Aldosterone (Aldo) penetrates the cell from the interstitial side and combines with the mineralocorticoid receptor (MR). The complex translocates to the nucleus—promotes gene mediated mRNA synthesis. The mRNA then directs synthesis of aldosterone induced proteins (AIPs). The AIPs include Na^+K^+ ATPase and renal epithelial (amiloride sensitive) Na^+ channels. More of these proteins are synthesized. The AIPs also activate these Na^+ channels and, translocate them from cytosolic site to luminal membrane. They also translocate Na^+K^+ATPase to the basolateral membrane. AIPs increase ATP production by mitochondria as well. All these changes promote Na^+ reabsorption which is not accompanied by Cl^- anions. Indirectly more K^+ is secreted as the lumen negative potential difference is augmented. The intercalated cells secrete more H^+ due to stronger lumen negative potential. Spironolactone binds to MR, prevents Aldo action and produces opposite effects.

Amiloride approaches the Na^+ channel from the luminal side and blocks it—reducing the lumen negative transepithelial potential difference which governs K^+ and H^+ secretion

is its entry through the Na^+ channel—luminal membrane is depolarized to a greater extent—driving force for K^+ secretion is augmented. As such, all diuretics acting proximally (loop diuretics, thiazides, CAse inhibitors) promote K^+ secretion. Amiloride and triamterene block the luminal Na^+ channels and indirectly inhibit K^+ excretion, while the net excess loss of Na^+ is minor, because this is only a small fraction of the total amount of Na^+ excreted in urine.

The intercalated cells in CD possess an ATP driven H^+ pump which secretes H^+ ions into the lumen. This pump is facilitated by the lumen negative potential. Amiloride, by reducing the lumen negative potential, decreases H^+ ion secretion as well and predisposes to acidosis. Thus, amiloride conserves both K^+ and H^+ while marginally increasing Na^+ excretion.

Both triamterene and amiloride are used in conjunction with a thiazide type or a high ceiling diuretic to prevent hypokalaemia and slightly augment the natriuretic response. The antihypertensive action of thiazide is also supplemented. Risk of hyperkalaemia is the most important adverse effect of amiloride and triamterene. These drugs should not be given to patients with renal insufficiency or those taking K^+ supplements because dangerous hyperkalaemia may develop. Hyperkalaemia is also more likely in patients receiving ACE inhibitors/ARBs, β blockers or NSAIDs.

Both amiloride and triamterene elevate plasma digoxin levels.

Triamterene It is incompletely absorbed orally, partly bound to plasma proteins, largely metabolized in liver to an active metabolite and excreted in urine. Plasma t½ is 4 hours, effect of a single dose lasts 6–8 hours.

Side effects are infrequent: consist of nausea, dizziness, muscle cramps and rise in blood urea. Impaired glucose tolerance and photosensitivity are reported, but urate level is not increased.

Dose: 50–100 mg daily;

DITIDE, triamterene 50 mg + benzthiazide 25 mg tab;
FRUSEMENE, triamterene 50 mg + furosemide 20 mg tab.

Amiloride It is 10 times more potent than triamterene (dose 5–10 mg OD–BD). At higher doses it also inhibits Na^+ reabsorption in PT, but this is clinically insignificant. It decreases Ca^{2+} and Mg^{2+} excretion but increases urate excretion. Thus, hypercalcaemic action of thiazides is augmented but hyperuricaemic action is partly annuled. A mild antihypertensive action is also reported.

Only ¼ of an oral dose is absorbed. It is not bound to plasma proteins and not metabolized. The t½ (20 hours) and duration of action are longer than triamterene.

BIDURET, KSPAR: Amiloride 5 mg + hydrochlorothiazide 50 mg tab, LASIRIDE, AMIFRU amiloride 5 mg + furosemide 40 mg tab.

Usual side effects are nausea, diarrhoea and headache.

Amiloride blocks entry of Li^+ through Na^+ channels in the CD cells and mitigates diabetes insipidus induced by lithium.

Given as an aerosol it affords symptomatic improvement in cystic fibrosis by increasing fluidity of respiratory secretions.

OSMOTIC DIURETICS

Mannitol

Mannitol is a nonelectrolyte of low molecular weight (182) that is pharmacologically inert—can be given in large quantities sufficient to raise osmolarity of plasma and tubular fluid. It is minimally metabolized in the body; freely filtered at the glomerulus and undergoes limited reabsorption: therefore excellently suited to be used as osmotic diuretic. Mannitol appears to limit tubular water and electrolyte reabsorption in a variety of ways:

1. Retains water isoosmotically in PT and descending limb of loop of Henle which are freely permeable to water. Luminal fluid is diluted and opposes NaCl reabsorption.
2. Inhibits transport processes in the TAL by an unknown mechanism.
3. Expands extracellular fluid volume (because it does not enter cells, mannitol draws water from the intracellular compartment)—increases g.f.r. and inhibits renin release.
4. Increases renal blood flow, especially to the medulla. The medullary hypertonicity is reduced (due to washing off) so that corticomedullary osmotic gradient is dissipated and passive salt reabsorption is reduced.

Though the primary action of mannitol is to increase urinary volume, excretion of all cations

Table 42.2: Urinary electrolyte pattern and natriuretic efficacy of some diuretics

	Urinary electrolyte excretion				*Max. % of filtered Na^+ excreted*	*Efficacy*
Diuretic	*Na^+*	*K^+*	*Cl^-*	*HCO_3^-*		
1. Furosemide	↑↑↑	↑	↑↑	↑,–	25%	High
2. Thiazide	↑↑	↑	↑	↑	8%	Intermediate
3. Acetazolamide	↑	↑↑	↑,–	↑↑	5%	Mild
4. Spironolactone	↑	↓	↑	–,↑	3%	Low
5. Amiloride	↑	↓	↑	–,↑	3%	Low
6. Mannitol	↑↑	↑	↑	↑	20%	High

↑ Increase; ↓ decrease; — no change

(Na^+, K^+, Ca^{2+}, Mg^{2+}) and anions (Cl^-, HCO_3^-, PO_4^{3-}) is also enhanced.

The urinary electrolyte pattern and natriuretic efficacy of different classes of diuretics is compared in Table 42.2.

Administration Mannitol is not absorbed orally; has to be given i.v. as 10–20% solution. It is excreted with a t½ of 0.5–1.5 hour.

MANNITOL 10%, 20%, in 100, 350 and 500 ml vac.

Uses Mannitol is never used for the treatment of chronic edema or as a natriuretic. Its indications are:

1. Increased intracranial or intraocular tension (acute congestive glaucoma, head injury, stroke, etc.): by osmotic action it encourages movement of water from brain parenchyma, CSF and aqueous humour. For this purpose 1–1.5 g/kg is infused over 1 hour as 20% solution to transiently raise plasma osmolarity. It is also infused before and after ocular or brain surgery to prevent acute rise in intraocular/intracranial pressure.

2. To maintain g.f.r. and urine flow in impending acute renal failure, e.g. in shock, severe trauma, cardiac surgery, haemolytic reactions. Mannitol 500–1000 ml of 10–20% solution may be infused over 24 hours. However, prognostic benefits in conditions other than cardiac surgery are still unproven. If acute renal failure has already set in, kidney is incapable of forming urine even after an osmotic load; mannitol is contraindicated: it will then expand plasma volume risking pulmonary edema and heart failure.

3. To counteract low osmolality of plasma and e.c.f. due to rapid haemodialysis or peritoneal dialysis (dialysis disequilibrium).

Mannitol along with large volumes of saline was infused i.v. to produce *'forced diuresis'* in acute poisonings in the hope of enhancing excretion of the poison. However, this has been found to be ineffective and to produce electrolyte imbalances. Not recommended now.

Mannitol is *contraindicated* in renal insufficiency, acute tubular necrosis, anuria, pulmonary edema; acute left ventricular failure, CHF and cerebral haemorrhage.

The most common side effect is headache. Nausea and vomiting may occur; hypersensitivity reactions are rare.

Isosorbide and glycerol These are orally active osmotic diuretics which may be used to reduce intraocular or intracranial tension. Intravenous glycerol can cause haemolysis. *Dose*: 0.5–1.5 g/kg as oral solution.

☞ PROBLEM DIRECTED STUDY

42.1 A 50-year-old male patient of hepatic cirrhosis with ascitis and pedal edema was treated with tab Furosemide 80 mg twice a day, in addition to bed rest, suitable dietary advice and vitamin supplementation. He started passing larger quantity of urine and the ascitis/edema started regressing. After a week, he was brought with incoherent talking, drowsiness, tremor and ataxia. The relatives informed that for the past 2 days he was no longer passing the increased amount of urine as at the start of medication. Serum K^+ measurement found a value of 2.8 mEq/L.

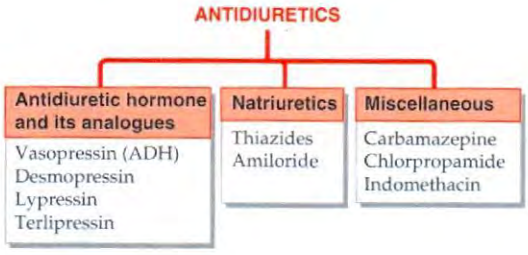
(a) What is the cause of the neurological symptoms and diminution of the diuretic response to furosemide? Was the choice of the diuretic appropriate?

(b) How should this patient be managed at the present stage?

(see Appendix-1 for solution)

Chapter 43 | Antidiuretics

Antidiuretics (more precisely 'anti-aquaretics', because they inhibit water excretion without affecting salt excretion) are drugs that reduce urine volume, particularly in *diabetes insipidus* (DI) which is their primary indication.



ANTIDIURETIC HORMONE (Arginine Vasopressin—AVP)

The human antidiuretic hormone (ADH) is 8-arginine vasopressin (AVP), which is a nonapeptide secreted by posterior pituitary (neurohypophysis) along with oxytocin (*see* Ch. 23). It is synthesized in the hypothalamic (supraoptic and paraventricular) nerve cell bodies as a large precursor peptide along with its binding protein 'neurophysin'. Both are transported down the axons to the nerve endings in the median eminence and pars nervosa. Osmoreceptors present in hypothalamus and volume receptors present in left atrium, ventricles and pulmonary veins primarily regulate the rate of ADH release governed by body hydration. Osmoreceptors are also present in the hepatic portal system which sense ingested salt and release ADH even before plasma osmolarity is increased by the ingested salt. Impulses from baroreceptors and higher centres also impinge on the nuclei synthesizing ADH and affect its release. The two main physiological stimuli for ADH release are rise in plasma osmolarity and contraction of e.c.f. volume.

Several neurotransmitters, hormones and drugs modify ADH secretion. It is enhanced by angiotensin II, prostaglandins (PGs), histamine, neuropeptide Y and ACh, while GABA and atrial natriuretic peptide (ANP) decrease its release. Opioids have agent-specific and dose dependent action. Low-dose morphine inhibits ADH secretion, but high doses enhance it. Opioid peptides are mostly inhibitory. Nicotine and imipramine stimulate, while alcohol, haloperidol, phenytoin and glucocorticoids decrease ADH release.

The 8-*lysine*-vasopressin (lypressin) is found in swine and has been synthetically prepared for clinical use. Other more potent and longer acting peptide analogues of AVP having agonistic as well as antagonistic action have also been prepared.

ADH (Vasopressin) receptors

These are G protein coupled cell membrane receptors; two subtypes V_1 and V_2 have been identified, cloned and structurally characterized.

V_1 Receptors All vasopressin receptors except those on renal collecting duct (CD) cells, thick ascending limb of loop of Henle (TAL) cells and vascular endothelium are of the V_1 type. These are further divided into V_{1a} and V_{1b} subtypes:

V_{1a} receptors are present on vascular smooth muscle (including that of vasa recta in renal medulla), uterine and other visceral smooth muscles, interstitial cells in renal medulla, cortical CD cells, adipose tissue, brain, platelets, liver, etc. The V_{1b} receptors are localized to the anterior pituitary, certain areas in brain and in pancreas.

The V_1 receptors function mainly through the phospholipase C–IP_3/DAG pathway—release Ca^{2+} from intracellular stores—causing vasoconstriction, visceral smooth muscle contraction, glycogenolysis, platelet aggregation, ACTH release, etc. These actions are augmented by enhanced influx of Ca^{2+} through Ca^{2+} channels as well as by DAG mediated protein kinase C activation which phosphorylates relevant proteins. V_1 receptors, in addition, activate phospholipase A2—release arachidonic acid resulting in generation of PGs and other eicosanoids which contribute to many of the V_1 mediated effects. Persistent V_1 receptor stimulation activates protooncogenes (possibly through IP_3/DAG pathway) resulting in growth (hypertrophy) of vascular smooth muscle and other responsive cells.

V_2 Receptors These are located primarily on the principal cells of collecting ducts (CDs) in the kidney and regulate their water permeability through cAMP production. Some V_2 receptors are also present on TAL cells which activate $Na^+K^+2Cl^-$ cotransporter. Vasodilatory V_2 receptors are present on endothelium of blood vessels.

The V_2 receptors are more sensitive (respond at lower concentrations) to AVP than are V_1 receptors.

Selective peptide agonists and antagonists of the subtypes of vasopressin receptors are:

	Selective agonist
V_{1a} Receptor	[Phe^2, Ile^3, Orn^8] AVP
V_{1b} Receptor	Deamino [D-3 {pyridyl)-Ala^2] AVP
V_2 Receptor	Desmopressin (dDAVP)
	Selective antagonist
V_{1a} Receptor	$d(CH_2)_5$ [Tyr (Me^2)] AVP
V_{1b} Receptor	dp [Tyr (me^2)] AVP
V_2 Receptor	$d(CH_2)_5$ [D-Ile^2, Ile^4, Ala-NH_2^9] AVP

Some orally active nonpeptide V_{1a}, V_{1b} and V_2 receptor antagonists have been produced. *Tolvaptan* and *Mozavaptan* are nonpeptide V_2 selective antagonists that are now in clinical use.

Actions

Kidney AVP acts on principal cells in the CD to increase their water permeability—water from the duct lumen diffuses to the interstitium by equilibrating with the hyperosmolar renal medulla (*see* Fig. IX.1). In man, maximal osmolarity of urine that can be attained is 4 times higher than plasma. When AVP is absent, CD cells remain impermeable to water so that dilute urine (produced by the diluting segment) is passed as such. Graded effect occurs at lower concentrations of AVP, and urine volume closely balances fluid intake.

Mechanism of action Vasopressin is instrumental in rapid adjustments of water excretion according to the state of body hydration, as well as in dealing with conditions prevailing over long-term. The V_2 subtype of ADH receptors are present on the basolateral membrane of principal cells in CDs (*see* Fig. 43.1). Activation of these receptors increases cAMP formation intracellularly → activation of cAMP dependent protein kinase A → phosphorylation of relevant proteins which promote exocytosis of *'aquaporin-2'* water channel containing vesicles (WCVs) through the apical membrane → more aqueous channels get inserted into the apical membrane. The rate of endocytosis and degradation of WCVs is concurrently reduced. The water permeability of CD cells is increased in proportion to the population of aquaporin-2 channels in the apical membrane at any given time. Continued V_2 receptor stimulation (during chronic water deprivation) in addition upregulates aquaporin-2 synthesis through cAMP response element of the gene encoding aquaporin-2.

Other aquaporins like aquaporin-1 (in PT) and aquaporin-3,4 (on basolateral membrane of CD cells) also participate in water transport at these sites.

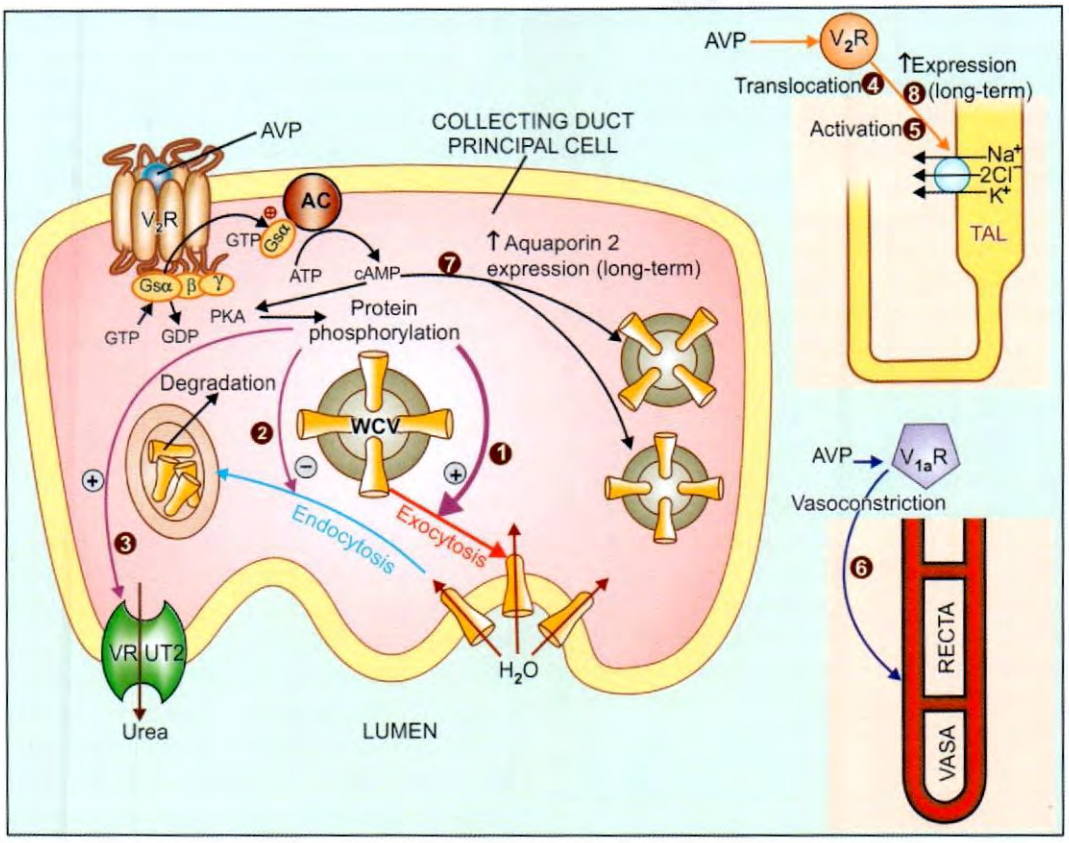


Fig. 43.1: Mechanisms of rapid and long-term anti-aquaretic action of vasopressin

All V_2 receptor (V_2R) mediated actions are exerted through the adenylyl cyclase (AC)-cyclic AMP (cAMP) pathway, while the V_{1a} receptor ($V_{1a}R$) mediated action is exerted *via* the phospholipase C—IP_3; DAG pathway.

Rapid actions

(1) Translocation of water channel containing vesicles (WCVs) and exocytotic insertion of aquaporin 2 water channels into the apical membrane of principal cells of collecting ducts. This is the primary action responsible for antidiuresis.

(2) Inhibition of endocytotic removal of aquaporin 2 channels from the apical membrane.

(3) Activation of vasopressin regulated urea transporter (VRUT) at apical membrane of collecting ducts in the inner medulla.

(4) Translocation of $Na^+K^+2Cl^-$ cotransporter to the luminal membrane of cells in thick ascending limb of loop of Henle (TAL).

(5) Activation of $Na^+K^+2Cl^-$ cotransporter in TAL cells.

(6) V_{1a} receptor ($V_{1a}R$) mediated vasoconstriction of vasa recta

Long-term actions

(7) Gene mediated increased expression of aquaporin 2 channels in collecting duct cells.

(8) Gene mediated increased expression of $Na^+K^+2Cl^-$ cotransporter in TAL cells.

PK_A—cAMP dependent protein kinase.

To achieve maximum concentration of urine, activation of V_2 receptors increases urea permeability of terminal part of CDs in inner medulla by stimulating a vasopressin regulated urea transporter (VRUT or UT-1)—which in turn augments medullary hypertonicity. Recently, V_2 receptor mediated actions of AVP on TAL cells have also been demonstrated which further reinforce medullary hypertonicity by translocating to luminal membrane and activating the $Na^+K^+2Cl^-$ cotransporter in the short-term and increasing its synthesis in the long-term.

The V_1 receptors also participate in the renal response to AVP. Activation of V_1 receptors constricts vasa recta to diminish blood flow to inner medulla which reduces washing off effect and helps in maintaining high osmolarity in this region. Thus, it contributes to antidiuresis. On the other hand, activation of medullary interstitial cell V_1 receptors enhance PG synthesis which attenuate cAMP generation in CD cells and oppose V_2 mediated antidiuresis. V_1 receptors are also present on CD cells. Their stimulation activates PKc which directly diminishes responsiveness of CD cells to V_2 receptors and restrains V_2 mediated water permeability. The logic of this apparent paradox may lie in the fact that these V_1 actions are produced at higher concentrations of AVP, so that physiologically they may serve to restrict V_2 effects only when blood levels of AVP are very high.

Lithium and demeclocycline partially antagonize AVP action (probably by limiting cAMP formation), reduce the urine concentrating ability of the kidney, produce polyuria and polydipsia. They have been used in patients with inappropriate ADH secretion. On the other hand NSAIDs (especially indomethacin) augment AVP-induced antidiuresis by inhibiting renal PG synthesis. Carbamazepine and chlorpropamide also potentiate AVP action on the kidney.

Blood vessels AVP constricts blood vessels through V_1 receptors and increases peripheral resistance. At lower doses of AVP, this is counterbalanced reflexly by lowering C.O., so that BP is not affected. Rise in BP occurs at higher doses (hence the name Vasopressin), as well as when the reflex is inoperative, as in hypotensive states. AVP is an effective pressor agent in shock patients. The cutaneous, mesenteric, skeletal muscle, fat depot, thyroid, and coronary beds are particularly constricted. Though vasoconstrictor action of AVP does not appear to be physiologically important in the healthy state, it may play a role in patients who have bled or other hypotensive states, CHF, etc. Prolonged exposure to AVP causes vascular smooth muscle hypertrophy.

The V_2 receptor mediated vasodilatation can be unmasked when AVP is administered in the presence of a V_1 antagonist. It can also be demonstrated by the use of selective V_2 agonist desmopressin, and is due to endothelium dependent NO production.

Other actions Most visceral smooth muscles contract. Increased peristalsis in gut (especially large bowel), results in evacuation of bowels and expulsion of gases.

Uterus is contracted by AVP acting on oxytocin receptors. In the nonpregnant and early pregnancy uterus, AVP is equipotent to oxytocin. Only at term sensitivity to oxytocin increases selectively.

CNS Exogenously administered AVP does not penetrate blood-brain barrier. However, it is now recognized to be a peptide neurotransmitter in many areas of brain and spinal cord. AVP may be involved in regulation of body temperature, systemic circulation, ACTH release, and in learning of tasks.

AVP induces platelet aggregation and hepatic glycogenolysis. It releases coagulation factor VIII and von Willebrand's factor from vascular endothelium by acting on V_2 receptors.

Pharmacokinetics AVP is inactive orally because it is destroyed by trypsin. It can be administered by any parenteral route or by intranasal application. The peptide chain of AVP is rapidly cleaved enzymatically in many organs, especially in liver and kidney; plasma $t_{1/2}$ is short ~25 min. However, the action of aqueous vasopressin lasts 3–4 hours.

Aqueous vasopressin (AVP) inj: POSTACTON 10 U inj; for i.v., i.m. or s.c. administration.

VASOPRESSIN ANALOGUES

Lypressin It is 8-lysine vasopressin. Though somewhat less potent than AVP, it acts on both V_1 and V_2 receptors and has longer duration of action (4–6 hours). It is being used in place of AVP—mostly for V_1 receptor mediated actions. PETRESIN, VASOPIN 20 IU/ml inj; 10 IU i.m. or s.c. or 20 IU diluted in 100–200 ml of dextrose solution and infused i.v. over 10–20 min.

Terlipressin This synthetic prodrug of vasopressin is specifically used for bleeding esophageal varices, and appears to produce less severe adverse effects than lypressin. It is also longer acting.

Dose: 2 mg i.v., repeat 1–2 mg every 4–6 hours as needed. GLYPRESSIN 1 mg freeze dried powder with 5 ml diluent for inj, T-PRESSIN, TERLINIS 1 mg/10 ml inj.

Desmopressin (dDAVP) This synthetic peptide is a selective V_2 agonist; 12 times more potent antidiuretic than AVP, but has negligible vasoconstrictor activity. It is also longer acting because enzymatic degradation is slow; t½ 1–2 hours, and the duration of action is 8–12 hours. Desmopressin is the preparation of choice for all V_2 receptor related indications. The intranasal route is preferred, though bioavailability is only 10–20%. An oral formulation has been marketed with a bioavailability of 1–2%; oral dose is 10–15 times higher than the intranasal dose, but systemic effects are produced and nasal side effects are avoided. Many patients find oral tablet more convenient.

Dose: Intranasal: Adults 10–40 µg/day in 2–3 divided doses, children (for bed wetting) 5–10 µg at bed time.

Oral: 0.1–0.2 mg TDS.

Parenteral (s.c. or i.v.) 2–4 µg/day in 2–3 divided doses.

MINIRIN 100 µg/ml nasal spray (10 µg per actuation); 100 µg/ml intranasal solution in 2.5 ml bottle with applicator; 0.1 mg tablets; 4 µg/ml inj.; D-VOID 100 µg/ml nasal spray.

Uses

A. Based on V_2 actions (Desmopressin is the drug of choice)

1. *Diabetes insipidus* DI of pituitary origin (neurogenic) is the most important indication for vasopressin, but it is ineffective in renal (nephrogenic) DI, because kidney is unresponsive to ADH. Life-long therapy is required, except in some cases of head injury or neurosurgery, where DI occurs transiently.

The dose of desmopressin is individualized by measuring 24 hour urine volume. Minimum effective dose should be used to avoid hyponatraemia. Aqueous vasopressin or lypressin injection is impracticable for long-term treatment, but it can be used in transient DI and to differentiate neurogenic from nephrogenic DI. Urine volume is reduced and its osmolarity increased by vasopression if DI is due to deficiency of ADH, but not when it is due to unresponsiveness of kidney to ADH. Desmopressin 2 µg i.m. is the preparation of choice now for the same purpose.

2. *Bedwetting in children and nocturia in adults* Intranasal or oral desmopressin at bedtime controls primary nocturia by reducing urine volume. Nocturnal voids are reduced to nearly half and first sleep period in adults is increased by ~2 hr. Fluid intake must be restricted 1 hr before and till 8 hr after the dose to avoid fluid retention. Monitor BP and body weight periodically to check fluid overload. Treatment should be withheld for one week every 3 months for reassessment.

3. *Renal concentration test* 5–10 U i.m. of aqueous vasopressin or 2 µg of desmopressin causes maximum urinary concentration which is measured by urinary specific gravity.

4. *Haemophilia, von Willebrand's disease* AVP may check bleeding by releasing coagulation factor VIII and von Willebrand's factor. Desmopressin is the preferred preparation in a dose of 0.3 µg/kg diluted in 50 ml saline and infused i.v. over 30 min.

B. Based on V_1 actions

1. *Bleeding esophageal varices* Vasopressin/terlipressin often stop bleeding by constricting mesenteric blood vessels and reducing blood flow through the liver to the varices, allowing clot formation. Terlipressin stops bleeding in ~80% and has been shown to improve survival. It has replaced AVP because of fewer adverse effects

and greater convenience in use. Octreotide (a somatostatin analogue) injected i.v. is an alternative. However, definitive therapy of varices remains endoscopic obliteration by sclerotherapy.

2. *Before abdominal radiography* AVP/lypressin has been occasionally used to drive out gases from bowel.

Adverse effects Because of V_2 selectivity, desmopressin produces fewer adverse effects than vasopressin, lypressin or terlipressin. However, transient headache and flushing are frequent.

Nasal irritation, congestion, rhinitis, ulceration and epistaxis can occur on local application.

Systemic side effects are: belching, nausea, abdominal cramps, pallor, urge to defecate, backache in females (due to uterine contraction). Fluid retention and hyponatraemia may develop.

Symptoms of hyponatremia are due to shift of water intracellularly resulting in cerebral edema producing headache, mental confusion, lassitude, nausea, vomiting and even seizures. Children are more susceptible.

AVP can cause bradycardia, increase cardiac afterload and precipitate angina by constricting coronary vessels. It is contraindicated in patients with ischaemic heart disease, hypertension, chronic nephritis and in psychogenic polydipsia.

Urticaria and other allergies are possible with any preparation.

THIAZIDES

Diuretic thiazides paradoxically exert an antidiuretic effect in DI. High ceiling diuretics are also effective but are less desirable because of their short and brisk action. Thiazides reduce urine volume in both pituitary origin as well as renal DI. They are especially valuable for the latter in which AVP/desmopressin is ineffective. However, efficacy of thiazides is low; urine can never become hypertonic as can occur with AVP in neurogenic DI. The mechanism of action is not well understood, the possible explanation is:

Thiazides induce a state of sustained electrolyte depletion so that glomerular filtrate is more completely reabsorbed iso-osmotically in PT. Further, because of reduced salt reabsorption in the cortical diluting segment, a smaller volume of less dilute urine is presented to the CDs and the same is passed out. That salt restriction has a similar effect, substantiates this mechanism of action. Secondly, thiazides reduce g.f.r. and thus the fluid load on tubules.

Hydrochlorothiazide 25–50 mg TDS or equivalent dose of a longer acting agent is commonly used. Though less effective than AVP, it is more convenient and cheap even for pituitary origin DI; may reduce polyuria to some extent.

K^+ supplements are needed.

Amiloride is the drug of choice for lithium-induced nephrogenic DI (*see* p. 637), because along with blocking entry of Na^+ in the principal cells of CD, it also blocks Li^+ entry.

Indomethacin has also been found to reduce polyuria in renal DI to some extent by reducing renal PG synthesis. It can be combined with a thiazide ± amiloride in nephrogenic DI. Other NSAIDs are less active.

Chlorpropamide It is a long-acting sulfonylurea oral hypoglycaemic, found to reduce urine volume in DI of pituitary origin but not in renal DI. It sensitizes the kidney to ADH action.

Carbamazepine It is an antiepileptic (*see* Ch. 30) which reduces urine volume in DI of pituitary origin, but mechanism of action is not clear. Higher doses are needed; adverse effects are marked; it is of little value in treatment of DI.

VASOPRESSIN ANTAGONISTS

Tolvaptan It is an orally active nonpeptide selective V_2 receptor antagonist that has been recently introduced for the treatment of hyponatraemia due to CHF, cirrhosis of liver or syndrome of inappropriate ADH secretion (SIADH). It increases free water clearance by the kidney (aquaretic) and helps to correct the low plasma Na^+ levels. In clinical trials symptoms of worsening heart failure were improved. However, too rapid correction of hyponatraemia should not be attempted, because thrombotic complications can occur due to haemoconcentration. The most frequent side effect is thirst and dry mouth. Others are fever, g.i. upset and hyperglycaemia. Tolvaptan is metabolized by CYP3A4; should not be given to patients receiving inhibitors of this isoenzyme. The t½ is 6–8 hours, and it is given once daily.

Mozavaptan (V_2 selective antagonist) and *Conivaptan* (V_{1a}+V_2 antagonist) are the other vasopressin antagonists that are in clinical use.

DRUGS AFFECTING BLOOD AND BLOOD FORMATION

Chapter 44 Haematinics and Erythropoietin

Haematinics These are substances required in the formation of blood, and are used for treatment of anaemias.

Anaemia occurs when the balance between production and destruction of RBCs is disturbed by:

(a) Blood loss (acute or chronic)

(b) Impaired red cell formation due to:

- Deficiency of essential factors, i.e. iron, vitamin B_{12}, folic acid.
- Bone marrow depression (hypoplastic anaemia), erythropoietin deficiency.

(c) Increased destruction of RBCs (haemolytic anaemia).

In this chapter essential factors required for normal formation or pigmentation of RBCs will be covered.

IRON

Iron has for long been considered important for the body. *Lauha bhasma* (calcined iron) has been used in ancient Indian medicine. According to Greek thought Mars is the God of strength, and iron is dedicated to Mars: as such, iron was used to treat weakness, which is common in anaemia. In 1713 iron was shown to be present in blood. In the early 19th century Blaud developed his famous 'Blaud's pill' consisting of ferrous sulfate and potassium carbonate for anaemia. All important aspects of iron metabolism have been learned in the past 70 years.

Distribution of iron in body Iron is an essential body constituent. Total body iron in an adult is 2.5–5 g (average 3.5 g). It is more in men (50 mg/kg) than in women (38 mg/kg). It is distributed into:

Haemoglobin (Hb)	: 62%
Iron stores as ferritin and haemosiderin	: 25%
Myoglobin (in muscles)	: 7%
Parenchymal iron (in enzymes, etc.)	: 6%

Haemoglobin is a protoporphyrin; each molecule having 4 iron containing haeme residues. It has 0.33% iron; thus loss of 100 ml of blood (containing 15 g Hb) means loss of 50 mg elemental iron. To raise the Hb level of blood by 1 g/dl—about 200 mg of elemental iron is needed. Iron is stored only in ferric form, in combination with a large protein *apoferritin*.

$$\text{Apoferritin} + Fe^{3+} \rightarrow \text{Ferritin} \xrightarrow{\text{aggregates}} \text{Haemosiderin (not reutilized)}$$

Ferritin can get saturated to different extents; at full saturation it can hold 30% iron by weight. The most important storage sites are reticuloendothelial (RE) cells. Parenchymal iron occurs as prosthetic group in many cellular enzymes—cytochromes, peroxidases, catalases, xanthine oxidase and some mitochondrial enzymes. Though, the primary reflection of iron deficiency occurs in blood, severe deficiency affects practically every cell.

Daily requirement To make good average daily loss, iron requirements are:

Adult male	:	0.5–1 mg (13 µg/kg)
Adult female (menstruating)	:	1–2 mg (21 µg/kg)
Infants	:	60 µg/kg
Children	:	25 µg/kg
Pregnancy (last 2 trimesters)	:	3–5 mg (80 µg/kg)

Dietary sources of iron

Rich : Liver, egg yolk, oyster, dry beans, dry fruits, wheat germ, yeast.

Medium : Meat, chicken, fish, spinach, banana, apple.

Poor : Milk and its products, root vegetables.

Iron absorption

The average daily diet contains 10–20 mg of iron. Its absorption occurs all over the intestine, but majority in the upper part. Dietary iron is present either as haeme or as inorganic iron. Absorption of haeme iron is better (upto 35% compared to inorganic iron which averages 5%), occurs with the aid of a haeme carrier protein (HCP1) and does not need to be first dissociated into free iron (Fig. 44.1). However, haeme iron is a smaller fraction of dietary iron. The major part of dietary iron is inorganic and in the ferric form. It needs to be dissociated from the complexes and reduced to the ferrous form before absorption. Two separate iron transporters in the intestinal mucosal cells function to effect iron absorption. At the luminal membrane the *divalent metal transporter* 1 (DMT1) carrys ferrous iron into the mucosal cell. This along with the iron released from haeme is transported across the basolateral membrane by another iron transporter *ferroportin* (FP). These iron transporters are regulated according to the body needs. Absorption of haeme iron is largely independent of other foods simultaneously ingested, but that of inorganic iron is affected by several factors.

Factors facilitating iron absorption

1. Acid: by favouring dissolution and reduction of ferric iron.
2. Reducing substances: ascorbic acid, amino acids containing SH radical. These agents reduce ferric iron and form absorbable complexes.

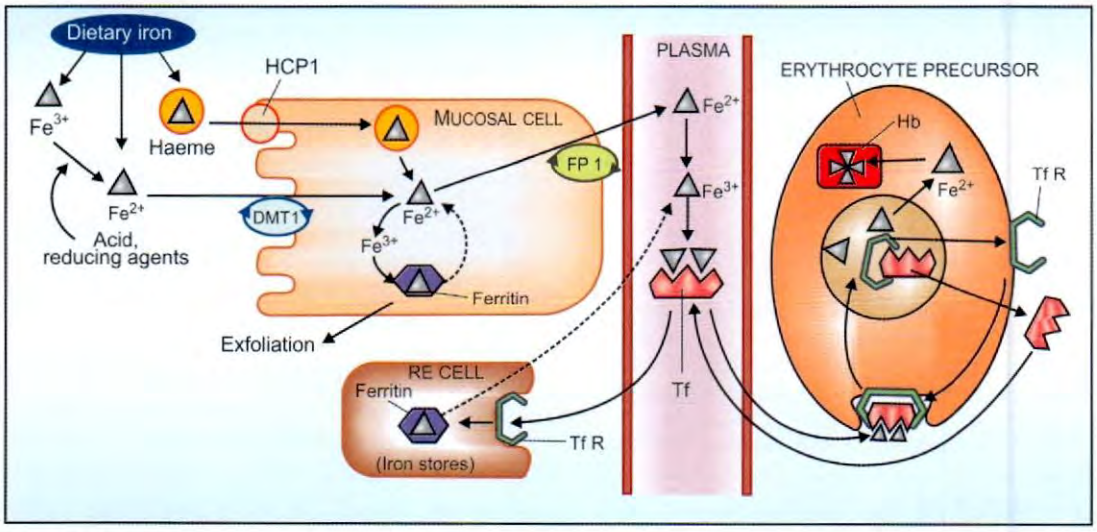


Fig. 44.1: Schematic depiction of intestinal absorption, transport, utilization and storage of iron (see text for description) Fe^{2+}—Ferrous iron; Fe^{3+}—Ferric iron; DMT1—Divalent metal transporter 1; HCP1—Haeme carrier protein 1; Hb—Haemoglobin; RE cell—Reticuloendothelial cell; FP1—Ferroportin; Tf—Transferrin; TfR—Transferrin receptor

3. Meat: by increasing HCl secretion and providing haeme iron.

Factors impeding iron absorption

1. Alkalies (antacids) render iron insoluble, oppose its reduction.
2. Phosphates (rich in egg yolk)
3. Phytates (in maize, wheat)
4. Tetracyclines

} By complexing iron

5. Presence of other foods in the stomach.

In general, bioavailability of iron from cereal based diets is low.

Mucosal block The gut has a mechanism to prevent entry of excess iron in the body. Iron reaching inside mucosal cell is either transported to plasma or oxidised to ferric form and complexed with apoferritin to form ferritin (Fig. 44.1). This ferritin generally remains stored in the mucosal cells and is lost when they are shed (lifespan 2–4 days). This is called the '*Ferritin curtain*'.

The iron status of the body and erythropoietic activity govern the balance between these two processes, probably through a 'haematopoietic transcription factor', and thus the amount of iron that will enter the body. A larger percentage is absorbed during iron deficiency. When body iron is low or erythropoiesis is occurring briskly, ferritin is either not formed or dissociates soon—the released iron is transported to the blood.

Mucosal block however, can be overwhelmed by gross excess of iron.

Transport, utilization, storage and excretion

Free iron is highly toxic. As such, on entering plasma it is immediately converted enzymatically to the ferric form and complexed with a glycoprotein *transferrin (Tf)*. Iron circulates in plasma bound to Tf (two Fe^{3+} residues per molecule). The total plasma iron content (~3 mg) is recycled 10 times everyday (turnover of iron is 30 mg/day).

Iron is transported inside erythropoietic and other cells through attachment of transferrin to a specific membrane bound glycoprotein that functions as transferrin receptor (TfR). The complex is engulfed by receptor mediated endocytosis. Iron dissociates from the complex at the acidic pH of the intracellular vesicles; the released iron is utilized for haemoglobin synthesis or other purposes, while Tf and TfR are returned to the cell surface to carry fresh loads. In iron deficiency and haemolytic states when brisk erythropoiesis is occurring, erythropoietic cells express more TfRs, but other cells do not. Thus, the erythron becomes selectively more efficient in trapping iron.

After entering the storage cells through TfRs, iron is stored in RE cells (in liver, spleen, bone marrow), as well as in hepatocytes and myocytes as ferritin and haemosiderin. Apoferritin synthesis is regulated by iron status of the body. When it is low—the 'iron regulating element' (IRE) on mRNA is blocked—transcription of apoferritin does not occur, while more Tf is produced. On the other hand, more apoferritin is synthesized to trap iron when iron stores are rich. Plasma iron derived from destruction of old RBCs (lifespan ~120 days), from iron stores and from intestinal absorption forms a common pool that is available for erythropoiesis, to all other cells and for restorage.

Iron is tenaciously conserved by the body; daily excretion in adult male is 0.5–1 mg, mainly as exfoliated g.i. mucosal cells, some RBCs and in bile (all lost in faeces). Other routes are desquamated skin, very little in urine and sweat. In menstruating women, monthly menstrual loss may be averaged to 0.5–1 mg/day. Excess iron is required during pregnancy for expansion of RBC mass, transfer to the foetus and loss during delivery; totalling to about 700 mg. This is to be met in the later 2 trimesters.

Preparations and dose

Oral iron

The preferred route of iron administration is oral. Dissociable ferrous salts are inexpensive, have high iron content and are better absorbed than ferric

Table 44.1: Some combination preparations of iron

Trade name	*Iron compound*	*Other ingredients*
CONVIRON Cap	Fe. sulfate (dried) 60 mg	B_{12} 15 µg, folic acid 1.5 mg, B_6 1.5 mg, vit. C 75 mg
FESOVIT-SPANSULE Cap	Fe. sulfate (dried) 150 mg	B_{12} 15 µg, folic acid 1 mg, nicotinamide 50 mg, B_6 2 mg
FERSOLATE-CM tab	Fe. sulfate (dried) 195 mg	Cu sulfate 2.6 mg, Mn. sulfate 2 mg
FEFOL SPANSULE Cap	Fe. sulfate 150 mg	Folic acid 0.5 mg
HEMGLOB syr (15 ml)	Fe. gluconate 300 mg	B_{12} 15 µg, B_1 5 mg, B_2 5 mg, B_6 1.5 mg, niacinamide 45 mg
AUTRIN Cap	Fe. fumarate 300 mg	B_{12} 15 µg, folic acid 1.5 mg
DUMASULES Cap	Fe. fumarate 300 mg	B_{12} 7.5 µg, folic acid 0.75 mg, B_1 5 mg, niacinamide 50 mg, vit. C 75 mg, B_6 1.5 mg
HEMSYNERAL Cap	Fe. fumarate 200 mg	B_{12} 15 µg, folic acid 1.5 mg
HAEMUP GEMS Cap	Fe fumarate 200 mg	Folic acid 1.5 mg, Copper sulf. 2.5 mg, Mn. sulf 2.5 mg
HEMSI syr. (5 ml)	Fe. fumarate 100 mg	Vit B_{12} 5 µg, folic acid 0.5 mg, Zn 3.3 mg, Cu 0.035 mg, Mn 0.2 mg
FERRICARB Cap	Carbonyl iron (100 mg iron)	Folic acid 1.5 mg, vit B_{12} 15 µg, zinc sulfate 88 mg, pyridoxine 3 mg, sod. selenite 60 µg
HBFAST tab	Carbonyl iron (100 mg iron)	Folic acid 0.35 mg
HEMATRINE Cap	Fe. succinate 100 mg	B_{12} 2.5 µg, folic acid 0.5 mg, vit. C 25 mg, niacinamide 15 mg
POLYRON tab, BIOFER tab POLYFER chewable tab	Ferric hydroxy polymaltose (Iron 100 mg)	Folic acid 0.35 mg
MUMFER syr (5 ml) drops (1 ml)	Ferric hydroxy polymaltose (50 mg iron) —do—(50 mg iron)	
FERROCHELATE syr (5 ml) drops (1 ml)	Ferric ammon. cit. (Iron 60 mg) —do—(Iron 20 mg)	B_{12} 5 µg, folic acid 1 mg B_{12} 4 µg, folic acid 0.2 mg
RARICAP tab	Iron cal. complex (Iron 25 mg)	Folic acid 0.3 mg
PROBOFEX Cap	Fe. aminoate (60 mg iron)	B_{12} 15 µg, folic acid 1.5 mg, B_6 3 mg
DEXORANGE Cap, syrup (15 ml)	Ferric ammon. cit. 160 mg	B_{12} 7.5 µg, folic acid 0.5 mg, Zn 7.5 mg (as sulfate)

Combination of iron with strychnine, arsenic and yohimbine and all fixed dose combination of haemoglobin in any form are banned in India.

salts, especially at higher doses. Gastric irritation and constipation (the most important side effects of oral iron) are related to the total quantity of elemental iron administered. If viewed in terms of iron content, nearly all preparations have the same degree of gastric tolerance, the limits of which are fairly well defined in individual patients. Some simple oral preparations are:

1. Ferrous sulfate: (hydrated salt 20% iron, dried salt 32% iron) is the cheapest; may be preferred on this account. It often leaves a metallic taste in mouth; FERSOLATE 200 mg tab.
2. Ferrous gluconate (12% iron): FERRONICUM 300 mg tab, 400 mg/15 ml elixer.
3. Ferrous fumarate (33% iron): is less water soluble than ferrous sulfate and tasteless; NORI-A 200 mg tab.
4. Colloidal ferric hydroxide (50% iron): FERRI DROPS 50 mg/ml drops.

5. Carbonyl iron: It is high purity metallic iron in very fine powder form (particle size < 5 μM), prepared by decomposition of iron pentacarbonyl, a highly toxic compound. It is claimed to be absorbed from intestines over a long time, and gastric tolerance may be better. However, bioavailability is about 3/4th that of ferrous sulfate.

Other forms of iron present in oral formulations are:

- Ferrous succinate (35% iron)
- Iron choline citrate
- Iron calcium complex (5% iron)
- Ferric ammonium citrate (20% iron)
- Ferrous aminoate (10% iron)
- Ferric glycerophosphate
- Ferric hydroxy polymaltose

These are claimed to be better absorbed and/or produce less bowel upset, but this is primarily due to lower iron content. They are generally more expensive.

A number of oral formulations containing one of the iron compounds along with one to many vitamins, yeast, amino acids and other minerals are widely marketed and promoted. Some of these are listed in Table 44.1, but are not better than simple ferrous salts.

A Technical Advisory Board (India) has recommended that B complex vitamins and zinc should not be ~~included in iron and folic acid~~ containing haematinic preparations.

The elemental iron content and not the quantity of iron compound per dose unit should be taken into consideration. Sustained release preparations are more expensive and not rational because most of the iron is absorbed in the upper intestine, while these preparations release part of their iron content lower down. Bioavailability of iron from such preparations, though claimed to be good, is actually variable. Liquid formulations may stain teeth: should be put on the back of tongue and swallowed. In general, they are less satisfactory.

A total of 200 mg elemental iron (infants and children 3–5 mg/kg) given daily in 3 divided doses produces the maximal haemopoietic response. Prophylactic dose is 30 mg iron daily. Absorption is much better when iron preparations are taken in empty stomach. However, side effects are also more; some prefer giving larger amounts after meals, while others like to give smaller doses in between meals.

Adverse effects of oral iron Side effects are common at therapeutic doses and are related to the elemental iron content. Individuals differ in susceptibility.

Epigastric pain, heartburn, nausea, vomiting, bloating, staining of teeth, metallic taste, colic, etc. are the frequent complaints. Tolerance to oral iron can be improved by initiating therapy at low dose and gradually escalating to the optimum dose. Constipation is more common (believed to be due to astringent action of iron) than diarrhoea (thought to reflect irritant action). However, these symptoms may be the result of alteration of intestinal flora as well.

Parenteral iron

Iron therapy by injection is indicated only when:

1. Oral iron is not tolerated: bowel upset is too much.
2. Failure to absorb oral iron: malabsorption; inflammatory bowel disease. Chronic inflammation (e.g. rheumatoid arthritis) decreases iron absorption, as well as the rate at which iron can be utilized.
3. Non-compliance to oral iron.
4. In presence of severe deficiency with chronic bleeding.
5. Along with erythropoietin in chronic kidney disease (CKD) patients: oral ion may not be absorbed at sufficient rate to meet the demands of induced rapid erythropoiesis.

Parenteral iron therapy needs calculation of the total iron requirement of the patient for which several formulae have been devised. A simple one is:

Iron requirement (mg) =

4.4 × body weight (kg) × Hb deficit (g/dl)

This formula includes iron needed for replenishment of stores. The rate of response with parenteral iron is not faster than with optimal doses given orally, except probably in the first 2–3 weeks when dose of oral iron is being built

up. However, iron stores can be replenished in a shorter time by parenteral therapy, because after correction of anaemia, a smaller fraction of ingested iron is absorbed.

The ionized salts of iron used orally cannot be injected because they have strong protein precipitating action and free iron in plasma is highly toxic. Four organically complexed formulations of iron are currently available in India; one of these *Iron-dextran* has been in use for over 50 years. Two relatively new ones *Ferrous sucrose* and *Ferric carboxymaltose* were added few years back, and the latest one is *Iron isomaltoside 1000*. The newer formulations are less risky and have improved ease of administration. Few other formulations are marketed elsewhere.

Iron-dextran It is a high molecular weight colloidal solution containing 50 mg elemental iron/ml. It is the only preparation that can be injected i.m. as well as i.v. By i.m. route it is absorbed through lymphatics, circulates without binding to transferrin and is engulfed by RE cells where iron dissociates and is made available to the erythron for haeme synthesis. In the injected muscle 10–30% of the dose remains locally bound and becomes unavailable for utilization for several weeks. Thus, 25% extra needs to be added to the calculated dose. Iron-dextran is not excreted in ~~urine or in bile.~~ Because dextran is antigenic, anaphylactic reactions are more common than with the newer preparations.

IMFERON, FERRI INJ: iron dextran 100 mg in 2 ml for i.m./i.v. injection.

Intramuscular: Injection is given deeply in the gluteal region using Z track technique (to avoid staining of the skin). Iron dextran can be injected 2 ml daily, or on alternate days, or 5 ml each side on the same day (local pain lasting weeks may occur with the higher dose).

Intravenous: A dose of 2 ml containing 100 mg iron is injected per day taking 10 min for the injection. Alternatively, the total calculated dose is diluted in 500 ml of glucose/saline solution and infused i.v. over 6–8 hours under constant observation. Injection should be terminated if the patient complains of giddiness, paresthesias or tightness in the chest.

The test dose prescribed earlier is no ~~longer~~ recommended, because the life threatening anaphylactic reaction can occur even when a previous dose or test dose has been well tolerated. Resuscitation facilities should be available before any iron preparation is injected i.v.

Adverse effects

Local Pain at site of i.m. injection, pigmentation of skin, sterile abscess—especially in old and debilitated patient.

Systemic Fever, headache, joint pains, flushing, palpitation, chest pain, dyspnoea, lymph node enlargement are more common than with the newer formulations.

An anaphylactoid reaction resulting in vascular collapse and death occurs occasionally.

Ferrous-sucrose This newer formulation is a high molecular weight complex of iron hydroxide with sucrose, that on i.v. injection is taken up by RE cells, where iron dissociates and is utilized. It is safer than the older iron dextran and a dose of 100 mg (max 200 mg) can be injected i.v. taking 5 min, once daily to once weekly till the total calculated dose (including that to replenish stores) is administered. However, total dose i.v. infusion is not possible. The solution is highly alkaline ruling out i.m./s.c. injection.

The incidence of hypersensitivity reaction is very low. Other side effects are also milder. This preparation is particularly indicated for anaemia in kidney disease patients, but reports of kidney damage are on record. Oral iron should not be given concurrently and till 5 days after the last injection.

UNIFERON, ICOR, MICROFER: ferrous sucrose 50 mg in 2.5 ml and 100 mg in 5 ml amp. for i.v. inj.

Ferric carboxymaltose In this formulation the ferric hydroxide core is stabilized by a carbohydrate shell. The macromolecule is rapidly taken up by the RE cells, primarily in bone marrow (upto 80%), as well as in liver and

spleen. Iron is released and delivered subsequently to the target cells. It is administered either as daily 100 mg i.v. injection, or upto 1000 mg is diluted with 100 ml saline (not glucose solution) and infused i.v. taking 15 min or more. Infusion may be repeated after a week. It should not be injected i.m. In clinical trials, it has caused a rapid increase in haemoglobin level in anaemia patients and replenished stores. The incidence of acute reaction is very low. Pain at injection site, and rashes have occurred, but anaphylaxis is rare. Headache, nausea, abdominal pain are generally mild. Hypotension, flushing and chest pain are infrequent. Due to lack of safety data, it is not recommended for children <14 years.

ENCICARB INJ: Ferric carboxymaltose 50 mg/ml in 2 ml and 10 ml vials.

Iron isomaltoside-1000 This is the latest injectable iron formulation for i.v. use marketed in India in 2016. It consists of iron bound tightly in a matrix of isomaltosie-1000, which is an oligosaccharide with mean M.W. of 1000. After i.v. injection, iron isomaltoside is rapidly taken up into the RE cells and then slowly released for use by the erythropoietic cells. The tight binding within the matrix releases very little labile iron which is responsible for toxicity. This permits administration of high single dose of 1–2 g (upto 20 mg/kg) i.v. over 15–30 min. Thus, full iron deficit can be corrected by a single short-period i.v. infusion, which is not only more convenient and cost saving, but also avoids multiple exposure of the patient to i.v. iron. Alternatively 100–200 mg i.v. may be injected over 5 min daily. The plasma t½ of this formulation is 20–32 hours; only 1% is excreted in the urine.

Efficacy of iron isomaltoside comparable to iron dextran or iron sucrose has been demonstrated in treating iron deficiency anaemia encountered in multiple clinical settings, including CKD and erythropoietin treatment, inflammatory bowel disease, heart failure, postpartum haemorrhage, etc. The immunogenic potential of iron isomaltoside-1000 is low, and it has been well tolerated in clinical trials with a favourable safety profile. Side effects reported are nausea, epigastric pain, abdominal cramps, constipation or loose motion. Serious hypersensitivity reaction is very rare.

ISOFER, JILAZO 100 mg iron/ml inj in 1 ml and 5 ml vial

It may be concluded that currently ferric carboxymaltose and iron isomaltoside-1000 are the two most convenient and safest i.v. iron formulations.

Use

1. *Iron deficiency anaemia* It is the most important indication for medicinal iron. Iron deficiency is the commonest cause of anaemia, especially in developing countries where a sizable percentage of population is anaemic. The RBCs are microcytic and hypochromic due to deficient Hb synthesis. Other metabolic manifestations are seen when iron deficiency is severe. Apart from nutritional deficiency, chronic bleeding from g.i. tract (ulcers, inflammatory bowel disease, hookworm infestation) is a common cause. Iron deficiency also accompanies repeated attacks of malaria and chronic inflammatory diseases. The cause of iron deficiency should be identified and treated. Iron should be normally administered orally; parenteral therapy is to be reserved for special circumstances (*see* p. 649). A rise in Hb level by 0.5–1 g/dl per week is an optimum response to iron therapy. It is faster in the beginning and when anaemia is severe. Later, the rate of increase in Hb% declines. However, therapy should be continued till normal Hb level is attained (generally takes 1–3 months depending on the severity of anaemia) and 2–3 months or more thereafter to replenish the stores.

Prophylaxis: The amount of iron available from average diet and the absorptive processes in the intestine place a ceiling on iron absorption of ~3 mg/day. Thus, iron balance is precarious in most menstruating women. Later half of pregnancy and infancy are periods when iron deficiency will develop unless medicinal iron is supplemented. In these situations as well as others (chronic illness, menorrhagia, after

acute blood loss, etc.) prophylactic use of iron is indicated.

2. *Megaloblastic anaemia* When brisk haemopoiesis is induced by vit B_{12} or folate therapy, iron deficiency may be unmasked. The iron status of these patients should be evaluated and iron given accordingly.

ACUTE IRON POISONING

It occurs mostly in infants and children: 10–20 iron tablets or equivalent of the liquid preparation (> 60 mg/kg iron) may cause serious toxicity in them. It is very rare in adults.

Manifestations are vomiting, abdominal pain, haematemesis, diarrhoea, lethargy, cyanosis, dehydration, acidosis, convulsions; finally shock, cardiovascular collapse and death. In few cases death occurs early (within 6 hours), but is typically delayed to 12–36 hours, with apparent improvement in the intervening period. The pathological lesion is haemorrhage and inflammation in the gut which may progress to necrotizing enteritis, hepatic necrosis and brain damage.

Treatment It should be prompt.

To prevent further absorption of iron from gut

(a) Induce vomiting or perform gastric lavage with sodium bicarbonate solution—to render iron insoluble.

(b) Give egg yolk and milk orally: to complex iron. Activated charcoal does not adsorb iron.

To bind and remove iron already absorbed

Desferrioxamine (an iron chelating agent—*see* Ch. 68) is the drug of choice. It should be injected i.m. (preferably) 0.5–1 g (50 mg/kg in children) repeated 4–12 hourly as required, or i.v. (if shock is present) 10–15 mg/kg/hour; max 75 mg/kg in a day till serum iron falls below 300 µg/dl. Early therapy with desferrioxamine has drastically reduced mortality of iron poisoning.

Alternatively, DTPA or calcium edetate (*see* Ch. 68) may be used if desferrioxamine is not available. BAL is contraindicated because its iron chelate is also toxic.

Supportive measures Fluid and electrolyte balance should be maintained and acidosis corrected by appropriate i.v. infusion. Respiration and BP may need support. Diazepam i.v. may be cautiously used to control convulsions, if they occur.

Miscellaneous/Adjuvant haematinics

1. Copper Haeme synthesis is interfered in copper deficiency. However, copper is a trace metal for man and clinical deficiency is very rare. Its routine use is, therefore, not justified. However, when copper deficiency is demonstrated, 0.5–5 mg of copper sulphate/day may be given therapeutically; prophylactic dose is 0.1 mg/day. It is present in some haematinic combinations (*see* Table 44.1)

2. Pyridoxine (*see* Ch. 69) Pyridoxine responsive anaemia is a rare entity. It is due to inherent abnormality in haeme synthesis. Sideroblastic anaemia associated with isoniazid and pyrazinamide therapy (which interfere with pyridoxine metabolism and action) needs to be treated with pyridoxine. Some other sideroblastic anaemias show partial improvement with large doses of pyridoxine. However, routine use of pyridoxine in anaemia is wasteful.

MATURATION FACTORS

Deficiency of *vit* B_{12} and *folic acid*, which are B group vitamins, results in megaloblastic anaemia characterized by the presence of large red cell precursors in bone marrow and their large and shortlived progeny in peripheral blood. Vit B_{12} and folic acid are therefore called maturation factors. The basic defect is in DNA synthesis. Apart from haemopoietic cells, other rapidly proliferating tissues also suffer.

VITAMIN-B_{12}

Cyanocobalamin and hydroxocobalamin are complex cobalt containing compounds present in the diet and referred to as vit B_{12}.

Thomas Addison (1849) described cases of anaemia not responding to iron. This was later called 'pernicious' (incurable, deadly) anaemia and its relation with atrophy of gastric mucosa was realized. Minot and Murphy (1926) treated such patients by including liver in the diet and received Nobel prize. Castle (1927–32) propounded the hypothesis that there was an *extrinsic factor* present in diet which combined with an *intrinsic factor* produced by stomach to give rise to the *haemopoietic principle*. Vit B_{12} was isolated in 1948 and was shown to be the extrinsic

factor as well as the haemopoietic principle, and that the intrinsic factor only helped in its absorption.

Vit B_{12} occurs as water soluble, thermostable red crystals. It is synthesized in nature only by microorganisms; plants and animals acquire it from them.

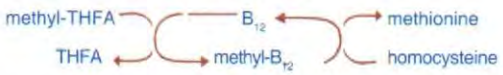
Dietary sources Liver, kidney, sea fish, egg yolk, meat, cheese are the main vit B_{12} containing constituents of diet. The only vegetable source is legumes (pulses) which get it from microorganisms harboured in their root nodules.

Vit B_{12} is synthesized by the colonic microflora, but this is not available for absorption in man. The commercial source is *Streptomyces griseus* which also produces streptomycin.

Daily requirement 1–3 µg, pregnancy and lactation 3–5 µg.

Metabolic functions Vit B_{12} is intricately linked with folate metabolism in many ways, so that megaloblastic anaemia occurring due to deficiency of either is indistinguishable. In addition, vit B_{12} has some independent metabolic functions as well. The active coenzyme forms of B_{12} generated in the body are *deoxyadenosyl-cobalamin* (DAB_{12}) and *methyl-cobalamin* (methyl B_{12}).

- Vit B_{12} is essential for the conversion of homocysteine to methionine



Methionine is needed as a methyl group donor in many metabolic reactions and for protein synthesis. This reaction is also critical in making tetrahydrofolic acid (THFA) available for reutilization. In B_{12} deficiency THFA gets trapped in the methyl form ('methylfolate trap') and a number of *one carbon* transfer reactions suffer (*see* under folic acid).

- Purine and pyrimidine synthesis is affected primarily due to defective 'one carbon' transfer because of 'folate trap'. The most important of these is inavailability of thymidylate for DNA production.

- Malonic acid $\xrightarrow{DAB_{12}}$ Succinic acid

is an important step in propionic acid metabolism. In vit B_{12} deficiency, methylmalonic acid accumulates which was considered to be mainly responsible for demyelination seen in B_{12} deficiency, but not in pure folate deficiency, because this reaction does not require folate.

- Now it appears that interference with the reaction:

Methionine $\xrightarrow{DAB_{12}}$ S-adenosyl methionine

may be more important in the neurological damage of B_{12} deficiency, because S-adenosyl methionine is needed in the synthesis of phospholipids and myelin.

- Vit B_{12} is essential for cell growth and multiplication.

Utilization of vit B_{12} Vit B_{12} is present in food as protein conjugates and is released by cooking or by proteolysis in stomach facilitated by gastric acid. Intrinsic factor (a glycoprotein, MW60,000) secreted by stomach forms a complex with B_{12}. This complex attaches to specific receptors present on intestinal mucosal cells and is absorbed by active carrier mediated transport. This mechanism is essential for absorption of vit B_{12} ingested in physiological amounts. However, when gross excess is taken, a small fraction is absorbed without the help of intrinsic factor.

Vit B_{12} is transported in blood in combination with a specific β globulin *transcobalamin II* (TCII). Congenital absence of TCII or presence of abnormal protein (TCI or TCIII, that occurs in liver and bone marrow disease) may interfere with delivery of vit B_{12} to tissues. Vit B_{12} is especially taken up by liver cells and stored: about 2/3 to 4/5 of body's content (2–8 mg) is present in liver.

Vit B_{12} is not degraded in the body. It is excreted mainly in bile (3–7 µg/day); all but 0.5–1 µg of this is reabsorbed—considerable enterohepatic circulation occurs. Thus, in the absence of intrinsic factor or when there is malabsorption, B_{12} deficiency develops much more rapidly than when it is due to nutritional deficiency. It takes 3–5 years of total absence of B_{12} in diet to deplete normal body stores.

Vit B_{12} is directly and completely absorbed after i.m. or deep s.c. injection. Normally, only

traces of B_{12} are excreted in urine, but when pharmacological doses (> 100 µg) are given orally or parenterally—a large part is excreted in urine, because the plasma protein binding sites get saturated and free vit B_{12} is filtered at the glomerulus. Hydroxocobalamin is more protein bound and better retained than cyanocobalamin.

Deficiency Vit B_{12} deficiency occurs due to:

1. Addisonian pernicious anaemia: is an autoimmune disorder which results in destruction of gastric parietal cells → absence of intrinsic factor in gastric juice (along with achlorhydria) → inability to absorb vit B_{12}. It is rare in India.
2. Other causes of gastric mucosal damage, e.g. chronic gastritis, gastric carcinoma, gastrectomy, etc.
3. Malabsorption (damaged intestinal mucosa), bowel resection, inflammatory bowel disease.
4. Consumption of vit B_{12} by abnormal flora in intestine (blind loop syndrome) or fish tape worm.
5. Nutritional deficiency: is a less common cause; may occur in strict vegetarians.
6. Increased demand: pregnancy, infancy.

Manifestations of deficiency are:

(a) Megaloblastic anaemia (generally the first manifestation), neutrophils with hypersegmented nuclei, giant platelets.

(b) Glossitis, g.i. disturbances: damage to epithelial structures.

(c) Neurological: subacute combined degeneration of spinal cord; peripheral neuritis—diminished vibration and position sense, paresthesias, depressed stretch reflexes, muscular weakness, ataxia; mental changes—poor memory, mood changes, hallucinations, etc. are late effects.

Preparations, dose, administration

Cyanocobalamin: 35 µg/5 ml liq.
Hydroxocobalamin: 500 µg, 1000 µg inj.
In India both oral and injectable vit B_{12} is available mostly as combination preparation along with other vitamins, with or without iron. The leading ones are listed in Tables 44.1 and 69.2. Some selected brands with their vit B_{12} content are:
NEUROBION FORTE (1000 µg/3 ml inj; 15 µg/tab.), OPTINEURON (1000 µg/3 ml inj.), NEUROXIN-12 (500 µg/10 ml inj.), POLYBION (15 µg/cap), BECOSULES (5 µg/cap), FESOVIT (15 µg/cap), AUTRIN (15 µg/cap) FERRICARB (15 µg/cap).

Because of higher protein binding and better retention in blood, hydroxocobalamin is preferred for parenteral administration to treat vit B_{12} deficiency. In British Pharmacopoeia (BP) stipulates that inj. hydroxocobalamin should be dispensed when inj. vit. B_{12} is prescribed. The National list of essential medicines (2015) of India has also included hydroxocobalamin in place of cyanocobalamin.

Prophylactic dose: 3–10 µg/day orally in those at risk of developing deficiency.

Therapeutic dose: Oral vit B_{12} is not dependable for treatment of confirmed vit B_{12} deficiency because its absorption from the intestine is unreliable. Injected vit B_{12} is a must when deficiency is due to lack of intrinsic factor (pernicious anaemia, other gastric causes), since the absorptive mechanism is totally nonfunctional. Various regimens are in use. The one followed in Britain is—hydroxocobalamin 1 mg i.m. daily or on alternate days for 2 weeks or till neurological symptoms (when present) abate, followed by 1 mg injected every 1–3 months for maintenance. The regimen popular in USA is vit B_{12} 100–1000 µg i.m. daily or on alternate days for 1–2 weeks followed by weekly injections for 6 months if neurologic deficit is present, and then monthly for maintenance indefinitely.

Methylcobalamin (methyl B_{12}) is the active coenzyme form of vit B_{12} for synthesis of methionine and S-adenosylmethionine that is needed for integrity of myelin. This preparation of vit B_{12} in a dose of 0.5–1.5 mg/day has been especially promoted for correcting the neurological defects in diabetic, alcoholic and other forms of peripheral neuropathy. However, in USA and many other countries, it is used only as a nutritional supplement, and not as a drug.
Methylcobalamin BIOCOBAL, DIACOBAL, METHYCOBAL, COBAMET, MECOBA 0.5 mg tab and 0.5 mg in 1 ml inj.

Uses

1. *Treatment of vit B_{12} deficiency:* vit B_{12} is used as outlined above. It is wise to add 1–5 mg of oral folic acid and an iron preparation, because

reinstitution of brisk haemopoiesis may unmask deficiency of these factors. Response to vit B_{12} is dramatic—symptomatic improvement starts in 2 days: appetite improves, patient feels better; mucosal lesions heal in 1–2 weeks; reticulocyte count increases; Hb% and haematocrit start rising after 2 weeks; platelet count normalises in 10 days and WBC count in 2–3 weeks. Time taken for complete recovery depends on the severity of anaemia to start with. Neurological parameters improve more slowly—may take several months. Full recovery may not occur if vit B_{12} deficiency has been severe or had persisted for 6 months or more.

2. *Prophylaxis*: needs to be given only when there are definite predisposing factors for development of vit B_{12} deficiency (*see* above).

3. Mega doses of vit B_{12} have been used in neuropathies, psychiatric disorders, cutaneous sarcoid and as a general tonic to allay fatigue, improve growth. The value of such therapy is questionable.

4. Tobacco amblyopia: hydroxocobalamin is of some benefit—it probably traps cyanide derived from tobacco to form cyanocobalamin.

Massive doses (5 g) of hydroxocobalamin have been injected i.v. to treat cyanide poisoning due to smoke inhalation (*see* p. 591).

Adverse effects Even large doses of vit B_{12} are quite safe. Allergic reactions have occurred on injection, probably due to contaminants. Anaphylactoid reactions (probably to sulfite contained in the formulation) have occurred on i.v. injection: this route should never be employed.

FOLIC ACID

It occurs as yellow crystals which are insoluble in water, but its sodium salt is freely water soluble. Chemically it is *Pteroyl glutamic acid (PGA)* consisting of pteridine + paraaminobenzoic acid (PABA) + glutamic acid.

Wills (1932–37) had found that liver extract contained a factor, other than vit B_{12}, which could cure megaloblastic anaemia. Mitchell in 1941 isolated an antianaemia principle from spinach and called it 'folic acid' (from leaf). Later the Will's factor was shown to be identical to folic acid.

Dietary sources Liver, green leafy vegetables (spinach), egg, meat, yeast. It is synthesized by gut flora, but this is largely unavailable for absorption.

Daily requirement of an adult is < 0.1 mg but dietary allowance of 0.2 mg/day is recommended. During pregnancy, lactation or any condition of high metabolic activity, 0.8 mg/day is considered appropriate.

Utilization Folic acid is present in food as polyglutamates; the additional glutamate residues are split off primarily in the upper intestine before being absorbed. Reduction to DHFA and methylation also occurs at this site. It is transported in blood mostly as methyl-THFA which is partly bound to plasma proteins. Small, physiological amounts of folate are absorbed by specific carrier-mediated active transport in the intestinal mucosa. Large pharmacological doses may gain entry by passive diffusion, but only a fraction is absorbed.

Folic acid is rapidly extracted by tissues and stored in cells as polyglutamates. Liver takes up a large part and secretes methyl-THFA in bile which is mostly reabsorbed from intestine: enterohepatic circulation occurs. Alcohol interferes with release of methyl-THFA from hepatocytes. The total body store of folates is 5–10 mg. Normally, only traces are excreted, but when pharmacological doses are given, 50–90% of the absorbed dose may be excreted in urine.

Metabolic functions Folic acid is inactive as such and is reduced to the coenzyme form in two steps: FA → DHFA → THFA by folate reductase (FRase) and dihydrofolate reductase (DHFRase) enzymes respectively. THFA mediates a number of *one carbon* transfer reactions by carrying a methyl group as an adduct (*see* under vit. B_{12} also).

1. Conversion of homocysteine to methionine: vit B_{12} acts as an intermediary carrier of methyl group (*see* p. 653). This is the most important reaction which releases THFA from the methylated form.

2. Generation of thymidylate, an essential constituent of DNA:



CHAPTER 44

This reaction consumes THFA, which needs to be regenerated by DHFRase. That is why rapidly proliferating tissues are highly susceptible to DHFRase inhibitor methotrexate.

3. Conversion of serine to glycine: needs THFA and results in the formation of methylene-THFA which is utilized in thymidylate synthesis.

4. Purine synthesis: *de novo* building of purine ring requires formyl-THFA and methenyl-THFA (generated from methylene-THFA) to introduce carbon atoms at position 2 and 8.

5. Generation and utilization of 'formate pool'.

6. Histidine metabolism: for mediating formimino group transfer.

Ascorbic acid protects folates in the reduced form. Other cofactors, e.g. pyridoxal, etc. are required for some of the above reactions.

Deficiency Folate deficiency occurs due to:

(a) Inadequate dietary intake

(b) Malabsorption: especially involving upper intestine—coeliac disease, tropical sprue, regional ileitis, etc. In these conditions, deficiency develops more rapidly because both dietary and biliary folate is not absorbed.

(c) Biliary fistula; bile containing folate for recirculation is drained.

(d) Chronic alcoholism: intake of folate is generally poor. Moreover, its release from liver cells and recirculation are interfered.

(e) Increased demand: pregnancy, lactation, rapid growth periods, haemolytic anaemia and other diseases with high cell turnover rates.

(f) Drug induced: prolonged therapy with anticonvulsants (phenytoin, phenobarbitone, primidone) and oral contraceptives. These drugs interfere with absorption and storage of folate.

Manifestations of deficiency are:

- Megaloblastic anaemia, indistinguishable from that due to vit B_{12} deficiency. However, folate deficiency develops more rapidly if external supply is cut off: body stores last 3–4 months only. In malabsorptive conditions megaloblastosis may appear in weeks.
- Epithelial damage: glossitis, enteritis, diarrhoea, steatorrhoea.
- Neural tube defects, including spina bifida in the offspring, due to maternal folate deficiency.
- General debility, weight loss, sterility.

However, neurological symptoms do not appear in pure folate deficiency.

Preparations and dose

Folic acid: FOLVITE, FOLITAB 5 mg tab;
Liquid oral preparations and injectables are available only in combination formulation (*see* Tables 44.1 and 69.2).
Oral therapy is adequate except when malabsorption is present or in severely ill patient—given i.m.
Dose: therapeutic 2 to 5 mg/day, prophylactic 0.5 mg/day.
Folinic acid; CALCIUM LEUCOVORIN 3 mg/ml inj. FASTOVORIN 3 mg, 15 mg amps, 50 mg vial; RECOVORIN 15 mg tab; 15 mg and 50 mg vial for inj.

Uses

1. *Megaloblastic anaemias* due to:

(a) Nutritional folate deficiency: folate deficiency manifests earlier than vit B_{12} deficiency. Oral folic acid 2–5 mg/day is adequate, but in acutely ill patients, therapy may be initiated with injection of folic acid 5 mg/day. Response occurs as quickly as that to vit B_{12}.

(b) Increased demand: which occurs in pregnancy, lactation, infancy, during treatment of severe iron deficiency anaemia or haemolytic anaemias.

(c) Pernicious anaemia: folate stores may be low and deficiency may be unmasked when vit B_{12} induces brisk haemopoiesis. Folic acid has only secondary and adjuvant role in this condition.

Folic acid should never be given alone to patients with vit B_{12} deficiency, because haematological response may occur, but neurological defect may worsen due to diversion of meagre amount of vit B_{12} present in the body to haemopoiesis.

(d) Malabsorption syndromes: tropical sprue, coeliac disease, idiopathic steatorrhoea, etc.

(e) Antiepileptic therapy: megaloblastic anaemia can occur due to prolonged phenytoin/phenobarbitone therapy (*see* Ch. 30). This is treated by folic acid, but large doses should be avoided, because large doses may diminish anticonvulsant effect.

2. *Prophylaxis* Prophylactic use of folic acid is justified only when definite predisposing factors are present. Routine folate supplementation

(1 mg/day) is recommended during pregnancy to reduce the risk of neural tube defects in the newborn.

3. *Methotrexate toxicity* Folinic acid (Leucovorin, citrovorum factor, 5-formyl-THFA) is an active coenzyme form of folate which does not need to be reduced by DHFRase before it can act. Methotrexate is a DHFRase inhibitor; its toxicity is not counteracted by folic acid, but antagonized by folinic acid (3.0 mg i.v. repeated as required).

Folinic acid is expensive and not needed for the correction of simple folate deficiency for which folic acid is good enough.

4. *Citrovorum factor rescue* In certain malignancies, high dose of methotrexate is injected i.v. and is followed within ½–1 hour with 1–3 mg i.v. of folinic acid to rescue the normal cells. It is of no use if given > 3 hours after methotrexate.

5. *To enhance anticancer efficacy of 5-fluorouracil (5-FU)* Folinic acid is now routinely infused i.v. along with 5-FU (*see* Ch. 64), because THFA is required for inhibition of thymidylate synthase by 5-FU.

Adverse effects Oral folic acid is entirely nontoxic. Injections rarely cause sensitivity reactions.

ERYTHROPOIETIN

Erythropoietin (EPO) is a sialoglycoprotein hormone (MW 34000) produced by peritubular cells of the kidney that is essential for normal erythropoiesis. Anaemia and hypoxia are sensed by kidney cells and induce rapid secretion of EPO, which acts on erythroid marrow and:

(a) Stimulates proliferation of colony forming cells of the erythroid series.

(b) Induces haemoglobin formation and erythroblast maturation.

(c) Releases reticulocytes in the circulation.

EPO binds to specific receptors on the surface of its target cells. The EPO receptor is a JAK-STAT-binding receptor that alters phosphorylation of intracellular proteins and activates transcription factors to regulate gene expression. It induces erythropoiesis in a dose dependent manner, but has no effect on RBC lifespan.

Epoetin α, β It is recombinant human erythropoietin (Epoetin α, β) is administered by i.v. or s.c. injection and has a plasma t½ of 6–10 hr, but action lasts several days.

Use The primary indication for epoetin is *anaemia of chronic renal failure* which is due to low levels of EPO. Only smptomatic patients with Hb ≤ 8 g/dl should be considered for EPO therapy. Epoetin 25–100 U/kg s.c. or i.v. 3 times a week (max. 600 U/kg/week) raises haematocrit and haemoglobin, reduces need for transfusions and improves quality of life. It is therefore increasingly used now in eligible patients. It is prudent to start with a low dose and titrate upwards to keep haematocrit between 30–36%, and Hb 10–11 g (max 12 g) per dl. Trials have found higher mortality if Hb level was raised to normal (13.5 g/dl). As such, lowest dose of epoetin sufficient to avoid blood transfusion or that to maintain Hb between 10–11 g/dl should be used. Some recent studies have indicated that dose reduction by about 30% is possible when epoetin is given s.c. compared to i.v. Exercise capacity and overall wellbeing of the patients is improved. Most patients have low iron stores; require concurrent parenteral/oral iron therapy for an optimum response. Other uses are:

1. Anaemia in AIDS patients treated with zidovudine.
2. Cancer chemotherapy induced anaemia.
3. Preoperative increased blood production for autologous transfusion during surgery.

Response to epoetin is poor in case of primary bone marrow disease, and in nutritional anaemias, because the endogenous circulating levels of EPO are already high.

Adverse effects Epoetin is nonimmunogenic. Adverse effects are related to sudden increase in haematocrit, blood viscosity and peripheral vascular resistance (due to correction of anaemia). These are—increased clot formation in the A-V shunts (most patients are on dialysis), hypertensive episodes or persistently raised

BP, serious thromboembolic events, occasionally seizures. Flu-like symptoms lasting 2–4 hr occur in some patients.

HEMAX 2000 IU/ml and 4000 IU/ml vials; EPREX 2000 IU, 4000 IU and 10000 IU in 1 ml prefilled syringes; ZYROP (epoetin β) 2000 IU and 4000 IU vials.

Darbepoetin α This is a hyperglycosylated modified preparation of EPO that has a t½ of 24–36 hours and is longer acting than epoetin. Accordingly, it needs to be injected once a week and is more convenient. Indications, efficacy and adverse effects are similar to epoetin.

Dose: Initially 0.45 µg/kg s.c./i.v. once a week; dose to be adjusted later according to rise in Hb level.

CRESP 40 µg/vial inj.

PROBLEM DIRECTED STUDY

44.1 A lady aged 40 years consults you for treatment of her anaemia that is not improving with medicine prescribed by a local doctor. She told that she is suffering from weakness, fatigue and occasional giddiness for the last 4–5 months. She went to a local doctor 2 months ago who got her blood tested, which showed Hb was 7.5 g/dl. A liquid medicine was prescribed, that she has been taking 1 tablespoonful daily without any benefit. The medicine was found to be syrup Ferric ammonium citrate 160 mg/15 ml along with folic acid 0.5 mg and vit B_{12} 7.5 µg. She also revealed that she suffers from heart burn, and has been taking a tablet (Rabeprazole 20 mg) once daily for the last 2–3 years. Repeat blood testing showed Hb to be 7.6 g/dl, haematocrit was 27%, RBCs were microcytic-hypochromic, and other values were consistent with iron deficiency anaemia. Her periods were normal and detailed examination showed no evidence of bleeding from any site.

(a) What could be the reason for her failure to improve with oral iron therapy that she has been taking?

(b) Can she still be treated with oral iron, or does she require parenteral iron therapy? What treatment would be appropriate for her?

(see Appendix-1 for solution)

Chapter 45 Drugs Affecting Coagulation, Bleeding and Thrombosis

Haemostasis (arrest of blood loss) and blood coagulation involve complex interactions between the injured vessel wall, platelets and coagulation factors. For blood to clot, a cascading series of proteolytic reactions (Fig. 45.1) is started by:
(i) Contact activation of Hageman factor: *intrinsic system*, in which all factors needed for coagulation are present in the plasma. This pathway is responsible for clotting when blood is kept in a glass tube, and for amplification of the common pathway. This is slow and takes several minutes to activate factor X.
(ii) Tissue thromboplastin: *extrinsic system*, needs a tissue factor, but activates factor X in seconds. In the normal course, coagulation after injury to vessel wall occurs by this pathway.

The subsequent events are common in the two systems and result in polymerization of fibrinogen to form fibrin strands. Blood cells are trapped in the meshwork of fibrin strands producing clot.

Two *in vitro* tests 'activated partial thromboplastin time' (aPTT) and 'prothrombin time' (PT) are employed for testing integrity of the intrinsic, extrinsic and common pathways of the coagulation cascade. The results are interpreted as:

	PT	*aPTT*
Intrinsic pathway interfered	Normal (12–14S)	Prolonged
Extrinsic pathway interfered	Prolonged	Normal (26–32S)
Common pathway interfered	Prolonged	Prolonged

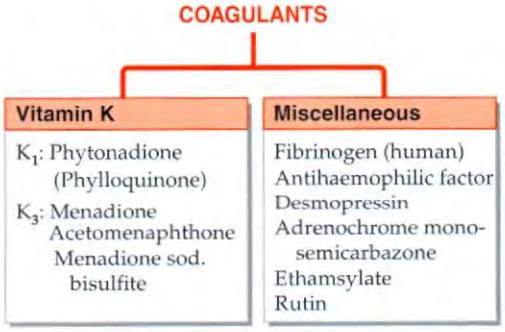
Most clotting factors are proteins present in plasma in the inactive (zymogen) form. By partial proteolysis they themselves become an active protease and activate the next factor. In addition to its critical role in cleaving and polymerizing fibrinogen, thrombin activates many upstream factors (especially f. XI, VIII and V) of the intrinsic and common pathways—amplifying its own generation and continuation of clot formation. It is also a potent activator of platelets.

On the other hand, factors like *antithrombin*, *protein C*, *protein S*, *antithromboplastin* and the *fibrinolysin system* tend to oppose coagulation and lyse formed clot. Thus, a check and balance system operates to maintain blood in a fluid state while in circulation and allows rapid haemostasis following injury.

COAGULANTS

These are substances which promote coagulation, and are indicated in haemorrhagic states.

Fresh whole blood or fresh frozen plasma provide all the factors needed for coagulation and are the best therapy for deficiency of any clotting factor. Moreover, they act immediately. Other drugs used to restore haemostasis are:



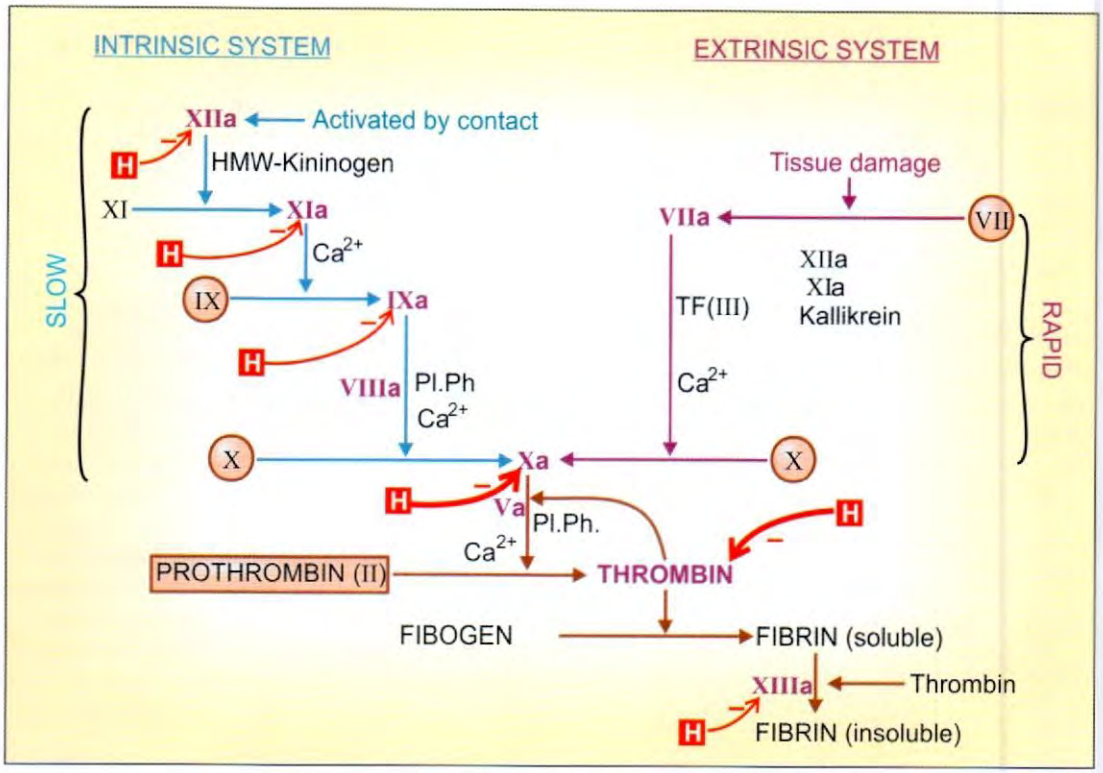
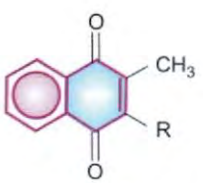


Fig. 45.1: The coagulation cascade. The vit. K dependent factors (factor II, VII, IX and X) have been encircled, Factors inactivated by heparin (H) in red; the more important inhibited steps are highlighted by thick arrow. a—activated form; Pl.Ph.—Platelet phospholipid; HMW—High molecular weight; TF—Tissue factor (factor III)

VITAMIN K

It is a fat-soluble dietary principle required for the synthesis of clotting factors.

Dam (1929) produced bleeding disorder in chicken by feeding deficient diet. This was later found to be due to decreased concentration of prothrombin in blood and that it could be cured by a fat soluble fraction of hog liver. This factor was called *Koagulations vitamin* (vit K) and soon its structure was worked out. A similar vitamin was isolated in 1939 from alfalfa grass and labelled vit K_1, while that from sardine (sea fish) meal was labelled K_2. In nature, vit K_2 (menaquinone) is produced only by bacteria, and that found in humans is derived from intestinal flora. Synthetic compounds have been produced and labelled K_3.



VITAMIN K

Chemistry and source Vit K has a basic naphthoquinone structure, with or without a side chain (R) at position 3. The side chain in K_1 is *phytyl*, in K_2 *prenyl*, while in K_3 there is no side chain.

Dietary sources are—green leafy vegetables, such as cabbage, spinach; and liver, cheese, etc.

Daily requirement It is uncertain, because a variable amount of menaquinone (vit K_2) produced by colonic bacteria

becomes available systemically. Even 3–10 µg/day external source may be sufficient. However, the total requirement of an adult has been estimated to be 50–100 µg/day.

Action Vit K acts as a cofactor at a late stage in the synthesis by liver of coagulation proteins—prothrombin, factors VII, IX and X. The vit K dependent change (γ carboxylation of glutamate residues of these zymogen proteins (Fig. 45.2) confers on them the capacity to bind Ca^{2+} and to get bound to phospholipid surfaces—properties essential for participation in the coagulation cascade.

Utilization Fat-soluble forms of vit K are absorbed from the intestine *via* lymph and require bile salts for absorption, while water-soluble forms are absorbed directly into portal blood. An active transport process in the jejunum has been demonstrated for K_1, while K_2 and K_3 are absorbed by simple diffusion. Vit K is only briefly concentrated in liver, but there are no significant stores in the body. It is metabolized in liver by side chain cleavage and glucuronide conjugation; metabolites are excreted in bile and urine.

Deficiency Deficiency of vit K occurs due to liver disease, obstructive jaundice, malabsorption and long-term antimicrobial therapy which alters intestinal flora, but deficient diet is rarely responsible. The most important manifestation is bleeding tendency due to lowering of the levels of prothrombin and other clotting factors in blood. Haematuria is usually first to occur; other common sites of bleeding are g.i.t., nose and under the skin—ecchymoses.

Preparations

Phytonadione: VITAMIN-K, KVI, K-WIN 10 mg/ml for i.m. injection.

Menadione: 0.66 mg in GYNAE CVP with vit C 75 mg, ferrous gluconate 67 mg, Cal. lactate 300 mg and citras bioflavonoid 150 mg per cap:

Acetomenaphthone: ACETOMENADIONE 5, 10 mg tab; KAPILIN 10 mg tab.

Menadione sod. bisulfite: 20 mg, in CADISPER-C with vit C 100 mg, adrenochrome monosemicarbazone, 1 mg, rutin 60 mg, methylhesperidin 40 mg, Cal. phosphate 100 mg per tab.

STYPTOCID 10 mg with adrenochrome monosemicarbazone 0.5 mg, rutin 50 mg, vit C 37.5 mg, vit D 200 i.u., Cal. phosphate 260 mg per tab.

Use The only use of vit K is in prophylaxis and treatment of bleeding due to deficiency of clotting factors in the following situations:

1. *Dietary deficiency:* of vit K is very rare in adults. However, when it occurs 5–10 mg/day oral or parenteral vit K rapidly corrects the defects.
2. *Prolonged antimicrobial therapy:* treat in the same way as dietary deficiency of vit K.
3. *Obstructive jaundice or malabsorption syndromes* (sprue, regional ileitis, steatorrhoea, etc.): vit K 10 mg i.m./day, or orally along with bile salts.
4. *Liver disease* (cirrhosis, viral hepatitis): associated bleeding responds poorly to vit K. Because of hepatocellular damage, synthesis of clotting factors is inadequate despite the presence of vit K. However, vit K may be of some use if its absorption had been affected due to lack of bile salts.
5. *Newborns:* All newborns have low levels of prothrombin and other clotting factors. Further decrease occurs in the next few days. The cause is both lower capacity to synthesize clotting factors as well as deficiency of vit K. The defect is exaggerated in the premature infant. Vit K 1 mg i.m. soon after birth has been recommended routinely. Some prefer administering 5–10 mg i.m. to the mother 4–12 hours before delivery. Haemorrhagic disease of the newborn can be effectively prevented/treated by such medication.

   Menadione (K_3) should not be used for this purpose (*see* below).
6. *Overdose of oral (coumarin) anticoagulants:* This is the most important indication of vit K. Phytonadione (K_1) is the preparation of choice, because it acts most rapidly; vit K_3 and its water soluble salts are relatively ineffective. The dose depends on the severity of hypoprothrombinaemia (measured INR) and bleeding. Unnecessarily high dose is to be avoided because it will render the patient unresponsive to oral anticoagulants for several days.

Severe deficiency: 10 mg i.m. followed by 5 mg 4 hourly; bleeding generally stops in 6–12 hours, but normal levels of coagulation factors are restored only after 24 hr. This dose of vit K will block anticoagulant action for 7–10 days.

Moderate deficiency: 10 mg i.m. followed by 5 mg once or twice according to response.

Mild deficiency: Just omit a few doses of the anticoagulant.

Adverse effects Phytonadione injected i.m. or given orally hardly produces any adverse effect; allergic reactions are rare. Severe anaphylactoid reactions can occur on i.v. injection of emulsified formulation; this route should not be used.

Menadione and its water-soluble derivatives can cause haemolysis in a dose-dependent manner. Patients with G-6-PD deficiency and neonates are especially susceptible. In the newborn menadione or its salts can precipitate kernicterus:

(a) by inducing haemolysis and increasing bilirubin load.
(b) by competitively inhibiting glucuronidation of bilirubin. Glucuronide conjugation is, as such, inadequate in neonates.

Because of lower efficacy and higher toxicity, there is little justification to use menadione and its water soluble salts for any indication.

Fibrinogen The fibrinogen fraction of human plasma is employed to control bleeding in haemophilia, antihaemophilic globulin (AHG) deficiency and acute afibrinogenemic states; 0.5 g is infused i.v.

FIBRINAL 0.5 g/bottle for i.v. infusion.

Antihaemophilic factor It is concentrated human AHG (factor VIII) prepared from pooled human plasma. It is indicated (along with human fibrinogen) in haemophilia which is due to AHG deficiency. It is highly effective in controlling bleeding episodes, but action is short-lasting (1 to 2 days).

Dose: 5–10 U/kg by i.v. infusion, repeated 6–12 hourly.

FIBRINAL-H, ANTIHAEMOPHILIC FACTOR: 150 U or 200 U + fibrinogen 0.5 g/bottle for i.v. infusion.

Desmopressin It releases factor VIII and von Willebrand's factor from vascular endothelium and checks bleeding in haemophilia and von Willebrand's disease (*see* p. 643).

Adrenochrome monosemicarbazone It is believed to reduce capillary fragility, control oozing from raw surfaces and prevent microvessel bleeding, e.g. epistaxis, haematuria, secondary haemorrhage from wounds, etc. Its efficacy is uncertain.

Dose: 1–5 mg oral, i.m.

STYPTOCHROME 3 mg/2 ml inj., STYPTOCID: 2 mg/2 ml inj.

Rutin It is a plant glycoside claimed to reduce capillary bleeding. It has been used in a dose of 60 mg oral BD–TDS along with vit C which is believed to facilitate its action. Its efficacy is uncertain.

In CADISPER-C 60 mg tab.

Ethamsylate It reduces capillary bleeding when platelets are adequate; probably corrects abnormalities of platelet adhesion, but does not stabilize fibrin (not an antifibrinolytic). Ethamsylate has been used in the prevention and treatment of capillary bleeding in menorrhagia, after abortion, epistaxis, malena, hematuria and after tooth extraction, but efficacy is unsubstantiated, therefore not recommended now. Side effects are nausea, rash, headache, and fall in BP (only after i.v. injection).

Dose: 250–500 mg TDS oral/i.v.; ETHAMSYL, DICYNENE, HEMSYL, ALSTAT 250, 500 mg tabs; 250 mg/2 ml inj.

LOCAL HAEMOSTATICS (STYPTICS)

After injury to arterioles and other smaller blood vessels, normal haemostasis occurs successively by contraction of injured vessel wall (lasting few minutes), adhesion and aggregation of platelets to form a plug (primary haemostasis), activation of the coagulation cascade and formation of a blood clot (secondary haemostasis). Finally in due course dissolution of the clot occurs by fibrinolysis. External bleeding is usually stopped by manual pressure, cotton-gauze pressure pack or by suturing. Control of bleeding may be aided by *local haemostatics (styptics)* that are substances used to stop bleeding from a local and approachable site. They are particularly effective on oozing surfaces, e.g. tooth socket, abrasions, etc. Absorbable materials like *fibrin* (prepared from human plasma and dryed as sheet or foam), *gelatin foam*, *oxidized cellulose* (as strips which can be cut and placed in the wound). It provide a meshwork which activates the clotting mechanism and checks bleeding. Left *in situ* these materials are absorbed in 1–4 weeks and generally cause no foreign body reaction. *Thrombin* obtained from bovine plasma may be applied as dry powder or freshly prepared solution to the bleeding surface in haemophiliacs. *Vasoconstrictors* like 0.1% Adr solution may be soaked in sterile cotton-gauze and packed in the bleeding tooth socket or nose in case of epistaxis to check bleeding when spontaneous vasoconstriction

SECTION 10

is inadequate. *Astringents* such as tannic acid or metallic salts are occasionally applied for bleeding gums, bleeding piles, etc.

SCLEROSING AGENTS

These are irritants, cause inflammation, coagulation and ultimately fibrosis, when injected into haemorrhoids (piles) or varicose vein mass. They are used only for local injection.

1. Sod. tetradecyl sulfate (3% with benzyl alcohol 2%): 0.5–2 ml at each site. SETROL 2 ml inj.
2. Polidocanol (3% inj): 2 ml; ASKLEROL 2 ml inj.

ANTICOAGULANTS

These are drugs used to reduce the coagulability of blood. They are classified in the chart.

HEPARIN

McLean, a medical student, discovered in 1916 that liver contains a powerful anticoagulant. Howell and Holt (1918) named it 'heparin' because it was obtained from liver. However, it could be used clinically only in 1937 when sufficient degree of purification was achieved.

Chemistry and occurrence Heparin is a non-uniform mixture of straight chain mucopolysaccharides with MW 10,000 to 20,000. It contains polymers of two sulfated disaccharide units:

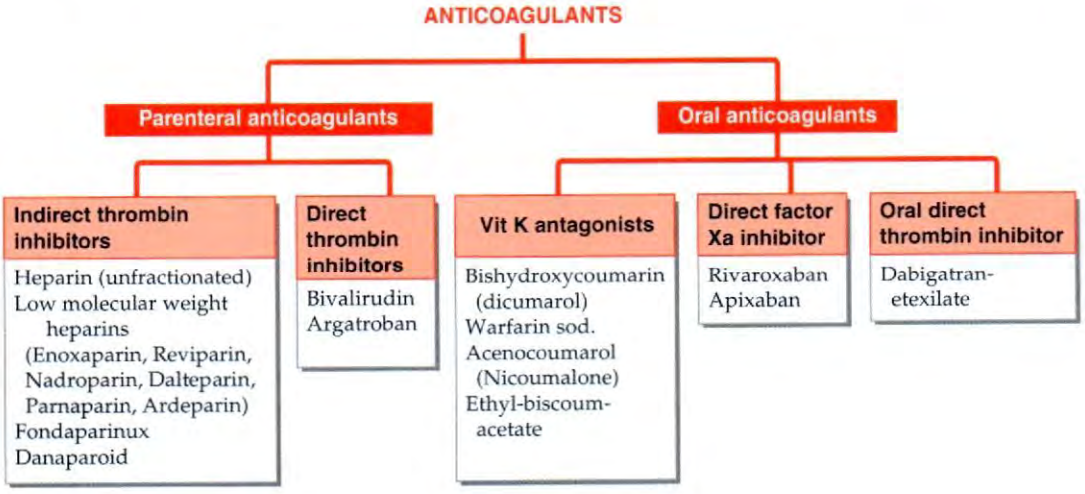
D-glucosamine-L-iduronic acid
D-glucosamine-D-glucuronic acid
} chain length and proportion of the two disaccharide units varies. Some glucosamine residues are N-acetylated.

Heparin carries strong electronegative charges and is the strongest organic acid present in the body. It occurs in mast cells as a much bigger molecule (MW ~75,000) loosely bound to the granular protein. Thus, heparin is present in all tissues containing mast cells; richest sources are lung, liver and intestinal mucosa. Commercially it is produced from ox lung and pig intestinal mucosa.

Actions

1. Anticoagulant Heparin is a powerful and instantaneously acting anticoagulant, effective both *in vivo* and *in vitro*. It acts indirectly by activating plasma antithrombin III (AT III, a serine proteinase inhibitor). The heparin-AT III complex then binds to clotting factors of the intrinsic and common pathways (Xa, IIa, IXa, XIa, XIIa and XIIIa) and inactivates them but not factor VIIa operative in the extrinsic pathway. At low concentrations of heparin, factor Xa mediated conversion of prothrombin to thrombin is selectively affected. The anticoagulant action is exerted mainly by inhibition of factor Xa as well as thrombin (IIa) mediated conversion of fibrinogen to fibrin.

Low concentrations of heparin prolong aPTT without significantly prolonging PT. High concentrations prolong both. Thus, low concentrations interfere selectively with the intrinsic pathway,



affecting amplification and continuation of clotting, while high concentrations affect the common pathway as well.

Antithrombin-III is itself a substrate for the protease clotting factors; binds with the protease to form a stable complex (suicide inhibitor). However, in the absence of heparin, the two interact very slowly. Heparin enhances the action of AT-III in two ways:

(a) The long heparin molecule provides a scaffolding for the clotting factors (mainly Xa and IIa) on one hand and AT-III on the other, so that they interact with each other.

(b) Heparin induces conformational change in AT-III to expose its interactive sites. A specific pentasaccharide sequence, which is present in only some of the heparin molecules, binds to AT III with high affinity to induce the conformational change needed for rapid interaction with clotting factors. This has been synthesized and named *fondaparinux*.

Inhibition of IIa requires both the mechanisms, but Xa inhibition can occur by mechanism 'b' alone. This probably explains why low molecular weight heparin, which is insufficient to provide a long scaffolding, selectively inhibits factor Xa.

Higher doses of heparin given for some time cause reduction in AT-III levels, probably a compensatory phenomenon. Sudden stoppage of conventional-dose therapy may result in rebound increase in coagulability for few days.

2. Antiplatelet Heparin in higher doses inhibits platelet aggregation and prolongs bleeding time.

3. Lipaemia clearing Injection of heparin clears turbid post-prandial lipaemic plasma by releasing a lipoprotein lipase from the vessel wall and tissues, which hydrolyses triglycerides of chylomicra and very low density lipoproteins to free fatty acids (FFAs). The FFAs then pass into tissues and the plasma looks clear. This action requires lower concentration of heparin than that needed for anticoagulation.

Facilitation of fatty acid transport may be the physiological function of heparin; but since, it is not found in circulating blood and its storage form in tissues is much less active, this seems only conjectural.

Pharmacokinetics

Heparin is a large, highly ionized molecule; therefore not absorbed orally. Injected i.v. it acts instantaneously, but after s.c. injection anticoagulant effect develops over ~60 min. Bioavailability of s.c. heparin is inconsistent. Heparin does not cross blood-brain barrier or placenta (it is the anticoagulant of choice during pregnancy). It is metabolized in liver by heparinase and fragments are excreted in urine.

Heparin released from mast cells is degraded by tissue macrophages, and it is not a physiologically circulating anticoagulant.

After i.v. injection of doses < 100 U/kg, the t½ averages 1 hr. Beyond this, dose-dependent inactivation is seen and pharmacokinetics is inconsistent; t½ is prolonged to 1–4 hrs. The t½ is longer in cirrhotics and kidney failure patients, and shorter in patients with pulmonary embolism. However UFH is safer than LMW heparins or fondaparinux in kidney failure patients.

Unitage and administration Because of variable molecular size of unfractionated heparin (UFH), it is standardized only by bioassay: 1 U is the amount of heparin that will prevent 1 ml of citrated sheep plasma from clotting for 1 hour after the addition of 0.2 ml of 1% $CaCl_2$ solution. Heparin sod. 1 mg has 120–140 U of activity.

HEPARIN SOD., BEPARINE, NUPARIN 1000 and 5000 U/ml in 5 ml vials for injection.

A quick penetrating solution (QPS) formulation of heparin 1000 u/ml has been recently developed for topical application to speed up healing of post-infusion superficial thrombophebitis.

PHLEBOTROY QPS 1000 u/ml topical solution; 5 ml bottle; apply on the lesion 3 times a day.

Heparin should not be mixed with penicillin, tetracyclines, hydrocortisone or NA in the same syringe or infusion bottle. Heparinized blood is not suitable for blood counts (alters the shape of RBCs and WBCs), fragility testing and complement fixation tests.

Dosage Heparin is conventionally given i.v. in a bolus dose of 5,000–10,000 U (children 50–100 U/kg), followed by continuous infusion of 750–1000 U/hr. Intermittent i.v. bolus doses of UFH are no longer recommended. The rate of infusion is controlled by aPTT measurement which is kept at 50–80 sec. or 1.5–2.5 times the patient's pretreatment value. Alternatively antiXa activity or protamine titration may be used. If these tests are not available, whole blood clotting time should be measured and kept at ~2 times the normal value.

Haematomas are more common with i.m. injection—this route should not be used.

Low dose (s.c.) regimen 5000 U of UFH is injected s.c. every 8–12 hours, started before surgery and continued for 7–10 days or till the patient starts moving about. This regimen has been found to prevent postoperative deep vein thrombosis without increasing surgical bleeding. It also does not prolong aPTT or clotting time. However, it should not be used in case of neurosurgery or when spinal anaesthesia is to be given. The patients should not be receiving aspirin or oral anticoagulants. This regimen is ineffective in high-risk situations, e.g. hip joint or pelvic surgery.

Adverse effects

1. Bleeding due to overdose is the most serious complication of heparin therapy. Since heparin (and other anticoagulants) interfere with secondary haemostasis, bleeding from deeper organs is more common. Haematuria is generally the first sign; other sites are g.i. tract, brain, joints, muscles, etc. With proper monitoring, serious bleeding occurs only in 1–3% patients.
2. Heparin-induced thrombocytopenia (HIT) is another common problem. Generally it is mild and transient; occurs due to aggregation of platelets. Occasionally serious thromboembolic events result. In some patients antibodies are formed to the heparin-platelet complex and marked depletion of platelets occurs—heparin should be discontinued in such cases. Even low molecular weight (LMW) heparins are not safe in such patients, and they should be treated with a direct thrombin inhibitor.
3. Transient and reversible alopecia is infrequent. Serum transaminase levels may rise.
4. Osteoporosis may develop on long-term use of relatively high doses.
5. Hypersensitivity reactions are rare; manifestations are urticaria, rigor, fever and anaphylaxis. Patients with allergic diathesis are more liable.

Contraindications

1. Bleeding disorders, history of HIT.
2. Severe hypertension (risk of cerebral haemorrhage), threatened abortion, piles, g.i. ulcers (risk of aggravated bleeding).
3. Subacute bacterial endocarditis (risk of embolism), large malignancies (risk of bleeding in the central necrosed area of the tumour), tuberculosis (risk of haemoptysis).
4. Ocular and neurosurgery, lumbar puncture.
5. Chronic alcoholics, cirrhosis, renal failure.
6. Aspirin and other antiplatelet drugs should be used very cautiously during heparin therapy.

Low molecular weight (LMW) heparins

Heparin has been fractionated into LMW forms (MW 3000–7000) by different techniques. LMW heparins have a different anticoagulant profile; i.e. they selectively inhibit factor Xa with little effect on IIa. They act only by inducing conformational change in AT III and not by providing a scaffolding for interaction of AT III with thrombin. As a result, LMW heparins have smaller effect on aPTT and whole blood clotting time than unfractionated heparin (UFH) relative to antifactor Xa activity. Also, they have lesser antiplatelet action—less interference with haemostasis. Thrombocytopenia is less frequent. A lower incidence of haemorrhagic complications compared to UFH has been reported in some studies, but not in others. However, major bleeding may be less frequent. The LMW heparins are eliminated primarily by renal excretion; are not to be used in patients with renal failure. The more important advantages of LMW heparins are pharmacokinetic:

- Better subcutaneous bioavailability (70–90%) compared to UFH (20–30%): Variability in response is minimized.
- Longer and more consistent monoexponential t½ (4–6 hours); making possible once daily s.c. administration.
- Since aPTT/clotting times are not prolonged, laboratory monitoring is not needed; dose is calculated on body weight basis.
- Risk of osteoporosis after long term use is much less with LMW heparin compared with UFH.

Most studies have found LMW heparins to be equally efficacious to UFH except during cardiopulmonary bypass surgery, in which high dose UFH is still the preferred anticoagulant, because LMW heparin and fondaparinux are

less effective in preventing catheter thrombosis. Moreover, effects are not fully reversed by protamine. Indications of LMW heparins are:

1. Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in high-risk patients undergoing surgery; stroke or other immobilized patients.
2. Treatment of established DVT.
3. Unstable angina (UA) and MI: they have largely replaced continuous infusion of UFH.
4. To maintain patency of cannulae and shunts in dialysis patients.

A number of LMW heparins have been marketed. They differ in composition, pharmacokinetics and dosage.

Enoxaparin: CLEXANE 20 mg (0.2 ml) and 40 mg (0.4 ml) prefilled syringes; 20–40 mg OD, s.c. (start 2 hour before surgery).

Reviparin: CLIVARINE 13.8 mg (eq. to 1432 anti Xa IU) in 0.25 ml prefilled syringe; 0.25 ml s.c. once daily for 5-10 days.

Nadroparin: FRAXIPARINE 3075 IU (0.3 ml) and 4100 IU (0.4 ml) inj., CARDIOPARIN 4000 anti Xa IU/0.4 ml, 6000 anti Xa IU/0.6 ml, 100,000 anti Xa IU/10 ml inj.

Dalteparin: 2500 IU OD for prophylaxis; 100 U/Kg 12 hourly or 200 U/Kg 24 hourly for treatment of deep vein thrombosis. FRAGMIN 2500, 5000 IU prefilled syringes.

Parnaparin: 0.6 ml s.c. OD for unstable angina and prophylaxis of DVT; FLUXUM 3200 IU (0.3 ml), 6400 IU (0.6 ml) inj.

Ardeparin: 2500-5000 IU OD; INDEPARIN 2500 IU, 5000 IU prefilled syringes.

Fondaparinux The pentasaccharide with the specific sequence that binds to AT-III with high affinity, induces an irreversible conformational change to selectively inactivate factor Xa without binding thrombin (factor IIa), has been produced synthetically, given the name *fondaparinux*, and is being increasingly used now. The bioavailability of fondaparinux injected s.c. is 100%, peak effect is produced in 2 hours and it is longer acting ($t_{½}$ 17 hours). Metabolism is minimal, and it is largely excreted unchanged by the kidney. As such, it is not to be used in renal failure patients. Fondaparinux is less likely to cause thrombocytopenia compared to even LMW heparins. Risk of bleeding is also less and incidence of osteoporosis after prolonged use is minimal. Fondaparinux does not require laboratory monitoring of aPTT, and is a longer acting alternative to LMW heparins with the above advantages. It is indicated for prophylaxis and treatment of DVT and PE, as well as in acute coronary syndromes (ACS) when immediate intervention is not planned.

Dose: Prophylaxis of DVT/PE in orthopedic surgery and medical patients 2.5 mg s.c. OD, Treatment of DVT/PE 5-10 mg s.c. OD.

FONDAPARINUX, ARIXTRA 5 mg/0.4 ml, 7.5 mg/0.6 ml and 10 mg/0.8 ml prefilled single dose syringe.

Danaparoid is a preparation containing mainly heparan sulfate which is a heparin-like substance found in many tissues, having less potent anticoagulant action than heparin. Danaparoid is obtained from pig gut mucosa, and is used in cases with heparin-induced thrombocytopenia.

HEPARIN ANTAGONIST

Protamine sulfate It is a strongly basic, low molecular weight protein obtained from the sperm of certain fish. Given i.v. it neutralises heparin mg for mg, i.e. 1 mg is needed for every 100 U of heparin. For the treatment of heparin induced bleeding, due consideration must be given to the amount of heparin that may have been degraded by the patient's body in the mean time. However, it is needed infrequently because the action of heparin disappears by itself in a few hours, and whole blood transfusion is needed to replenish the loss when bleeding occurs. Protamine is more commonly used when heparin action needs to be terminated rapidly, e.g. after cardiac or vascular surgery. Protamine does not neutralize fondaparinux, and it only partially reverses the anticoagulant effect of LMW heparins.

In the absence of heparin, protamine itself acts as a weak anticoagulant by interacting with platelets and fibrinogen. Being basic in nature it can release histamine in the body. Hypersensitivity reactions have occurred. Protamine should be injected slowly (5 mg/min i.v.). Rapid i.v. injection causes flushing and breathing difficulty.

PROTA, PROTAMINE SULFATE 50 mg in 5 ml inj.

DIRECT THROMBIN INHIBITORS (DTIs)

Unlike heparin, these recently developed anticoagulants bind directly to thrombin and

inactivate it without the need to combine with and activate AT-III.

Bivalirudin It is a synthetically prepared 20 amino acid peptide congener of the larger polypeptide anticoagulant *hirudin* secreted by the salivary glands of leech. Bivalirudin binds firmly to the catalytic as well as the substrate recognition sites of thrombin and inhibits it directly. Thus, it does not need ~~AT-III~~ to exert its action. Circulating as well as clot-bound thrombin is inhibited. However, it is a substrate as well for thrombin, which slowly cleaves its peptide bonds, and the action reverses gradually. Bivalirudin is cleared from the plasma by both proteolysis as well as renal excretion, confering a short biological t½ of 25 min in subjects with normal renal function. Thus, it is a specific and reversible DTI with quick onset and short lasting anticoagulant action, which is more predictable and consistent than that of UFH. However, protamine does not antagonize its action and there is no specific antidote of bivalirudin. ~~Thrombin mediated platelet aggregation~~ is also inhibited. There is no ~~risk of HIT~~ with bivalirudin, and this probably is its most significant feature.

Bivalirudin is indicated as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI) for STEMI. It is to be used along with an antiplatelet drug *viz.* aspirin and/or clopidogrel or a glycoprotein IIb/IIIa inhibitor (GPI). It can also be used in unstable angina (UA) and NSTEMI when urgent or early PCI is planned. It is specifically of value in patients at risk of HIT.

Dose: 0.75 mg/kg bolus i.v. injection followed by 1.75 mg/kg/hour i.v. infusion for upto 24 hours. Continuation of i.v. infusion 4 hours after the PCI is optional.
BIVAFLO, BIVASTAT, BIVASAVE 250 mg/vial inj.

Apart from risk of bleeding, the adverse effects are headache, back pain and hypotension.

Bivalirudin has been evaluated in multicentric clinical trials involving >25000 patients undergoing PCI, and has demonstrated similar angiographic, and procedural outcomes as with UFH + a GPI. Rates of stent thrombosis have also been similar.

Argatroban This is a synthetic nonpeptide compound which binds reversibly to the catalytic site of thrombin, but not to the substrate recognition site, and acts as a DTI. Administered by i.v. bolus (350 µg/kg over 3-5 min) followed by 25 µg/kg/min infusion, it produces a rapid onset short-lasting antithrombin action. Argatroban prolongs aPTT, and its dose is regulated by measuring INR. As such, care needs to be exercised while shifting patients to warfarin prophylaxis. It is indicated for prophylaxis and treatment of thrombosis and for PCI in patients with HIT or in those who are at risk of developing HIT. Argatroban is cleared by liver with a biological t½ of 45 min. Thus, it can be given to patients with renal disease.

ORAL ANTICOAGULANTS

VITAMIN K ANTAGONISTS

A haemorrhagic disease was described in cattle in 1924 which was due to feeding them on spoiled sweet clover hay. The disorder was found to be due to prothrombin deficiency and the toxic principle was identified as *bishydroxycoumarin* in 1939. It was cured by feeding alfalfa grass. First clinical use of bishydroxycoumarin was made in 1941 and many congeners were added later. *Warfarin* was initially used as rat poison; demonstration of its safety led to clinical trial; it is now the principal coumarin oral anticoagulant.

By convention, the term 'Oral anticoagulant' refers to the warfarin-like drugs which act by blocking synthesis of clotting factors. However lately, several orally active direct factor Xa inhibitors and direct thrombin inhibitors have also become available, and are increasingly used.

Action and mechanism

Warfarin and its congeners act as anticoagulants only *in vivo*, not ~~*in vitro*~~. This is so because they act indirectly by interfering with the synthesis of vit K dependent clotting factors in liver. They apparently behave as competitive antagonists of vit K and lower the plasma levels of functional clotting factors in a dose-dependent manner. In fact, they inhibit the enzyme vit K epoxide reductase (VKOR) and interfere with regeneration of the active hydroquinone form of vit K (Fig. 45.2) which acts as a cofactor for the enzyme γ-glutamyl carboxylase that carries out the final step of γ carboxylating glutamate residues of prothrombin and factors VII, IX and X. This carboxylation is essential for the ability of the clotting factors to bind Ca^{2+} and to get bound to phospholipid surfaces, necessary for the coagulation sequence to proceed.

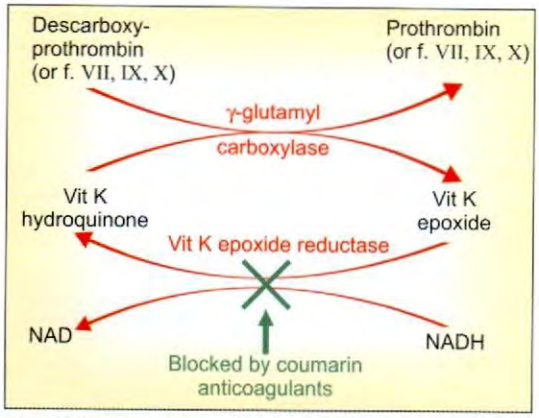


Fig. 45.2: Mechanism of action of coumarin anticoagulants
NAD—Nicotinamide adenine dinucleotide; NADH—its reduced form

Factor VII has the shortest plasma t½ (6 hr), its level falls first when warfarin is given, followed by factor IX (t½ 24 hr), factor X (t½ 40 hr) and prothrombin (t½ 60 hr). Though the synthesis of clotting factors diminishes within 2–4 hours of warfarin administration, anticoagulant effect develops gradually over the next 1–3 days as the levels of the clotting factors already present in plasma decline according to their half lives. Thus, there is always a delay between administration of coumarin drugs and the anticoagulant effect. Larger initial doses hasten the effect only slightly.

The therapeutic effect occurs when synthesis of clotting factors is reduced by 40–50%.

Protein C, protein S (both having anticoagulant property) and osteocalcin contain glutamate residues that require vit. K dependent γ carboxylation. These are also inhibited by coumarin anticoagulants. However, effect of decline in levels of protein C and protein S is overshadowed by the decline in the levels of clotting factors. While osteocalcin deficit may depress new bone formation, density of adult bone is little affected.

The differences between different coumarin vit. K antagonists are primarily pharmacokinetic and in the adverse side effects produced by them. These are summarized in Table 45.1.

Racemic Warfarin sod. It is the most popular coumarin anticoagulant. The commercial preparation of warfarin is a mixture of R (dextrorotatory) and S (levorotatory) enantiomers. The S form is more potent and is metabolized relatively faster by ring oxidation carried out by CYP2C9, while R form is less potent and degraded by side chain reduction carried out by CYP1A and CYP3A4. Both are partially conjugated with glucuronic acid and undergo some enterohepatic circulation; finally excreted in urine.

Warfarin is rapidly and completely absorbed from intestines and is 99% plasma protein bound. It crosses placenta and is secreted in milk; however, quantity of active form is generally insufficient to affect the suckling infant.

Table 45.1: Pharmacokinetic and adverse effect profile of vit K antagonist oral anticoagulants

	Drug	*t½ (hour)*	*Duration of action (days)*	*Dose (mg)*		*Adverse side effects (other than bleeding)*
				Loading	*Maintenance**	
1.	Bishydroxycoumarin	25–100 (dose dependent)	4–7	200 for 2 days	50–100	Frequent g.i.t. disturbances
2.	Warfarin sod.	36–48	3–6	5–10	2–10£	Alopecia, dermatitis, diarrhoea
3.	Acenocoumarol (Nicoumalone)	18–24	2–3	8–12	2–8	Oral ulceration, g.i.t. disturbances, dermatitis, urticaria, alopecia
4.	Ethylbiscoumacetate	2	1–3	900	300–600	Alopecia, bad taste

* Daily maintenance dose: to be adjusted by measurement of prothrombin time (INR).
£ To be taken in a single dose at the same hour (usually bed time) each day.

SECTION 10

UNIWARFIN 1, 2, 5 mg tabs; WARF-5: 5 mg tab.

Bishydroxycoumarin (Dicumarol) It is slowly and unpredictably absorbed orally. Its metabolism is dose dependent—t½ is prolonged at higher doses. Has poor g.i. tolerance; not preferred now.

Acenocoumarol (Nicoumalone) The t½ of acenocoumarol as such is 8 hours, but an active metabolite is produced so that overall t½ is about 24 hours. Acts more rapidly.
ACITROM 0.5, 1, 2, 4 mg tabs.

Ethyl biscoumacetate It has a rapid and brief action; occasionally used to initiate therapy, but difficult to maintain.

Adverse effects Bleeding as a result of extension of the desired pharmacological action is the most important problem causing ecchymosis, epistaxis, hematuria, bleeding in the g.i.t. Intracranial or other internal haemorrhages may even be fatal. Bleeding is more likely if therapy is not properly monitored, or when the International normalized ratio (INR) exceeds 4, or interacting drugs/contraindications are present.

Treatment: of bleeding due to vit K antagonists consists of:

- Withhold the anticoagulant.
- Give fresh blood transfusion; this supplies ready made clotting factors and replenishes lost blood. Alternatively fresh frozen plasma may be used as a source of clotting factors.
- Give vit K, which is the specific antidote (*see* p. 661-62), but it takes 6–24 hours for the clotting factors to be resynthesized and released in the blood after vit K administration.

Adverse effects unrelated to anticoagulation are given in Table 45.1. Cutaneous necrosis is a rare complication that can occur with any coumarin anticoagulant.

Warfarin and acenocoumarol are considered to be the most suitable and better tolerated drugs.

Dose regulation The dose of vit K antagonist oral anticoagulant must be individualised by repeated measurement of *prothrombin time*; the aim is to achieve a therapeutic effect without unduly increasing the chances of bleeding.

The optimum ratio of PT during treatment with the oral anticoagulant to the normal value (of the testing laboratory) has been defined for various indications. But this value differs depending on the source of the thromboplastin (Tp) that has been used for the test. A standardized system called the International Normalized Ratio (INR) based on the use of human brain Tp has been developed by WHO and adopted in all countries.

Recommended INR for various indications of oral anticoagulants

		INR
1.	Prophylaxis of deep vein thrombosis and similar indications	2–2.5
2.	Treatment of deep vein thrombosis, pulmonary embolism, TIAs, hip surgery	2–3
3.	Recurrent thromboembolism, arterial disease (MI), prosthetic heart valves	3–3.5

Factors enhancing effect of coumarin anticoagulants are:

- Debility, malnutrition, malabsorption and prolonged antibiotic therapy: the supply of vit K to the liver is reduced in these conditions.
- Liver disease, chronic alcoholism: synthesis of clotting factors may be deficient.
- Hyperthyroidism: the clotting factors are degraded faster.
- Newborns: have low levels of vit K and clotting factors (there should be no need of these drugs in neonates anyway).

Factors decreasing effect of coumarin anticoagulants are:

- Pregnancy: plasma level of clotting factors is higher.
- Nephrotic syndrome: drug bound to plasma protein is lost in urine.
- Genetic warfarin resistance: the affinity of warfarin (as well as that of vit K epoxide) to bind to the reductase (VKOR) enzyme, which generates the active vit K hydroquinone, is low. Dose of oral anticoagulant is 4–5 times higher.

Contraindications All contraindications to heparin (*see* p. 665) apply to these drugs

as well. Factors which enhance the effect of coumarin anticoagulants (*see* above) should also be taken into consideration.

Coumarin oral anticoagulants should not be used during pregnancy. Warfarin given in early pregnancy increases birth defects, especially skeletal abnormalities. It can produce *foetal warfarin syndrome*—hypoplasia of nose, eye socket, hand bones, and growth retardation. Given later in pregnancy, it can cause CNS defects, foetal haemorrhage, foetal death and accentuates neonatal hypoprothrombinemia.

Drug interactions A large number of drugs interact with these oral anticoagulants at pharmacokinetic or pharmacodynamic level, and either enhance or decrease their effect. These interactions are clinically important (may be fatal if bleeding occurs) and may involve more than one mechanism; the exact mechanism of an interaction is not always definable.

A. Enhanced anticoagulant action

1. Broad-spectrum antibiotics: inhibit gut flora and reduce vit K production.
2. Some cephalosporins (ceftriaxone, cefoperazone) cause hypoprothrombinaemia by the same mechanism as warfarin—produce additive action.
3. Aspirin: inhibits platelet aggregation and causes g.i. bleeding—this may be hazardous in anticoagulated patients. High doses of salicylates have synergistic hypoprothrombinemic action and also displace warfarin from protein binding site.
4. Long acting sulfonamides, indomethacin, phenytoin and probenecid: displace warfarin from plasma protein binding.
5. Chloramphenicol, erythromycin, celecoxib, cimetidine, allopurinol, amiodarone and metronidazole: inhibit warfarin metabolism.
6. Tolbutamide and phenytoin: inhibit warfarin metabolism and *vice versa*.
7. Liquid paraffin (habitual use): reduces vit K absorption.

B. Reduced anticoagulant action

1. Barbiturates (but not benzodiazepines), carbamazepine, rifampin and griseofulvin induce the metabolism of warfarin. The dose of anticoagulant determined during therapy with these drugs would be higher: if the same is continued after withdrawing the inducer—marked hypoprothrombinemia can occur—fatal bleeding is on record.
2. Oral contraceptives: increase blood levels of clotting factors.

The important features of heparin and warfarin are compared in Table 45.2.

DIRECT FACTOR Xa INHIBITORS

Warfarin has been the standard prophylactic maintenace oral anticoagulant for the past 5 decades. However, there are several problems in its use, *viz.* delayed onset of action, slow recovery on stoppage, narrow therapeutic range, need for repeated laboratory monitoring and dose adjustment as well as numerous drug interactions. To overcome these, some oral direct factor Xa inhibitors and oral direct thrombin inhibitor (oDTI) have been lately introduced. These drugs act rapidly without a lag time, and have short-lasting action, but there is no antidote.

Rivaroxaban

It is an orally active direct inhibitor of activated factor Xa which has become available for prophylaxis and treatment of DVT. Its anticoagulant action develops rapidly within 3–4 hours of ingestion and lasts for ~24 hours. It is largely metabolized, but also excreted unchanged in urine; plasma t½ is 7–11 hours. Another advantage is that it requires no laboratory monitoring of PT or aPTT. Rivaroxaban is now routinely used in a fixed dose of 10 mg once daily starting 6–10 hours after surgery for prophylaxis of venous thromboembolism following total knee/hip replacement. Duration of prophylaxis is 12–14 days after knee replacement and 35 days after hip replacement. In comparative trials, its efficacy has been found similar to a regimen of LMW heparin followed by warfarin. Rivaroxaban has also been found equally effective as warfarin for preventing stroke in

Table 45.2: Some comparative aspects of heparin and warfarin

		Heparin	*Warfarin*
1.	Chemistry	Mucopolysaccharide	Coumarin derivative
2.	Source	Hog lung, pig intestine	Synthetic
3.	Route of admin.	Parenteral (i.v., s.c.)	Oral
4.	Onset of action	Immediate	Delayed (1–3 days)
5.	Duration of action	4–6 hrs	3–6 days
6.	Activity	*In vitro* and *in vivo*	*In vivo* only
7.	Mechanism	Blocks action of factor X and thrombin	Inhibits synthesis of clotting factors
8.	Antagonist	Protamine sulphate	Vit K
9.	Variability in response	Limited	Marked
10.	Lab. control	aPTT/clotting time (desirable)	Prothrombin time/INR (essential)
11.	Drug interactions	Few and not significant	Many and significant
12.	Use	To initiate therapy	For maintenance

patients with atrial fibrillation. For the treatment of DVT and PE, it is recommended in a dose of 15 mg twice daily for 3 weeks followed by 20 mg/day. It is now also approved in a dose of 2.5 mg/day for coadministration with aspirin and clopidogrel for prophylaxis of ACS. Side effects reported are bleeding, nausea, hypotension, tachycardia and edema.

XARELTO 2.5 mg, 10 mg, 15 mg, 20 mg tabs.

Apixaban This is another oral factor Xa inhibitor having properties and indications similar to rivaroxaban. The oral bioavailability of apixaban is 85% and peak effects are produced in 3 hours. It is partly metabolized by CYP3A4 and eliminated in both faeces as well as urine. The plasma t½ is 12 hours. Drug interactions with inducers and inhibitors of CYP3A4 are possible, and it should not be used in patients with hepatic or renal impairment.

Efficacy of apixaban in the prevention and treatment of venous thromboembolism (VTE) as well as risk of major bleeding appears to be similar to that of rivaroxaban and dabigatran. A lower rate of stroke and systemic embolism has been reported with apixaban compared to warfarin by the ARISTOTLE trial conducted on >18000 patients of AF. A lower risk of major bleeding was also noted. Apixaban is approved for:

- Prophylaxis of VTE following knee/hip replacement (dose: 2.5 mg BD)
- Prophylaxis of stroke in AF patients (dose: 5 mg BD).
- Treatment of DVT and PE (dose: 10 mg BD for 7 days followed by 5 mg BD).

ELIQUIS 2.5 mg, 5 mg tabs.

Advantages of newer oral anticoagulants (direct factor Xa/thrombin inhibitors) over warfarin

- Rapid onset and offset of therapeutic effect
- Short half life
- No laboratory monitoring required
- Fixed dosage guidelines depending on the indication
- Antithrombotic efficacy equal to/better than warfarin.
- Lower risk of bleeding compared to warfarin
- Fewer drug interactions.

ORAL DIRECT THROMBIN INHIBITOR

Dabigatran etexilate It is a prodrug which after oral administration is rapidly hydrolysed to *dabigatran*. This direct thrombin inhibitor.

reversibly blocks the catalytic site of thrombin and produces a rapid (within 2 hours) anticoagulant effect. Though oral bioavailability is low, the anticoagulant effect is consistent, and no laboratory monitoring is required. The bioavailability is increased by P-gp (efflux transporter) inhibitors (verapamil, amiodarone, etc.) and dose reduction is needed in patients taking these drugs. Dabigatran is excreted by the kidney. No interaction with CYP3A4 inhibitors/inducers occurs. Plasma t½ is 14 hours and duration of action 24 hours. It is approved for prevention of VTE following hip/knee joint replacement surgery. Administered in a dose of 110 mg (75 mg for elderly > 75 years) once daily, it has been found comparable to warfarin. In another large trial dabigatran etexilate 150 mg twice daily has yielded superior results to warfarin for prevention of embolism and stroke in patients of atrial fibrillation, and has been approved for this indication as well. The incidence of major and minor bleeding was also less with dabigatran compared to warfarin. However, like any anticoagulant, bleeding is the most important adverse effect. Dyspepsia is a fraquent side effect; hepatobiliary disorder is occasional.

PRADAXA 75, 110 and 150 mg caps.

A monoclonal antibody *idarucizumab* has been developed as a reversal agent for dabigatran.

Notes on clinical use of anticoagulants

Use of anticoagulants can be life saving. They have proven prophylactic value, but can be risky (may provoke fatal bleeding). Their use requires great caution and expertise. Conditions in which they are indicated are summarized in the box. Some notable points about use of anticoagulants are highlighted below.

1. The aim of using anticoagulants is to prevent thrombus extension and embolic complications by reducing rate of fibrin formation. They do not dissolve already formed clot, but prevent recurrences.

Choice of anticoagulants for various clinical indications

	Clinical indications	*Drugs utilized*
1.	Prophylaxis of VTE after knee/hip replacement	Rivaroxaban/apixaban/dabigatran/LMW heparin/ Fonda./low dose s.c. UFH
2.	Prophylaxis of DVT and PE in high risk, bed-ridden medical/surgical patients	Fonda./LMW heparin/rivaroxaban/UFH followed by warfarin
3.	Treatment of DVT and/or PE	LMW heparins/fonda./UFH (kidney disease patients)/bivalirudin (if risk of HIT) followed by warfarin or rivaroxaban
4.	Prophylaxis of stroke and systemic embolism in nonvalvular AF	Rivaroxaban/apixaban/dabigatran/warfarin
5.	Primary PCI in patients of STEMI or in high risk cases of NSTEMI/UA	LMW heparins/UFH/bivalirudin (if risk of HIT)
6.	Along with aspirin ± clopidogrel to prevent reocclusion following fibrinolytic therapy of STEMI/ high risk NSTEMI	UFH followed by warfarin
7.	To maintain patency of intravascular cannulae/ catheters	Heparin flushes every 4–8 hours
8.	To preserve clotting factors in defibrination syndrome (disseminated intravascular coagulation)	UFH

VTE—Venous thromboembolism; DVT—Deep vein thrombosis; PE—Pulmonary embolism; LMW—Low molecular weight; UFH—Unfractionated heparin; Fonda—Fondaparinux; AF—Atrial fibrillation; PCI—Percutaneous coronary intervention; STEMI—ST segment elevation myocardial infarction; NSTEMI—NonSTEMI; UA—Unstable angina; HIT—Heparin induced thrombocytopenia

2. Parenteral anticoagulants, *viz.* UFH, LMW heparins, fondaparinux are utilized for rapid and short-term action, while oral anticoagulants warfarin, factor Xa inhibitors (f.XaIs) and oral DTIs are suitable for maintenance therapy.
3. Anticoagulants are most effective for prevention and treatment of VTE, because venous thrombi are mainly fibrin thrombi.
4. Oral f.XaIs and DTIs have surpassed low dose s.c. heparin and LMW heparins for prevention of VTE in post-knee/hip replacement surgery patients.
5. LMW heparins and fondaparinux have almost replaced UFH, except in kidney disease patients, because clearance of UFH is affected to a lesser extent by renal failure. UFH is also preferred as prophylactic in major surgery and high risk cases, because its action can be rapidly reversed by protamine, which neutralizes LMW heparins to a lesser extent, and does not neutralise fondaparinux.
6. Anticoagulants are of limited and inconsistent benefit in arterial thrombosis, because arterial thrombi are mainly composed of platelets. Their use in MI and UA is short term and secondary to that of antiplatelet drugs.
7. Oral anticoagulants (warfarin, f.XaIs, DTI) are more effective than antiplatelet drugs for preventing stroke in nonvalvular AF cases.
8. Anticoagulants are of little value in thrombotic stroke. Neurological sequelae are similar whether they are given or not. Moreover, in the initial stages it is difficult to rule out haemorrhagic stroke. However, they may be given in cerebral embolism because showers of emboli are often recurrent, and can be prevented by anticoagulants. Antiplatelet drugs are superior to anticoagulants in transient ischaemic attacks (TIAs).
9. The parenteral DTI bivalirudin is specifically indicated in patients with HIT, or those who are at risk of developing HIT.

FIBRINOLYTIC DRUGS (Thrombolytics)

These are drugs used to lyse thrombi/clot to recanalize occluded blood vessels (mainly coronary artery). They are therapeutic rather than prophylactic and work by activating the natural fibrinolytic system (Fig. 45.3).

Haemostatic plug of platelets formed at the site of injury to blood vessels is reinforced by fibrin deposition to form a thrombus. Once repair is over, the fibrinolytic system is activated to remove the fibrin. The enzyme responsible for digesting fibrin is a serine protease *Plasmin* generated from *plasminogen* by tissue plasminogen activator (t-PA), which is produced primarily by vascular endothelium. Plasminogen circulates in plasma as well as remains bound to fibrin. The t-PA selectively activates fibrin-bound plasminogen within the thrombus, and any plasmin that leaks is inactivated by circulating antiplasmins. Fibrin bound plasmin is not inactivated by antiplasmins because of common binding site for both fibrin and antiplasmin. The t-PA itself is inactivated by plasminogen activator inhibitor-1 and -2 (PAI-1, PAI-2).

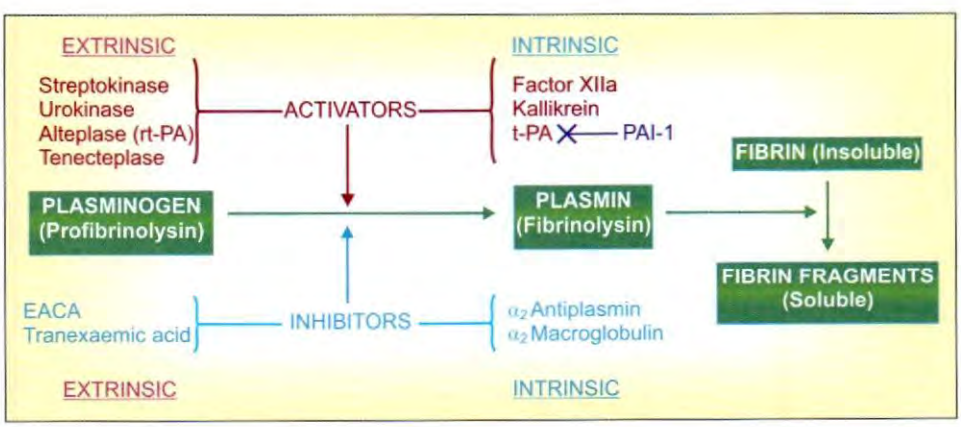


Fig. 45.3: The plasminogen-plasmin system
t-PA—Tissue plasminogen activator; rt-PA—Recombinant t-PA; PAI-1—Plasminogen activator inhibitor-1

When excessive amounts of plasminogen are activated (by administered fibrinolytics), the α_2 antiplasmin is exhausted and active plasmin persists in plasma. Plasmin is a rather nonspecific protease: degrades coagulation factors (including fibrinogen) and some other plasma proteins as well. Thus, activation of circulating plasminogen induces a lytic state whose major complication is haemorrhage. Even selective activation of thrombus bound plasmin can cause bleeding by dissolving physiological thrombi.

In general, venous thrombi are lysed more easily by fibrinolytics than arterial, and recent thrombi respond better. Fibrinolytics have little effect on thrombi > 3 days old. The fibrinolytic drugs are:

Streptokinase	Alteplase (rt-PA)
Urokinase	Reteplase
	Tenecteplase

Streptokinase (Stk) Obtained from β haemolytic *Streptococci* group C, it is the first fibrinolytic drug to be used clinically, but is not employed now because it is non-fibrin specific, i.e. activates both circulating as well as fibrin bound plasminogen. Therefore, it depletes circulating fibrinogen and predisposes to bleeding. Compared to newer more fibrin-specific tissue plasminogen activators (alteplase, etc.) it is less effective in opening occluded coronary arteries, and causes less reduction in MI related mortality.

Other disadvantages are need for a loading dose due to presence of anti-streptococcal antibodies. Streptokinase is antigenic—can cause hypersensitivity reactions; anaphylaxis occurs in 1–2% patients. It cannot be used second time due to neutralization by antibodies generated in response to the earlier dose. Fever, hypotension and arrhythmias are reported.

Urokinase It is an enzyme isolated from human urine; but commercially prepared from cultured human kidney cells. Due to availability of better fibrinolytics, it has gone out of use.

Alteplase *(recombinant tissue plasminogen activator (rt-PA)* Produced by recombinant DNA technology from human tissue culture, it catalyses the cleavage of endogenous plasminogen to generate plasmin, and is moderately specific for fibrin-bound plasminogen, so that circulating fibrinogen is lowered only by ~ 50%. It is rapidly cleared by liver and inactivated by plasminogen activator inhibitor-1 (PAI-1). The plasma $t_{1/2}$ is 4–8 min. Because of the short $t_{1/2}$, it needs to be given by slow i.v. infusion and often requires heparin coadministration. Aspirin is also routinely given after establishing reperfusion. Risk of bleeding (0.5–5%) is the most important concern. Alteplase is nonantigenic, but nausea, mild hypotension and fever may occur. It is expensive.

ACTILYSE 50 mg vial with 50 ml solvent water.

For MI: (accelerated regimen) 15 mg i.v. bolus injection followed by 50 mg over 30 min, then 35 mg over the next 1 hr. (total 100 mg in 90 min).

For pulmonary embolism: 100 mg i.v. infused over 2 hr.

For ischaemic stroke: 0.9 mg/kg by i.v. infusion over 60 min, with 10% of the dose injected in the first minute.

Reteplase It is a nonglycosylated deletion mutant of rt.PA produced by recombinant technology in which some amino acids of native t-PA are missing. This change makes it longer acting, but somewhat less selective for fibrin bound plasminogen. It is cleared by both liver and kidney with an effective $t_{1/2}$ of 13–16 min. The longer action permits a double bolus i.v. administration of 18 mg (10U) over 2 min each 30 min apart in cases of STEMI and in PE. Dose adjustment is needed in liver and kidney damage.

RETELEX 18 mg (10U)/vial injection kit.

Tenecteplase This genetically engineered substitution mutant of native t-PA has higher fibrin selectivity, slower plasma clearance (longer duration of action) and resistance to inhibition by PAI-1. It is the only fibrinolytic agent that can be injected i.v. as a single bolus dose over 10 sec, while alteplase requires 90 min infusion and reteplase needs 2 injections at 30 min interval. This feature makes it possible to institute fibrinolytic therapy immediately on diagnosis of STEMI, even during transport of the patient to the hospital. Several randomized multicentric trials have assessed its efficacy in STEMI and found it to be at least equally efficacious to alteplase. Risk of noncerebral bleeding was found to be lower with tenecteplase in the ASSENT-2 trial, but cranial bleeding incidence was similar.

Dose: 0.5 mg/kg single i.v. bolus injection.

ELAXIM 30 mg, 50 mg per vial inj.

Uses of fibrinolytics

1. *Acute myocardial infarction* The chief indication for fibrinolytic therapy is STEMI. They are not indicated, or may even be harmful

in UA and in low risk NSTEMI. In STEMI fibrinolytics are an alternative first line approach to emergency percutaneous coronary intervention (PCI) with stent placement. Recanalization of thrombosed coronary artery has been achieved in 50–90% cases. Time lag in starting the infusion is critical for reducing area of necrosis, preserving ventricular function and reducing mortality. The benefits of i.v. thrombolytic therapy have been established by large randomised studies. Aspirin with or without heparin is generally started concurrently or soon after thrombolysis to prevent reocclusion.

Recanalization efficacy is similar with alteplase, reteplase and tenecteplase, but tenecteplase has the simplest regimen. Risk of hypotension and allergic reactions is also comparable among the three.

2. *Deep vein thrombosis (DVT)* in leg, pelvis, shoulder etc.; up to 60% patients of DVT can be successfully treated by fibrinolytics. They can decrease subsequent pain and swelling, but the main advantage is preservation of venous valves and may be a reduced risk of PE, though at the risk of haemorrhage. Comparable results have been obtained with Stk, urokinase and alteplase.

3. *Pulmonary embolism (PE)* Fibrinolytic therapy is indicated in large, life-threatening PE. Lung function may be better preserved, but reduction in mortality is not established.

4. *Peripheral arterial occlusion* Fibrinolytics recanalise ~40% limb artery occlusions, especially those treated within 72 hr. However, it is indicated only when surgical thrombectomy is not possible. Regional intraarterial fibrinolytics have been used for limb arteries with greater success. Peripheral arterial thrombolysis is followed by short-term heparin and long-term aspirin therapy.

Fibrinolytics have no role in chronic peripheral vascular diseases.

5. *Stroke:* Thrombolytic therapy of ischaemic stroke is dependent on time-lapse since symptom onset; earlier, the better. Possibility of improved neurological outcome is to be balanced with risk of intracranial haemorrhage. Alteplase is approved for use in ischaemic stroke, and current opinion strongly recommends use of i.v. alteplase in carefully selected patients who can be treated within 3–4.5 hours of onset, and in whom intracranial haemorrhage is ruled out along with all risk factors for bleeding (*see* contraindications in the box). After 4.5 hours of symptom onset, the risk of intracranial haemorrhage outweighs the likelihood of benefit.

Contraindications to thrombolytic therapy

1. H/o intracranial haemorrhage
2. H/o ischaemic stroke in past 3 months
3. H/o head injury in past 3 months
4. Intracranial tumour/vascular abnormality/ aneurysms
5. Active bleeding/bleeding disorders
6. Patients receiving anticoagulants
7. Peptic ulcer, esophageal varices
8. Any wound or recent fracture or tooth extraction
9. H/o major surgery within 3 weeks
10. Uncontrolled hypertension
11. Pregnancy

Evaluation All patients with STEMI are candidates for reperfusion therapy. No consistent benefit of fibrinolytics has been demonstrated in non-STEMI cases, while possibility of haemorrhage is increased. Only high risk cases of NSTEMI may be treated with fibrinolytics. Both short-term and long-term outcome is determined by early restoration of flow in the occluded artery, regardless of whether it is achieved by thrombolysis or by PCI. Best results are obtained if perfusion can be restored within the first hour (the golden hour). While the efficacy of fibrinolytics in dissolving the thrombus diminishes with passage of time (little benefit after 6 hours of MI onset), reperfusion by PCI is affected to a lesser extent by the time lapse. Thrombolysis may be favoured if it can be started within 1–2 hours of onset. After 3 hours, PCI is favoured. Moreover, PCI has the advantage of lower bleeding risk, higher grade of flow in the canalized artery and reduction in the rate of nonfatal recurrent MI compared to thrombolysis. As such, PCI has

yielded superior results compared to fibrinolytics and is being preferred at centres where it can be performed swiftly with requisite expertise. Primary PCI is the procedure of choice for patients with contraindications to thrombolytics (*see* box). Fibrinolytic therapy requires careful patient selection, but often it can be instituted with less delay, and even at centres not well equipped for PCI.

Another approach is 'facilitated PCI' wherein full or reduced dose fibrinoytic therapy is followed at the earliest by PCI. The results of this approach are comparable to those of primary PCI. The European as well as American (ACC, AHA) guidelines provide that STEMI patients should be treated with primary PCI or with fibrinolytic drugs followed by immediate rescue PCI, if reperfusion fails with the fibrinolytic. Aspirin and heparin are continued after thrombolysis.

ANTIFIBRINOLYTIC DRUGS

These are drugs which inhibit plasminogen activation and dissolution of clot, and are used to check fibrinolysis associated bleeding.

Epsilon amino-caproic acid (EACA) It is a lysine analogue which combines with the lysine-binding sites of plasminogen and plasmin so that the latter is not able to bind to fibrin and lyse it. It is a specific antidote for fibrinolytic agents and has been used in many hyperplasminaemic states associated with excessive intravascular fibrinolysis resulting in bleeding. The primary indication of EACA is to counteract the effect of fibrinolytic drugs and bleeding due to their use. In haemophiliacs, it has adjunctive value for controlling bleeding due to tooth extraction, prostatectomy, trauma, etc.

EACA is active orally and can be infused i.v. as well. It is excreted by the kidney. The major concern in the use of EACA is that it can cause intravascular thrombosis. Rapid i.v. injection results in hypotension, bradycardia and may be arrhythmias. Ureteric obstruction may occur due to unlysed clots, and it should be used cautiously when renal function is impaired. Myopathy occurs rarely. The large dose needed is a limitation, and tranexamic acid is mostly preferred.

Initial priming dose is 5 g oral/i.v., followed by 1 g hourly till bleeding stops (max. 30 g in 24 hrs).

AMICAR, HEMOCID, HAMOSTAT 0.5 g tab., 1.25 g/5 ml syr., 5 g/20 ml inj.

Tranexamic acid Like EACA, it binds to the lysine binding site on plasminogen and prevents its combination with fibrin leading to fibrinolysis. It is 7 times more potent than EACA, and is preferred for prevention/control of excessive bleeding due to:

- Fibrinolytic drugs.
- Cardio-pulmonary bypass surgery.
- Tonsillectomy, prostatic surgery, tooth extraction in haemophiliacs.
- Menorrhagia, especially due to IUCD.
- Recurrent epistaxis, hyphema due to ocular trauma, peptic ulcer.

Main side effects are nausea and diarrhoea. Thromboembolic events, disturbed colour vision and allergic reactions are infrequent. Thrombophlebitis of injected vein can occur.

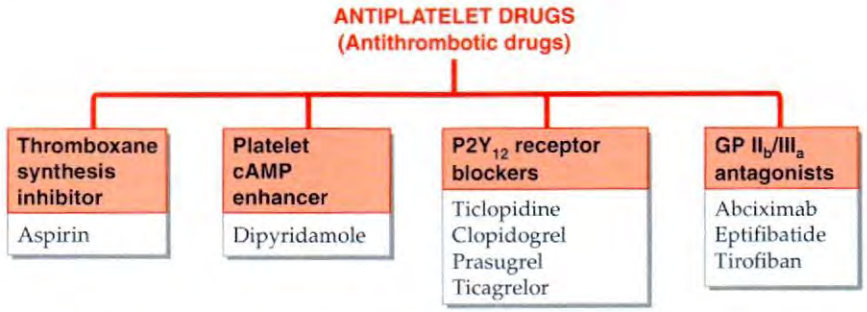
Dose: 1–1.5 g TDS oral, 0.5–1 g TDS by slow i.v. infusion.

DUBATRAN, PAUSE, TRANAREST 500 mg tab, 500 mg/5 ml inj.

ANTIPLATELET DRUGS (Antithrombotic drugs)

These are drugs which interfere with platelet function and are useful in the prophylaxis of thromboembolic disorders.

Platelets express several glycoprotein (GP) integrin receptors on their surface. Reactive proteins like collagen and von Willebrand factor (vWF) are exposed when there is damage to vascular endothelium, and they react respectively with platelet GPI$_a$ and GPI$_b$ receptors. This results in platelet activation and release of proaggregatory and vasoconstrictor mediators like TXA_2, ADP and 5-HT. The platelet GPII$_b$/III$_a$ receptor undergoes a conformational change favouring binding of fibrinogen and vWF that crosslink platelets inducing aggregation and anchorage to vessel wall/other surfaces. Thus, a 'platelet plug' is formed. In veins, due to sluggish blood flow, a fibrinous tail is formed which traps RBCs 'the red tail'. In arteries, platelet mass is the main constituent of the thrombus. Antiplatelet drugs are, therefore, more useful in arterial thrombosis, while anticoagulants are more effective in venous thrombosis.



Prostacyclin (PGI_2), synthesized in the intima of blood vessels, is a strong inhibitor of platelet aggregation. A balance between TXA_2 released from platelets and PGI_2 released from vessel wall appears to control intravascular thrombus formation. Platelets also play a role in atherogenesis.

In the above scheme, various drugs act on different targets to interfere with platelet function. Therefore, given together, their actions are synergistic. The clinically important antiplatelet drugs are classified in the chart:

Aspirin It acetylates the enzyme COX1 and TX-synthase—inactivating them irreversibly. TXA_2 activates platelets to change shape and release mediator rich granules which promote aggregation. Because TXA_2 is the major arachidonic acid product generated by platelets, and that platelets are exposed to aspirin in the portal circulation before it is deacetylated during first pass in the liver, and because platelets cannot synthesize fresh enzyme (have no nuclei), TXA_2 formation is suppressed at very low doses and till fresh platelets are formed. Thus, aspirin induced prolongation of bleeding time lasts for 5–7 days. Effect of daily doses cumulates and it has been shown that doses as low as 40 mg/day have some effect on platelet aggregation. Maximal inhibition of platelet function occurs at 75–150 mg aspirin per day. The American (ACC/AHA)* guidelines recommend a dose of 75–162 mg/day for long-term aspirin prophylaxis. However, aspirin may not effectively inhibit platelet aggregation in certain individuals, who are labelled as 'aspirin resistant'.

Inhibition of COX-1 by aspirin in vessel wall decreases PGI_2 synthesis as well. However, since intimal cells can synthesize fresh enzyme, COX activity returns rapidly. It is possible that at low doses (75–150 mg/day or 300 mg twice weekly), TXA_2 formation by platelets is selectively suppressed, whereas higher doses (> 900 mg/day) may decrease both TXA_2 and PGI_2 production.

Aspirin inhibits the release of ADP from platelets and their sticking to each other, but has no effect on platelet survival time and their adhesion to damaged vessel wall.

ASA 50 mg tab., COLSPRIN, DISPRIN CV-100: aspirin 100 mg soluble tab, LOPRIN 75 mg tab, ASPICOT 80 mg tab, ECOSPRIN 75, 150 mg tab.

Other NSAIDs are reversible inhibitors of COX, produce short-lasting inhibition of platelet function—are not clinically useful.

Dipyridamole It is a vasodilator that was introduced for angina pectoris (*see* Ch. 40). It inhibits phosphodiesterase as well as blocks uptake of adenosine to increase platelet cAMP which in turn potentiates PGI_2 and interferes with aggregation. Levels of TXA_2 or PGI_2, are not altered, but platelet survival time reduced by disease is normalized.

Dipyridamole alone has little clinically significant effect, but improves the response to warfarin, along with which it is used to decrease the incidence of thromboembolism in patients with prosthetic heart valves.

Dipyridamole has also been used to enhance the antiplatelet action of aspirin. This combination may additionally lower the risk of stroke in patients with transient ischaemic attacks (TIAs),

* ACC/AHA—American College of Cardiology/American Heart Association

but trials have failed to demonstrate additional benefit in prophylaxis of MI.

Dose: 150–300 mg/day. PERSANTIN 25, 100 mg tabs, THROMBONIL 75, 100 mg tabs, DYNASPRIN: dipyridamole 75 mg + aspirin 60 mg e.c. tab., CARDIWELL PLUS: dipyridamole 75 mg + aspirin 40 mg tab.

Ticlopidine It is the first thienopyridine drug that acts by blocking the $P2Y_{12}$ type of purinergic receptors on the surface of platelets and inhibits ADP-induced aggregation. Ticlopidine produced beneficial effects in TIAs, stroke prevention, UA, secondary prophylaxis of MI, and synergized with aspirin to lower the incidence of restenosis after PCI and stent thrombosis. However, it produced serious adverse effects like neutropenia, thrombocytopenia, haemolysis, jaundice, and has been superseded by other $P2Y_{12}$ inhibitors (clopidogrel, etc.). *Dose*: 250 mg BD with meals; effect persists several days after discontinuation; TYKLID, TICLOVAS, 250 mg tab; ASTIC ticlopidine 250 mg + aspirin 100 mg tab.

Clopidogrel This is a more potent congener of ticlopidine which has similar mechanism of action, i.e. irreversibly blocks the $P2Y_{12}$ type of purinergic receptor on the surface of platelets. This Gi-coupled GPCR mediates ADP-induced platelet aggregation by inhibiting adenylyl cyclase and decreasing cAMP. Clopidogrel resembles ticlopidine in inhibiting platelet function irreversibly, and has the same range of therapeutic efficacy, but is safer and better tolerated (CLASSICS study). While neutropenia occurs in about 1% patients taking ticlopidine, it is rare with clopidogrel. The 'clopidogrel *vs* aspirin in patients at risk of ischaemic events' (CAPRIE) trial has found clopidogrel recipients to have a slightly lower annual risk of primary ischaemic events than aspirin recipients. Combination of clopidogrel and aspirin is synergistic in preventing ischaemic episodes. The CURE trial has reported 20% reduction in MI, stroke and cardiovascular death by addition of clopidogrel to aspirin in cases with UA and NSTEMI. This 'dual antiplatelet therapy' (DAPT) is also utilized for checking restenosis of stented coronaries.

Like ticlopidine, clopidogrel is also a prodrug. About 50% of the ingested dose is absorbed, and only a fraction of this is slowly activated in liver by two step metabolism into an active thiol metabolite involving CYP2C19, while the rest is inactivated by other enzymes. Therefore, it is a slow acting drug; antiplatelet action takes about 4 hours to start and develops over days. Since CYP2C19, exhibits genetic polymorphism, the activation of clopidogrel and consequently its antiplatelet action shows high interindividual variability. Some patients are nonresponsive. Omeprazole, an inhibitor of CYP2C19, reduces metabolic activation of clopidogrel and its antiplatelet action. The action of clopidogrel lasts for 5 days due to irreversible blockade of platelet $P2Y_{12}$ receptors.

The most important adverse effect is bleeding. Addition of aspirin to clopidogrel has been found to double the incidence of serious bleeding among high risk stroke patients (MATCH study). However, neutropenia, thrombocytopenia and other bone marrow toxicity is rare. Side effects are diarrhoea, epigastric pain and rashes. *Dose:* 300 mg loading, then 75 mg OD; CLODREL, CLOPILET, DEPLATT 75 mg tab.

Prasugrel This is a newer more potent and faster acting $P2Y_{12}$ purinergic receptor blocker, that is being increasingly used in ACS as well as when strong antiplatelet action is required. Like its predecessors, it is also a prodrug, but is more rapidly absorbed. It is also more rapidly and more completely activated, resulting in faster and more consistent platelet inhibition. Though CYP2C19 is involved in activation of prasugrel as well, it is a faster one step process, and genetic polymorphism related decrease in response, or interference by omeprazole treatment has not been prominent. Recovery of platelets from prasugrel action takes longer (7 days) than with clopidogrel (5 days).

Because of rapid action, prasugrel is particularly suitable for use in STEMI. It is the preferred thienopyridine in ACS to cover angioplasty with or without stent placement. The TRITON trial compared prasugrel with clopidogrel in STEMI and NSTEMI. There was 19% greater reduction in death from cardiovascular causes in the prasugrel group. Superior clinical outcomes and reduction in stent thrombosis have been obtained with prasugrel. Bleeding complications are also

more frequent and more serious. Patients with history of ischaemic stroke and TIAs are at greater risk of intracranial haemorrhage. Prasugrel is contraindicated in such patients.

Dose: Loading dose 60 mg, followed by 10 mg OD; elderly or those <60 kg body weight 5 mg OD.

PRASULET, PRASUSAFE, PRASUREL 5 mg, 10 mg tabs.

Ticagrelor It is the latest $P2Y_{12}$ receptor inhibitor which acts directly without needing metabolic activation. Ticagrelor is not a thienopyridine but blocks platelet aggregation by inhibiting binding of ADP to the $P2Y_{12}$ receptor. Unlike clopidogrel and prasugrel the action of ticagrelor is reversible. Thus, it has a faster onset and quicker offset of action; the biological t½ is 12 hours, and it needs twice daily administration. The PLATO trial compared ticagrelor with clopidogrel (both combined with low dose aspirin) in >18000 patients with ACS and reported lower cardiovascular mortality as well as all cause mortality with ticagrelor. The risk of intracranial bleeding was higher with ticagrelor, but that of all major bleeds was similar.

It has been observed that high dose aspirin may interfere with the action of ticagrelor, but not low dose aspirin. The European guidelines now recommend that all patients at high risk of ACS be given prophylactic ticagrelor. Side effects are dizziness, nausea, shortness of breath, tightness in chest and irregular pulse. Thus, ticagrelor is a faster, more potent and more consistent acting $P2Y_{12}$ inhibitor antiplatelet drug.

Dose: For ACS requiring urgent PCI 180 mg loading dose followed by 90 mg BD; may be continued for upto 12 months

BRILINTA 90 mg tab

Glycoprotein (GP) II_b/III_a receptor antagonists

GP II_b/III_a antagonists are a newer class of potent platelet aggregation inhibitors which act by blocking the key receptor involved in platelet aggregation. The $GPII_b/III_a$ is an adhesive receptor (integrin) on platelet surface for fibrinogen and vWF through which agonists like collagen, thrombin, TXA_2, ADP, etc. finally induce platelet aggregation. Thus, GP II_b/III_a antagonists block aggregation induced by all platelet agonists. They are used only in patients with ACS and to cover PCI or coronary artery bypass grafting (CABG).

Abciximab It is the Fab fragment of a chimeric monoclonal antibody against GP II_b/III_a protein, but is relatively nonspecific and binds to some other surface proteins as well. Given along with aspirin + heparin during PCI it has markedly reduced the incidence of restenosis, subsequent MI and death. In the ISAR-REACT2 trial addition of abciximab to clopidogrel (600 mg oral loading dose) for PCI in high-risk ACS patients, reduced ischaemic events by 25%. After a bolus dose, platelet aggregation remains inhibited for 12–24 hr, while the remaining antibody is cleared from blood with a t½ of 10–30 min.

Dose: 0.25 mg/kg i.v. 10–60 min before PCI, followed by 10 µg/min for 12 hr. REOPRO, FAXIMAB 2 mg/ml in 5 ml vial.

Abciximab is nonantigenic. The main risk is haemorrhage, incidence of which can be reduced by carefully managing the concomitant heparin therapy. Thrombocytopenia is another complication. It should not be used second time, since risk of thrombocytopenia increases. Constipation, ileus and arrhythmias can occur. It is expensive, but is being used in unstable angina and as adjuvant to coronary thrombolysis/PCI with stent placement.

Eptifibatide It is a synthetic cyclic peptide that selectively binds to platelet surface $GPII_b/III_a$ receptor and inhibits platelet aggregation. Though its plasma t½ (2.5 hours) is longer than that of abciximab, platelet inhibition reverses in a shorter time (within 6–10 hours) because it quickly dissociates from the receptor. Infused i.v., eptifibatide is indicated in:

Unstable angina: 180 µg/kg i.v. bolus, followed by 2 µg/kg/min infusion upto 72 hours.

Coronary angioplasty: 180 µg/kg i.v. bolus immediately before procedure; follow with 2 µg/kg/min for 12–24 hours.

CLOTIDE, COROMAX, UNIGRILIN, EPTIFAB 20 mg/10 ml and 75 mg/100 ml vials.

Aspirin and heparin are generally given concurrently.

Bleeding and thrombocytopenia are the major adverse effects. Rashes and anaphylaxis are rare.

Tirofiban This is a nonpeptide but specific $GPII_b/III_a$ antagonist that is similar in properties to eptifibatide. Its plasma t½ is 2 hours, and it dissociates rapidly from the receptors. The indications and adverse effects are also similar to eptifibatide.

Acute coronary syndromes undergoing PCI: 0.4 µg/kg/min for 30 min followed by 0.1 µg/kg/min for upto 48 hours. If angioplasty is performed, infusion to continue till 12–24 hours thereafter.

AGGRAMED, AGGRITOR, AGGRIBLOC 5 mg/100 ml infusion. TIROBAN 12.5 mg/50 ml and 5 mg/100 ml inj.

Uses of antiplatelet drugs

The aim of using antiplatelet drugs is to prevent intravascular thrombosis and embolization, with minimal risk of haemorrhage. The intensity of antiplatelet therapy is selected according to the thrombotic influences present in a patient. Those with CAD or risk factors for stroke are generally given a single drug (aspirin/clopidogrel). For indications like ACS, maintenance of vascular recanalization, stent placement, vessel grafting, etc. potent inhibition of platelet function is required. This is provided by combining two antiplatelet drugs which act by different mechanisms (dual antiplatelet therapy).

1. *Coronary artery disease* On the basis of trials in post-MI patients as well as in those with no such history, it is recommended that aspirin 75–150 mg/day be given to all individuals with evidence of coronary artery disease and in those with risk factors for the same, but routine use in the whole population is not warranted. Primary prevention of ischaemia with aspirin is of no proven benefit. It reduces the incidence of fatal as well as nonfatal MI, but increases the risk of cerebral haemorrhage. Clopidogrel is an alternative to aspirin in symptomatic patients of ischaemia. Continued aspirin/clopidogrel prophylaxis in post-MI patients clearly prevents reinfarction and reduces mortality.

2. *Acute coronary syndromes (ACSs)* These comprise of a range of acute cardiac ischaemic states from unstable angina (UA) to non-ST elevation myocardial infarction (NSTEMI) to STEMI (*see* p. 602).

The coronary obstruction in UA and NSTEMI is partial, while that in STEMI is total. UA and NSTEMI are differentiated on the basis of absence or presence of laboratory markers of cardiac myocyte necrosis (myoglobin, CK-MB, troponin I, etc.). The ischaemic status is often dynamic and the patient may rapidly shift from one category to the next.

Soluble aspirin (325 mg oral) and a LMW heparin (s.c.) are given at presentation to all patients with ACS.

Unstable angina (UA) Aspirin reduces the risk of progression to MI and sudden death. Clopidogrel is generally combined with aspirin, or may be used as alternative if aspirin cannot be given. For maximum protection the antiplatelet drugs are supplemented with LMW heparin followed by warfarin.

NSTEMI Patients of NSTEMI who are managed without PCI/thrombolysis are generally put on a combination of aspirin + clopidogrel or ticagrelor, which is continued for upto one year.

STEMI Primary PCI with or without stent placement is the procedure of choice for all STEMI as well as high risk NSTEMI patients who present within 12 hours. Prasugrel or ticagrelor + aspirin is the antiplatelet regimen most commonly selected for patients who are to undergo PCI. Prasugrel and ticagrelor act rapidly and more predictably than clopidogrel. Prasugrel is also perferred over clopidogrel in diabetics. The $GPII_b/III_a$ antagonists are the most powerful antiplatelet drugs. They are combined with aspirin for high risk patients undergoing PCI. Abciximab/eptifibatide/tirofiban infused i.v. along with oral aspirin and s.c. heparin markedly reduce incidence of restenosis and subsequent MI after coronary angioplasty. The $GPII_b/III_a$ antagonists are infused for a maximum of 72 hours.

Aspirin and/or clopidogrel/ticagrelor are routinely given to ACS patients treated with thrombolysis. Coronary artery bypass surgery is

also covered by intensive antiplatelet regimen including aspirin + $GPII_b/III_a$ antagonists/prasugrel.

The patency of recanalized coronary artery or implanted vessel is improved and incidence of reocclusion is reduced by continuing aspirin + clopidogrel/prasugrel/ticagrelor for upto 12 months. Dual antiplatelet therapy (DAPT) is recommended after stent placement. Prasugrel is used when stent thrombosis occurs during clopidogrel treatment.

3. *Cerebrovascular disease* Antiplatelet drugs do not alter the course of stroke due to cerebral thrombosis. However, aspirin has reduced the incidence of TIAs and of stroke in patients with TIAs. Occurrence of stroke is also reduced in patients with persistent atrial fibrillation and in those with history of stroke in the past. Aspirin or clopidogrel is given to all patients of TIAs who are not to be treated with anticoagulants. Though short-term use of aspirin + clopidogrel DAPT may be beneficial, long-term use of the combination increases the risk of haemorrhage. The European stroke prevention study-2 (ESPS) has found combination of dipyridamole with low dose aspirin to be synergistic in secondary prevention of stroke.

4. *Prosthetic heart valves and arteriovenous shunts* Antiplatelet drugs, used with warfarin reduce formation of microthrombi on artificial heart valves and the incidence of embolism. Aspirin is clearly effective but increases risk of bleeding due to warfarin. Dipyridamole does not increase bleeding risk, but incidence of thromboembolism is reduced when it is combined with an oral anticoagulant. Antiplatelet drugs also prolong the patency of chronic arteriovenous shunts implanted for haemodialysis and of vascular grafts.

5. *Venous thromboembolism* Anticoagulants are routinely used in DVT and PE. Trials have shown antiplatelet drugs also to have a prophylactic effect, but their relative value in comparison to, or in addition to anticoagulants is not established; they are infrequently used.

6. *Peripheral vascular disease* Aspirin/clopidogrel may produce some improvement in intermittent claudication and reduce the incidence of thromboembolism.

PROBLEM DIRECTED STUDY

45.1 A 35-year-old woman was on maintenance therapy with warfarin for leg vein thrombosis that she had developed during a complicated delivery 2 months back. The dose was adjusted by repeated measurement of INR, and for the last one month it was maintained between 2.4–2.8 with 4 mg taken daily at bed time. She developed a pelvic infection for which she was admitted to the hospital and given Inj. Ceftriaxone 1 g i.v. 8 hourly. On the 3rd day she started bleeding per-vaginum and reported passing dark urine. The haemoglobin level fell to 9.0 g/dl, while on admission 3 days back, it was 11.0 g/dl. The INR was measured to be 5.4.

(a) What could be the cause of bleeding per-vaginum, passing dark urine; fall in Hb level and rise in INR value? Could this complication be prevented?

(b) How should this patient be managed?

(see Appendix-1 for solution)

Chapter 46 Hypolipidaemic Drugs

Hypolipidaemic drugs are those which lower the levels of lipids and lipoproteins in blood.

The hypolipidaemic drugs have attracted considerable attention because of their potential to prevent cardiovascular disease by retarding the accelerated atherosclerosis in hyperlipidaemic individuals.

Lipid transport

Lipids are carried in plasma in lipoproteins after getting associated with several apoproteins; plasma lipid concentrations are dependent on the concentration of lipoproteins. The hydrophobic core of lipoprotein globules consists of triglycerides (TGs) or cholesteryl esters (CHEs) while the outer polar layer has phospholipids, free cholesterol (CH) and apoproteins. The lipoproteins have been divided into 6 classes on the basis of their particle size and density. They also differ in the nature of apoproteins, the ratio of TG and CHE, tissue of origin and fate. These are given in Table 46.1.

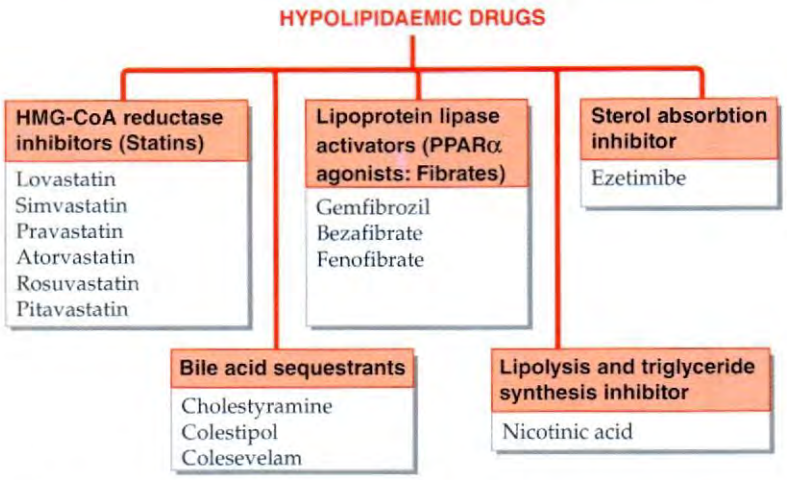
Dietary lipids are absorbed in the intestine with the help of bile acids. Chylomicrons (Chy) are formed and passed into lacteals—reach blood stream *via* thoracic duct. During their passage through capillaries, the endothelium bound lipoprotein lipase hydrolyses the TGs into fatty acids which pass into muscle cells to be utilized as energy source and in fat cells to be reconverted into TGs and stored. The remaining part—chylomicron remnant (Chy. rem.) containing mainly CHE and little TG is engulfed by liver cells, which have receptors for the surface apoproteins of Chy. rem., and digested. Free CH that is liberated is either stored in liver cells after reesterification or incorporated into a different lipoprotein and released in blood or excreted in bile as CH or bile acids.

Liver secretes *very low density lipoproteins (VLDL)* containing mainly TG and some CHE into blood. VLDL is acted upon by endothelial lipoprotein lipase in the same

Table 46.1: Characteristics and function of plasma lipoproteins

	Lipoprotein class	*Diameter (nm)*	*Lipid contained*	*Source of lipid*	*Function*
1.	Chy.	100–500	TG >> CHE	Diet	Dietary TG transport
2.	Chy. rem.	30–50	CHE >> TG	Diet, Chy.	Dietary CH transport
3.	VLDL	40–80	TG >> CHE	Liver	Endogenous TG transport
4.	IDL	30–35	CHE ≥ TG	VLDL	Transport CHE and TG to liver, source of LDL
5.	LDL	20–25	CHE	IDL	Transport CH to tissues and liver
6.	HDL	5–10	Phospholipid, CHE	Tissues, cell memb.	Removal of CH from tissues

Chy—Chylomicrons; Chy. rem.—Chylomicron remnant; VLDL—Very low density lipoprotein; IDL—Intermediate density lipoprotein; LDL—Low density lipoprotein; HDL—High density lipoprotein; CHE—Cholesteryl esters; TG—Triglyceride; CH—Cholesterol



way as on Chy and the fatty acids pass into adipose tissue and muscle; the remnant called *intermediate density lipoprotein* (IDL) now contains more CHE than TG. About half of the IDL is taken back by the liver cells by attachment to another receptor (LDL receptor), while the rest loses the remaining TGs gradually and becomes *low density lipoprotein* (LDL) containing only CHE. The LDL circulates in plasma for a long time; its uptake into liver and other tissues is dependent on the need for CH. The rate of LDL uptake is regulated by the rate of LDL receptor synthesis in a particular tissue. Cholesterol is also synthesized in the body by reduction of 3-Hydroxy-3 methyl glutaryl coenzyme A (HMG-CoA) to mevalonate (rate limiting step).

The CHE of LDL is deesterified and used mainly for cell membrane formation. The CH released into blood from degradation of membranes is rapidly incorporated in *high density lipoproteins* (HDL), esterified with the help of an enzyme lecithin: cholesterol acyltransferase (LCAT) and transferred back to VLDL or IDL, completing the cycle.

The excess lipoproteins in plasma are phagocytosed by macrophages for disposal. When too much of lipoproteins have to be degraded in this manner, CH is deposited in *atheromas* (in arterial walls) and *xanthomas* (in skin and tendons). Raised levels of VLDL, IDL and LDL (rarely Chy and Chy. rem. also) are atherogenic, while HDL may be protective, because HDL facilitates removal of CH from tissues.

Hyperlipoproteinaemias can be:

(i) *Secondary*: associated with diabetes, myxoedema, nephrotic syndrome, chronic alcoholism, drugs (corticosteroids, oral contraceptives, β blockers) etc.

(ii) *Primary*: due to:

(a) A single gene defect: is familial and called 'monogenic' or *genetic*.

(b) Multiple genetic, dietary and physical activity related causes: 'polygenic' or *multifactorial*.

On the whole, LDL is the primary carrier of plasma CHE, and VLDL that of TGs. The important features of major types of hyperlipoproteinaemias are given in Table 46.2.

The mechanism of action and profile of lipid lowering effect of important hypolipidaemic drugs is summarized in Table 46.3.

HMG-COA REDUCTASE INHIBITORS (Statins)

Introduced in the 1980s, this class of compounds are the most efficacious, most commonly used and best tolerated hypolipidaemic drugs. They competitively inhibit conversion of 3-Hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) to mevalonate (rate limiting step in CH synthesis) by the enzyme HMG-CoA reductase. Therapeutic doses reduce CH synthesis by 20–50%. This results in compensatory increase in LDL receptor expression on liver cells and causes increased receptor mediated uptake and catabolism of IDL and LDL. Over long-term, feedback induction of HMG-CoA reductase tends to increase CH synthesis, but a steady-state is finally attained with a dose-dependent lowering of LDL-CH levels.

Different statins differ in their potency and maximal efficacy in reducing LDL-CH. The dose dependent effect of various statins on plasma

Table 46.2: Types of primary hyperlipoproteinaemias

Type	Disorder	Cause	Occurrence	Elevated plasma lipoprotein	Plasma lipids	
					CH	TG
I	Familial lipoprotein lipase deficiency	G	Very rare	Chylomicron	↑↑	↑↑↑
IIa	Familial hypercholesterolaemia	G	Less common	LDL	↑↑	N
IIb	Polygenic hypercholesterolaemia	MF	Commonest	LDL	↑	N
III	Familial dysbetalipoproteinaemia	G	Rare	IDL, Chy. rem.	↑	↑
IV	Hypertriglyceridaemia	MF, G	Common	VLDL	N	↑↑
V	Familial combined hyperlipidaemia	G	Less common	VLDL, LDL	↑	↑

CH—Cholesterol; TG—Triglycerides; G—Genetic; MF—Multifactorial; Chy. rem.—Chylomicron remnants; VLDL—Very low density lipoprotein; IDL—Intermediate density lipoprotein; LDL—Low density lipoprotein.
The genetic defect in some of the monogenic disorders are:
Type I: absence of lipoprotein lipase—TG in Chy cannot be utilized.
Type IIa: deficiency of LDL receptor—LDL and IDL are taken up very slowly by liver and tissues.
Type III: the apoprotein in IDL and Chy. rem. (apoE) is abnormal, these particles are cleared at a lower rate.
Type IV: this type of hypertriglyceridaemia is both multifactorial and monogenic, the former is more prevalent than the latter.

LDL-CH level is presented in Table 46.4. While lovastatin, pravastatin and simvastatin are low-to-moderate efficacy (20–45% LDL reduction) and potency statins, atorvastatin and rosuvastatin are high efficacy (upto 55% LDL-CH reduction) compounds. Though dose-to-dose most potent, efficacy of pitavastatin is limited by its ceiling dose of 4 mg/day. All statins produce peak LDL-CH lowering after 1–2 weeks therapy. Hepatic synthesis of VLDL is concurrently reduced and its removal from plasma is enhanced. A concurrent fall by 10–30% in plasma TG level, probably due to reduction of VLDL, occurs. A modest rise in HDL-CH by 5–15% is also noted. Statins are effective in secondary hypercholesterolaemias as well. The more efficacious statins (atorvastatin, rosuvastatin) given at their higher doses effectively reduce TGs (by 25% to 35%) when TG levels are moderately raised, but not when they are markedly raised.

Because HMG-CoA reductase activity is maximum at midnight, all statins are administered at bed time to obtain maximum effectiveness. However, this is not necessary for atorvastatin and rosuvastatin, which have long plasma t½.

All statins, except rosuvastatin are metabolized primarily by CYP3A4. Inhibitors and inducers of this isoenzyme respectively increase and decrease statin blood levels.

Lovastatin This is the first clinically used statin, which is lipophilic and given orally in the precursor lactone form. Absorption is incomplete and first pass metabolism is extensive. Metabolites are excreted mainly in bile. The t½ is short (2–4 hours). The LDL-CH lowering efficacy is low-to-moderate.

Dose: 10–40 mg/day (max. 80 mg).
ROVACOR, AZTATIN, LOVAMEG 10, 20 mg tabs.

Simvastatin It is nearly twice as potent as lovastatin; also more efficacious. A greater rise in HDL-CH (when low) has been noted with simvastatin than lovastatin or pravastatin. Like lovastatin, it is lipophilic and given in the lactone precursor form. Oral absorption is better and first pass metabolism extensive; t½ is 2–3 hr.

Dose: 10–40 mg/day (max. 80 mg)
SIMVOTIN, SIMCARD, ZOSTA 5, 10, 20 mg tabs.

Higher risk of myopathy has been noted with 80 mg/day dose of simvastatin. This dose should

Table 46.3: Mechanism of action and pattern of lipid lowering effect of hypolipidaemic drugs

Drug (daily dose)	*Mechanism of action*	*Effect on plasma lipids (%)*
HMG-CoA reductase inhibitors		
Lovastatin (20–80 mg) Simvastatin (10–40 mg) Atorvastatin (10–80 mg) Rosuvastatin (5–40 mg) Pravastatin (10–80 mg) Pitavastatin (1–4 mg)	↓ CH synthesis by inhibition of rate limiting HMG-CoA reductase	LDL ↓ 20–55 HDL ↑ 5–15 TG ↓ 10–35
Bile acid sequestrants		
Cholestyramine (4–16 g) Colestipol (5–30 g) Colesevelam (3–4 g)	↓ bile acid absorption, ↑ hepatic conversion of CH to bile acids, ↑ LDL receptors on hepatocytes	LDL ↓ 15–25 HDL ↑ 3–5 TG not affected, may ↑ in some
Fibric acid derivatives		
Gemfibrozil (1200 mg) Bezafibrate (600 mg) Fenofibrate (200 mg)	↑ Activity of lipoprotein lipase, ↓ release of fatty acids from adipose tissue	LDL ↓ 5–15* HDL ↑ 10–20 TG ↓ 20–50
Nicotinic acid (2–4 g)	↓ Production of VLDL,↓ lipolysis in adipocytes	LDL ↓ 15–25 HDL ↑ 20–35 TG ↓ 20–50
Ezetimibe (10 mg)	↓ intestinal absorption of CH and phytosterols	LDL ↓15–20% HDL ↑ 5% TG –

* Gemfibrozil may ↑ LDL-CH when TG levels are high; bezafibrate and fenofibrate not likely to raise LDL-CH

be given only when there is no alternative, and expected benefits outweigh risks.

Pravastatin It is hydrophilic and given in the active form. The LDL-CH lowering potency and efficacy is almost similar to lovastatin. An additional action of decrease in plasma fibrinogen level has been observed. The t½ is 1–3 hours.
PRAVATOR 10, 20 mg tabs.

Atorvastatin This is a high efficacy and one of the most commonly used statin capable of lowering LDL-CH by 55–60% at the 80 mg/day ceiling dose. At this dose a greater reduction in TGs is noted if the same was raised at baseline. Atorvastatin has a much longer plasma t½ of 14–18 hr, and has additional antioxidant property.
Dose: 10-40 mg/day (max. 80 mg)
AZTOR, ATORVA, ATORLIP 5, 10, 20 mg tabs.

Rosuvastatin This is another newer commonly used high potency and high efficacy statin (10 mg rosuvastatin ≃ 20 mg atorvastatin), with a plasma t½ of 18–24 hours. Greater LDL-CH reduction can be obtained in severe hypercholesterolaemia; partly due to its longer persistence in the plasma. In patients with raised TG levels, rosuvastatin raises HDL-CH by 10–15% (greater rise than other statins).
Dose: 5–20 mg OD, (max 40 mg/day)
ROSUVAS, ROSYN, ROZUTIN 5, 10, 20 mg tabs.

Pitavastatin This is the latest and dose-to-dose the most potent statin. However, no specific advantage compared to other statins has been demonstrated, and experience with its use is limited. A ceiling response of 40% LDL-CH reduction with the maximum recommended daily dose of 4 mg is noted. The plasma t½ is 12 hours. Use of pitavastatin in combination with gemfibrozil should be avoided, as the latter decreases its clearance.
Dose: 1–4 mg per day; FLOVAS 1.0, 2.0 mg tabs.

Table 46.4: Dose-dependent lowering of plasma low-density lipoprotein cholesterol (LDL-CH) by statins**

Dose mg/day	Reduction in plasma LDL-CH				
	Lovastatin	*Pravastatin*	*Simvastatin*	*Atorvastatin*	*Rosuvastatin*
5	–	–	–	–	38%
10	–	20%	27%	37%	43%
20	25%	24%	32%	43%	48%
40	32%	29%	37%	49%	53%
80	40%	–	42%*	55%	–

* High risk of myopathy; this dose of simvastatin not advised.
** Based on NICE (National Institute of Health Care Excellence—UK.) guidelines (2014); *nice.org.uk/guidance/cg181*

Adverse effects All statins are remarkably well tolerated; overall incidence of side effects not differing from placebo. Notable side effects are:

Gastrointestinal complaints and headache are usually mild. Rashes and sleep disturbances are uncommon. Rise in serum transaminase can occur, but liver damage is infrequent. Monitoring of liver function is recommended.

Muscle aches are the commonest (10%) side effect. Rise in CPK levels occurs infrequently. Myopathy is the only serious reaction, but is rare (< 1 per 1000). Few fatalities due to rhabdomyolysis are on record. Myopathy and liver injury is more common when nicotinic acid/gemfibrozil or CYP3A4 inhibitor—ketoconazole/erythromycin/cyclosporine/HIV protease inhibitor is given concurrently. Gemfibrozil inhibits the hepatic uptake of statins by the organic anion transporter OATP2 and should not be given with them. Fenofibrate interferes the least with statin uptake/metabolism and should be preferred for combining with them. A lower dose of statin is advisable when a fibrate is given concurrently. Statins should not be given to pregnant women, since there is no data on their safety. A 10% increase in the risk of diabetes has been noted with the use of statins.

Use Statins are the first choice drugs for primary hyperlipidaemias with raised LDL-CH and total CH levels, with or without raised TG levels (Type IIa, IIb, V), as well as for secondary (diabetes, nephrotic syndrome) hypercholesterolaemia. Evidence for efficacy of statins in reducing raised LDL-CH associated mortality and morbidity is robust. Incidence of all types of atherosclerotic cardiovascular disease (ASCVD) including new onset angina, myocardial infarction (MI) or other acute coronary syndromes (ACS), thrombotic stroke, peipheral arterial disease is reduced. Statins also afford secondary prophylaxis of MI in patients who already had an attack.

Beneficial effects in subjects who have raised CH levels but no evidence of CAD may relate to improved coronary artery compliance and atheromatous plaque stabilization due to suppression of macrophage mediated inflammation, reducing chances of plaque rupture and thrombus formation. Improvement in endothelial function due to increased NO production and reduction in LDL oxidation are other putative mechanisms by which statins may exert antiatherosclerotic action. Lately, a reduction in venous thromboembolism, especially following knee surgery, has also been observed with rosuvastatin, and it is being used in post-knee/hip replacement patients. On the basis of these results as well as the excellent patient acceptability, the statins are being increasingly used for primary and secondary hypercholesterolaemia with or without raised TG levels. They are the first choice drugs for dyslipidaemia in diabetics. Statin therapy is continued indefinitely, unless adverse effects occur.

BILE ACID SEQUESTRANTS (Resins)

Cholestyramine, Colestipol and Colesevelam These are basic ion exchange resins supplied in the chloride form.

They are neither digested nor absorbed in the gut: bind bile acids in the intestine interrupting their enterohepatic circulation. Faecal excretion of bile salts and CH (which is absorbed with the help of bile salts) is increased. This indirectly leads to enhanced hepatic metabolism of CH to bile acids. More LDL receptors are expressed on liver cells: clearance of plasma IDL, LDL and indirectly that of VLDL is increased.

Resins have been shown to retard atherosclerosis and coronary events, but no significant effect on total mortality. They are not popular clinically because they are unpalatable, inconvenient, have to be taken in large doses, cause flatulence and other g.i. symptoms, interfere with absorption of many drugs and have poor patient acceptability.

LIPOPROTEIN-LIPASE ACTIVATORS (Fibrates)

The fibrates (isobutyric acid derivatives) primarily activate lipoprotein lipase which is a key enzyme in the degradation of VLDL resulting in lowering of circulating TGs. This effect is exerted through nuclear peroxisome proliferator-activated receptor α (PPARα) that is a gene transcription regulating receptor expressed in liver, fat and muscles. Activation of PPARα enhances lipoprotein lipase synthesis and fatty acid oxidation. PPARα may also mediate enhanced LDL receptor expression in liver seen particularly with second generation fibrates like bezafibrate, fenofibrate. Fibrates decrease hepatic TG synthesis as well.

Drugs in this class primarily lower TG levels by 20–50%, with greater effect when baseline level is higher. This is generally accompanied by 10–15% decrease in LDL-CH and a 10–15% increase in HDL-CH. In some patients with hypertriglyceridaemia LDL-CH may rise, partly because of inability of LDL receptor to clear the excess LDL particles generated by enhanced VLDL catabolism. The increase in HDL-CH is at least in part due to transfer of surface lipid components from catabolized VLDL to HDL, and partly due to increased production of HDL apoproteins (apo A-I, apo A-II) by liver. Gemfibrozil also appears to reduce VLDL secretion by liver.

Gemfibrozil This fibric acid derivative effectively lowers plasma TG level by enhancing breakdown and suppressing hepatic synthesis of TGs. In the 'Helsinki Heart Study' men without known CAD treated with gemfibrozil had a 34% reduction in fatal and nonfatal MI, though overall mortality was not affected. The beneficial effect was restricted to subjects who had high TG levels and lower HDL-CH. That these benefits extend to secondary prevention of coronary events in men with existing CAD and low HDL-CH, has been demonstrated in another trial.

Pharmacokinetics Gemfibrozil is completely absorbed orally, metabolized by glucuronidation and undergoes some enterohepatic circulation. It is excreted in urine; elimination t½ is 1–2 hr.

Adverse effects Common side effects are epigastric distress, loose motions.

Skin rashes, body ache, eosinophilia, impotence, headache and blurred vision have been reported. Myopathy and hepatitis are uncommon. Gemfibrozil + statin increases risk of myopathy and they should not be combined. Risk of CH-gallstones is slightly increased.

Gemfibrozil is contraindicated during pregnancy.

GEMPAR, NORMOLIP 300 mg cap. LOPID 300 mg cap, 600 mg tabs.

Use In a dose of 600 mg BD taken before meals, gemfibrozil is a first line drug for patients with markedly raised TG levels, whether or not CH levels are also raised. Episodes of acute pancreatitis are prevented in patients with chylomicronaemia and severe hypertriglyceridaemia. It is most effective in type III hyperlipoproteinaemia; also beneficial in type IV and type V disease. Patients with raised TG and low HDL-CH levels (as is the case with metabolic syndrome, type 2 diabetes) are the most suitable to be treated with fibrates.

Bezafibrate This second generation fibric acid derivative is an alternative to gemfibrozil in mixed hyperlipidaemias (type III, IV and V). Bezafibrate has not shown propensity to increase LDL-CH in hypertriglyceridaemic patients and appears to have greater LDL-CH lowering action than gemfibrozil. Circulating fibrinogen

and glucose levels may decrease. The 5 year 'Bezafibrate Coronary Atherosclerosis Intervention Trial' (BECAIT) in young male post-MI subjects showed an atherosclerosis slowing effect and reduction in coronary events. The Bezafibrate Infarction Prevention (BIP) registry has also noted reduction in coronary events in subjects with high TG and low HDL-CH levels.

Adverse effects and contraindications are similar to other fibrates. Main side effects are g.i. upset, myalgia, rashes. Dose reduction is needed in elderly and in renal insufficiency. Action of oral anticoagulants may be enhanced.

Dose: 200 mg BD or TDS with meals.

BEZALIP 200 mg tab, 400 mg SR tab.

Fenofibrate Another 2nd generation prodrug fibric acid derivative which has greater HDL–CH raising and greater LDL-CH lowering action than other fibrates: may be more appropriate as an adjunctive drug in subjects with raised LDL-CH levels in addition to raised TG levels. No rise in LDL-CH has been observed in patients with high TG levels. Its t½ is 20 hr. Adverse effects are myalgia, hepatitis, rashes. Cholelithiasis and rhabdomyolysis are rare. Fenofibrate appears to be the most suitable fibrate for combining with statins, because statin metabolism is minimally affected and enhancement of statin myopathy risk is lower. Indications of fenofibrate are similar to that of gemfibrozil.

Dose: 200 mg OD with meals.

FENOLIP, LIPICARD 200 mg cap.

Fibrate therapy should be discontinued after 2 months if an adequate lowering of TG level is not obtained. The National Institute for Health and Care Excellence (NICE) of UK guidelines (2014) discourage routine use of fibrates for primary or secondary prevention of CVD, as well as their prophylactic use in patients with chronic kidney disease (CKD) or diabetes. Combination of a fibrate with a statin for primary or secondary prevention of CVD is also not recommended.

Saroglitazar It is a novel plasma glucose as well as lipid lowering drug that is at present marketed only in India. It is a dual PPARα and PPARγ agonist, but chemically different from thiazolidinediones and fibrates. Saroglitazar has been tested in 3 small clinical trials and one 9 month observational study on diabetic dyslipidemia patients. Plasma TG and total CH was lowered, while HDL-CH increased marginally. Fasting plasma glucose as well as HbA_{1c} also dropped. Side effects were weakness, fever and gastritis. It did not appear to cause edema or weight gain, but the whole adverse effect profile of saroglitazar is still to unfold, particularly because PPAR agonists are known to cause many off-target toxicities. Saroglitazar is currently approved only in India for diabetic dyslipidaemia and hyper-triglyceridaemia not controlled by a statin.

Dose: 4 mg OD

LIPAGLYN 4 mg tab.

LIPOLYSIS AND TRIGLYCERIDE SYNTHESIS INHIBITOR

Nicotinic Acid (Niacin)

It is a B group vitamin (*see* Ch. 69) which in much higher doses reduces plasma lipids. This action is unrelated to its vitamin activity and not present in nicotinamide. When nicotinic acid is given, TGs and VLDL decrease rapidly, followed by a modest fall in LDL-CH and total CH. A 20–50% reduction in plasma TGs and 15–25% reduction in CH levels have been recorded. Nicotinic acid is the most effective drug to raise HDL-CH, probably by decreasing rate of HDL destruction; a 20–35% increase is generally obtained. Relatively lower dose (1 g/day) suffices to raise HDL-CH. Niacin also reduces lipoprotein Lp (a), which is considered more atherogenic.

Nicotinic acid inhibits intracellular lipolysis by lipases in adipocytes and decreases flow of free fatty acids (FFAs) from adipose tissue to liver. This reduces availability of FFAs for production of TGs and VLDL in the liver. A direct inhibition of hepatocyte TG synthesis is also possible. Indirectly, the VLDL degradation products IDL and LDL are also reduced, but no direct effect on CH and bile acid metabolism has been found. Enhanced clearance of TGs by lipoprotein lipase contributes to lowering of plasma TGs.

A cell surface Gi-protein coupled receptor which negatively regulates adipocyte adenylyl cyclase has been found to selectively bind nicotinic acid, and has been called 'niacin receptor' (also termed GPR109A). Nicotinic acid appears to inhibit lipolysis in adipose tissue by decreasing hormone stimulated intracellular cAMP formation through this receptor.

Adverse effects The large doses needed for hypolipidaemic action are poorly tolerated. Only about half of the patients are able to take full doses.

Nicotinic acid is a cutaneous vasodilator: marked flushing, heat and itching (especially in the blush area) occur after every dose. This is associated with release of PGD$_2$ in the skin, and can be minimized by starting with a low dose taken with meals and gradually increasing as tolerance develops. Use of sustained release (SR/ER) tablet also subdues flushing. Aspirin taken before niacin substantially attenuates flushing by inhibiting PG synthesis. *Laropiprant*, a prostanoid receptor inhibitor, is a specific antiflushing drug with no hypolipidaemic action of its own, that has been combined with nicotinic acid to minimize flushing. An ER tablet containing 1.0 g nicotinic acid and 20 mg laropiprant is used in UK and Europe.

Dyspepsia is very common; vomiting and diarrhoea occur when full doses are given. Peptic ulcer may be activated.

Dryness and hyperpigmentation of skin can be troublesome. Other long-term effects are:

Liver dysfunction and jaundice. Serious liver damage is the most important risk.

Hyperglycaemia, precipitation of diabetes (should not be used in diabetics).

Hyperuricaemia and gout, atrial arrhythmias. Niacin is contraindicated during pregnancy and in children.

Interaction Postural hypotension may occur in patients on antihypertensives when they take nicotinic acid.

Risk of myopathy due to statins is increased.

Dose: Start with 100 mg TDS, gradually increase to 2–4 g per day in divided doses. It should be taken just after food to minimize flushing and itching.

NIALIP, NEASYN-SR 375, 500 mg tabs.

Use Nicotinic acid is highly efficacious in hypertriglyceridaemia (type III, IV, V) whether associated with raised CH level or not. It is mostly used to lower VLDL and raise HDL levels, but outcome benefits in terms of ASCVD reduction are uncertain (*see* p. 693).

The NICE guidelines (2014) do not recommend use of nicotinic acid alone or in combination with a statin for primary as well as secondary prevention of CVD. It is also not advised for prophylaxis of CVD in patients with diabetes or CKD.

The most important indication of niacin is to control pancreatitis associated with severe hypertriglyceridaemia, mainly in genetic type IV and type V disorders. Continued use prevents further attacks of pancreatitis. Doses above 2 g/day are poorly tolerated. This dose should seldom be exceeded for maintenance purposes. Because of potential toxicity, use of nicotinic acid is restricted to high-risk cases only.

Acipimox It is a nicotinic acid derivative that is better tolerated, but has weaker effect on plasma lipids.

STEROL ABSORPTION INHIBITOR

Ezetimibe It is a novel drug that acts by inhibiting intestinal absorption of dietary as well as biliary CH and phytosterols by interfering with a specific CH transporter protein NPC1L1 in the intestinal mucosa. There is compensatory increase in hepatic CH synthesis, but LDL-CH level is lowered by 15–20%. The enhanced CH synthesis can be blocked by statins, and the two drugs have synergistic LDL-CH lowering effect.

Due to very poor aqueous solubility, ezetimibe is not absorbed as such. A fraction is absorbed after getting conjugated with glucuronic acid in the intestinal mucosa. This is secreted in bile and undergoes enterohepatic circulation to be mainly excreted in faeces. A plasma t½ of 22 hours has been calculated.

Used alone, ezetimibe is a weak hypocholesterolaemic drug; LDL-CH lowering beyond 15–20% is not obtained by increasing the dose. Its main value is to supplement statins without increasing their dose. The combination of ezetimibe + low dose of a statin is as effective in lowering LDL-CH as high dose of statin alone. Upto 60% decrease in LDL-CH level has been obtained with a combination of simvastatin + ezetimibe. However, in clinical

trials no cardiovascular outcome benefit has yet been demonstrated either by ezetimibe monotherapy or by its combination with a statin. Only in one study (IMPROVE-IT) a small (2%) additional cardiovascular event reduction by adding ezetimibe to simvastatin was noted.

Ezetimibe is primarily indicated as an adjunct to statin treatment of primary hypercholestrolemia, or to supplement dietary measures when statins are not tolerated.

No specific adverse effect, except reversible hepatic dysfunction and rarely myositis has been noted with ezetimibe.

Dose: 10 mg OD; ZETICA, EZEDOC 10 mg tab. BITORVA, LIPIVAS-EZ, LIPONORM-EZ: Atorvastatin 10 mg + ezetimibe 10 mg tab; SIMVAS-EZ, STARSTAT-EZ: Simvastatin 10 mg + ezetimibe 10 mg tabs.

Summary guidelines on the use of hypolipidaemic drugs

Raised plasma CH is a major risk factor for coronary artery disease (CAD) and stroke. Higher the CH level, greater is the risk. Abundant data has confirmed that lowering the level of LDL-CH, when the same is high, results in lowering of cardiovascular mortality and morbidity. Subsequent evidence (HPS, 2002; ASCOT-LLA, 2003 studies)[1,2] has shown that prophylactic use of a statin in CAD/hypertensive patients even with average or lower than average CH levels decreases coronary and stroke events. With the availability of statins which are effective, well tolerated and safe hypolipidaemic drugs, it has become a standard practice to prescribe statin therapy after an acute coronary event irrespective of lipid levels. Evidence that elevated plasma TG level or low plasma HDL-CH level poses independent high risk of CAD and stroke is also quite strong now.

Whereas raised LDL-CH is atherogenic, a higher HDL-CH level is either itself protective or indicates a low atherogenic state.

The US National Cholesterol Education Programme (NCEP) in its third report (2001)[3] delineated the optimal levels of plasma lipids and various grades of hyperlipidaemias (Table 46.5).

Lifestyle modification, such as low fat, low cholesterol diet, limitation of saturated and trans-fats, regular exercise, body weight control, smoking cessation, restriction of alcohol are the primary approach, whether drugs are used or not.

All patients who are at risk of CAD or thrombotic stroke should be put on low dose aspirin prophylaxis unless it is contraindicated. The decision to prescribe hypolipidaemic drugs depends not only on the LDL-CH level and the type of lipid abnormality, but also on associated CAD risk factor(s) or existing CAD or its equivalent like diabetes, peripheral/cerebral vascular disease, etc. in an individual patient (*see* box).

Table 46.5: Interpretation of plasma lipid levels*

	Plasma lipid levels (mg/dl)			
	Total CH	*LDL-CH*	*HDL-CH*	*TGs*
1. Optimal/desirable	< 200	< 100 (< 70 for CAD pts)	> 40 (men) > 50 (women)	< 150
2. Borderline high	200–239	130–159	—	150–199
3. High	≥ 240	160–189	> 60	200–499
4. Very high	—	≥ 190	—	≥ 500

* Adopted from NCEP (2001)

1. HPS (2002, 2004): Heart protection study. *Lancet* (2002) **360**, 7-22, and *Lancet* (2004) **363**, 757-767.
2. ASCOT-LLA (2003): Anglo-Scandinavian cardiac outcomes trial–Lipid lowering arm. *Lancet* (2003) **361**, 1149-1158.
3. NCEP-ATP III (2004 revision). Grundy SM' *et al. Circulation* (2004) **110**, 227-239.

Treatment of high plasma LDL-CH The earlier NCEP (2001) as well as current American (ACC/AHA-2013)* and British (NICE-2014) guidelines recommend that all subjects who require LDL-CH lowering therapy should be treated with a statin. Several studies compared mortality as well as CAD and stroke prevention benefits of standard *vs* intensive CH lowering regimens. Metaanalysis by Cholesterol Treatment Trialists collaborators and others concluded that standard statin therapy lowering LDH-CH by 30–40% reduces cardiovascular events by 30–35%, while intensive LDL-CH lowering by ~50% curtails cardiovascular events by nearly 50%. The JUPITER trial (2008) demonstrated a 44% reduction in combined end-point of stroke, MI, unstable angina and cardiovascular death by using high potency rosuvastatin.

Since statins cause a dose dependent reduction in LDL-CH, the current guidelines divide statin therapy into 3 categories, *viz.* 'high intensity', 'moderate intensity' and 'low intensity'. The LDL-CH reduction achieved by these 3 categories of statin therapy is compiled in Table 46.6. Not withstanding minor differences in criteria** both guidelines recognize atorvastatin (20–80 mg/day) and rosuvastatin (10–40 mg/day) to be the drugs for high intensity statin therapy.

Risk factors for coronary artery disease*

- Men > 45 years, women > 55 years
- Family history of MI/sudden cardiac death before 55 year (men), 65 year (women) age in first degree relative
- Smoking
- Hypertension (BP > 140/90 or use of anti-hypertensive medication)
- Diabetes mellitus[ε]
- Low HDL-CH (< 40 mg/dl in men, < 50 mg/dl in women)
- High LDL-CH (≥ 160 mg/dl) or total CH ≥ 240 mg/dl
- Obesity (BMI > 25 Kg/m^2)[†] or waist > 40" (men), > 35" (women)

* Adopted from the NCEP-ATP III (2001)
[ε] Diabetes is considered equivalent to existing CAD
[†] Not included in NCEP guideline (2001)

Lower doses of these two statins as well as all others (in their theraputic dose range) may be used for low-to-moderate intensity statin therapy.

On the basis of randomized clinical trials (RCTs) and metaanalysis the ACC/AHA guidelines (2013) have identified 4 major groups of subjects who are most likely to obtain a net benefit in terms of ASCVD risk reduction *vs* potential for adverse effects. These groups have

Table 46.6: Daily doses of statins for high, medium and low intensity statin therapy

Statin therapy	*High intensity*		*Moderate intensity*		*Low intensity*	
Guideline source	ACC/AHA[1]	NICE[2]	ACC/AHA	NICE	ACC/AHA	NICE
LDL-CH reduction	≥ 50%	>40%	30–50%	31–40%	<30%	20–30%
1. Atorvastatin	40–80 mg	20–80 mg	10–20 mg	10 mg	–	–
2. Rosuvastatin	20–40 mg	10–40 mg	5–10 mg	5 mg	–	–
3. Simvastatin	–	80 mg*	20–40 mg	20–40 mg	10 mg	10 mg
4. Pravastatin	–	–	40–80 mg	–	10–20 mg	10–40 mg
5. Lovastatin	–	–	40 mg	–	20 mg	–
6. Pitavastatin	–	–	2–4 mg	–	1 mg	–

* Increased risk of myopathy; to be used only when benefits outweigh risks.
1. ACC/AHA: American College of Cardiology/American Heart Association guidelines (2013).
2. NICE: National Institute of Health Care Excellence (UK) guideline. cg181 (2014).

* 2013 ACC/AHA (American College of Cardiology/American Heart Association) guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease in adults. Stone NJ, et. al. *Circulation* (2014), **129** (25 suppl 2);S1-45.

** The difference in criteria may be due to use of non-HDL-CH as LDL-CH by the NICE guidelines.

Indications for high intensity and moderate intensity statin therapy*

Statin benefit group	*Recommended treatment*
1. Clinical ASCVD present	• Age ≤ 75 yr: High intensity statin (moderate intensity statin if high intensity statin not tolerated or C/I) • Age > 75 yr: Moderate intensity statin
2. No clinical ASCVD, but plasma LDL-CH ≥ 190 mg/dL (primary hypercholesterolemia)	• High intensity statin (moderate intensity statin if high intensity statin not tolerated or C/I)
3. Diabetics aged 40–75 yr with LDL-CH 70–189 mg/dL and no clinical ASCVD	• Moderate intensity statin or • High intensity statin if estimated 10 yr ASCVD risk ≥ 7.5%
4. Non-diabetics aged 40–75 yr without clinical ASCVD, with LDL-CH 70–189 mg/dL and estimated 10 yr ASCVD risk ≥ 7.5%	• Moderate-to-high intensity statin therapy

* Based on ACC/AHA guidelines 2013
ASCVD—Atherosclerotic cardiovascular disease; C/I—contraindicated

SECTION 10

been asigned to high intensity and moderate intensity statin therapy which is expected to afford optimum benefit (*see* box). Low intensity statin therapy has not been recommended, but may be appropriate on the basis of tolerability or other criteria in individual patients.

In summary, current indications for statin therapy are:

1. All subjects with ASCVD irrespective of plasma CH level.
2. All subjects with LDL-CH above 190 mg/dL.
3. All diabetics aged 40 years or more.
4. Subjects aged 40 years or more with estimated 10 yr ASCVD risk more than 7.5%, irrespective of plasma CH level.

Intensive lipid lowering by adequate dose of statin is considered to imporove endothetial function and stabilize atherosclerotic plaques in addition to the antiatherosclerotic effect; all of these leading to reduction in CAD, stroke and death.

Treatment of low HDL-CH level Epidemiological data has shown that most patients with premature CAD have low HDL-CH level. Recent trials have shown that statin therapy reduces CAD endpoints in subjects with low HDL-CH even though LDL-CH may be in the normal range. Most low HDL-CH subjects have metabolic syndrome (obesity, hypertriglyceridaemia, insulin resistance/diabetes, hypertension). Therapy directed towards components of this syndrome often helps to normalise HDL-CH. In addition to these measures, the primary approach of therapy in subjects with low HDL-CH is to reduce LDL-CH by intensive statin therapy. None of the currently available lipid modifying drugs has a marked effect to raise HDL-CH, but nicotinic acid has the highest efficacy followed by fibrates. However, addition of these drugs to statin therapy has not been unequivocally demonstrated to further reduce ASCVD. In two recent randomized studies AIM-HIGH (2011) and HPS-2 THRIVE (2014) addition of nicotinic acid to statin therapy failed to improve outcome end points, while adverse effects increased. Patients in these trials already had low LDL-CH levels (due to statin therapy). Therefore, it has been suggested that niacin may benefit if the LDL-CH remains high despite statin therapy.

Treatment of raised TG level: Though elevated plasma TG has been recognized as an independent risk factor for CAD, it remains to be established that specific drug therapy to lower plasma TGs alone improves CAD outcomes. Treatment strategy for hypertriglyceridaemia depends on its severity and upon its cause (obesity, physical inactivity, high carbohydrate–high calorie diet, saturated and trans fats, alcohol, smoking, diabetes, kidney disease, drugs like

corticosteroids, estrogens, high dose β blockers, and genetic disorders). Reversible causes (from the above list) must be addressed first. The initial drug treatment is to reduce LDL-CH by statin therapy. This may itself decrease plasma TG level.

Patients whose fasting plasma TG remains above 500 mg/dL inspite of the above measures run the risk of developing acute pancreatitis, especially after a fatty meal or alcohol intake. Treatment with a specific TG lowering drug, *viz.* nicotinic acid or fibrate (preferably fenofibrate) is indicated in addition to the statin with the aim of preventing acute pancreatitis.

The CAD and stroke preventing benefit of specific TG lowering therapy (by fibrate or niacin) for subjects whose plasma TG remains high (between 200–499 mg/dL) despite statin therapy is uncertain and discretionary.

The NICE (2014) guidelines advise against routine addition of fibrates or nicotinic acid to a statin for preventing ASCVD. Extra vigilance is required to guard against risk of myopathy when niacin or fibrate is added to a statin.

☞ PROBLEM DIRECTED STUDY

46.1 The routine medical checkup of a 50-year-old male, asymptomatic, non-smoker business executive with sendentary job and no past history of coronary artery disease or stroke, as well as no family history of premature cardiac death has yielded the following findings:

Body mass index—27, waist circumferance—92 cm (38"), BP—130/86 mm Hg, fasting blood glucose—98 mg/dl, total plasma cholesterol (CH) 268 mg/dl, LDL-CH 198 mg/dl, HDL-CH 38 mg/dl, serum triglyceride 160 mg/dl. Liver, kidney and thyroid function test values and ECG are within normal limits. There are no remarkable findings on physical examination.

(a) Apart from counselling on life-style modification, does this person require any medication?

(b) In case he needs medication, which drug and dose would be appropriate? What should be the goal of drug therapy?

(see Appendix-1 for solution)

SECTION 11

GASTROINTESTINAL DRUGS

Chapter 47 Drugs for Peptic Ulcer and Gastroesophageal Reflux Disease

PEPTIC ULCER

Peptic ulcer occurs in that part of the gastrointestinal tract (g.i.t.) which is exposed to gastric acid and pepsin, i.e. the stomach and duodenum. The etiology of peptic ulcer is not clearly known. It results probably due to an imbalance between the *aggressive* (acid, pepsin, bile and *H. pylori*) and the *defensive* (gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide, high mucosal blood flow, innate resistance of the mucosal cells) factors. A variety of psychosomatic, humoral and vascular derangements have been implicated and the causative role of *Helicobacter pylori* infection in majority of duodenal ulcers and many gastric ulcers (which are not due to NSAIDs) has been realized.

In *gastric ulcer*, generally acid secretion is normal or low, while deficient mucosal defence (mostly impaired mucus and bicarbonate secretion) plays a greater role. In *duodenal ulcer*, acid secretion is high in about half of the patients but normal in the rest. Notwithstanding whether production of acid is normal or high, it does contribute to ulceration as an aggressive factor, reduction of which is the main approach to ulcer treatment. An understanding of the mechanism and control of gastric acid secretion will elucidate the targets of antisecretory drug action.

Regulation of gastric acid secretion

The mechanisms operating at the gastric parietal cells are summarized in Fig. 47.1. The terminal enzyme H^+K^+ATPase (proton pump) which secretes H^+ ions in the apical canaliculi of parietal cells can be activated by histamine, ACh and gastrin acting *via* their own receptors located on the basolateral membrane of these cells. Out of the three physiological secretagogues, histamine, acting through H_2 receptors, plays the dominant role, because the other two, gastrin and ACh act partly directly and to a greater extent indirectly by releasing histamine from paracrine enterochromaffin-like (ECL) cells called "histaminocytes" located in the oxyntic glands. While H_2 receptors activate H^+K^+ATPase by generating cAMP, muscarinic and gastrin/cholecystokinin (CCK_2) receptors appear to function through the phospholipase C $\rightarrow$ IP_3–DAG pathway that mobilizes intracellular Ca^{2+}. The cAMP mediated proton pump activation also involves Ca^{2+}. The secretomotor response to gastrin and cholinergic agonists is expressed fully only in the presence of cAMP generated by H_2 activation. As such, histamine participates in the acid response to gastrin and ACh at more than one levels, and H_2 antagonists suppress not only histamine, but also ACh, pentagastrin and in fact any gastric acid secretory stimulus.

Gastrin is secreted from the antrum in response to rise in antral pH, food constituents, especially peptides, and vagally mediated reflexes involving ganglion cells of the enteric nervous system (ENS). The postganglionic ENS neurones elicit gastrin release from gastrin secreting 'G' cells by elaborating ACh as well as gastrin releasing peptide (GRP). The dominant muscarinic receptor mediating vagal responses is of the M_1 subtype. Its location on the ganglion cells of the intramural plexuses has been confirmed. The parietal cell and ECL cell muscarinic receptors are of the M_3 subtype. Vagus releases ACh in close proximity to ECL cells and 'G' cells, but apparently at a distance

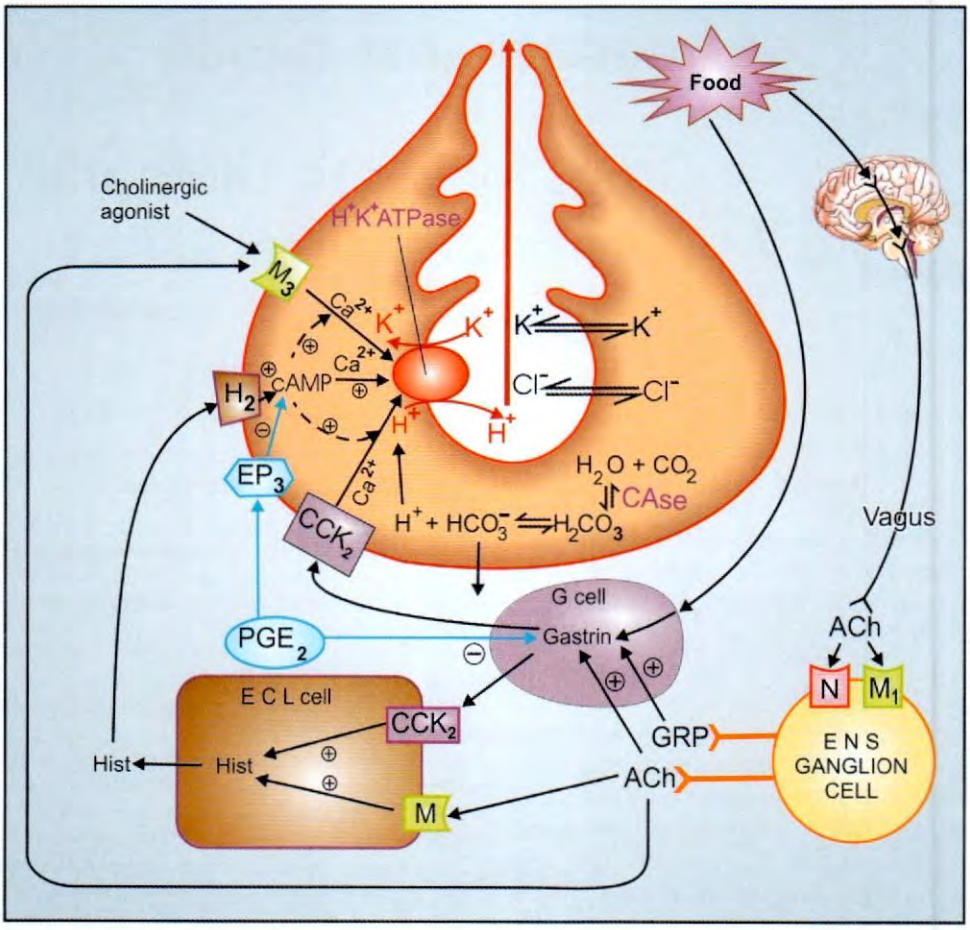


Fig. 47.1: Secretion of HCl by gastric parietal cell and its regulation
C.Ase.—Carbonic anhydrase; Hist.—Histamine; ACh.—Acetylcholine; CCK_2—Gastrin cholecystokinin receptor; M.—Muscarinic receptor; N—Nicotinic receptor; H_2—Histamine H_2 receptor; EP_3—Prostaglandin receptor; ENS—Enteric nervous system; ECL cell—Enterochromaffin-like cell; GRP—Gastrin releasing peptide; + Stimulation; – Inhibition.

from the parietal cells. As such, vagal effects are exerted largely indirectly through histamine and gastrin.

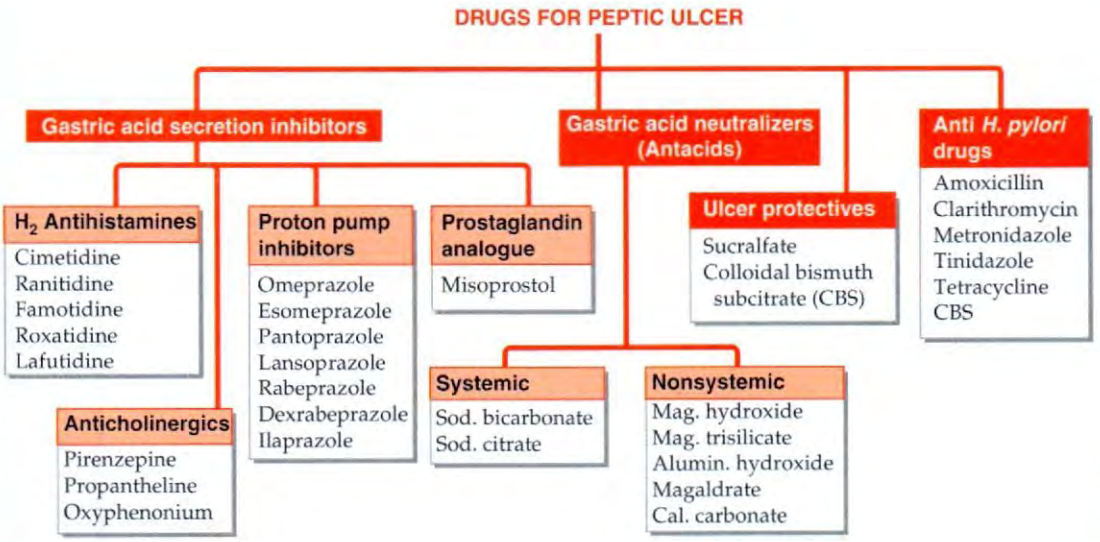
Prostaglandins have been ascribed a "cytoprotective" role in the gastric mucosa by augmenting mucus and bicarbonate secretion from gastric mucosal epithelial cells, as well as other actions. Soon after secretion, the gastric mucus transforms into an adherent gell-like film over the mucosa which traps the secreted HCO_3 ions and prevents their neutralization by creating a barrier for the H^+ ions in the juice. It also sheilds the mucosa from attack by pepsin. PGE_2 produced by gastric mucosa, inhibits acid secretion by opposing cAMP generation (in parietal cells) and gastrin release (from antral G cells).

Peptic ulcer (especially duodenal) is a chronic remitting and relapsing disease lasting several years. The goals of antiulcer therapy are:

- Relief of pain
- Ulcer healing
- Prevention of complications (bleeding, perforation)
- Prevention of relapse.

H_2 ANTAGONISTS

These are the first class of highly effective drugs for acid-peptic disease, but have now been surpassed by proton pump inhibitors (PPIs). Cimetidine was the first H_2 blocker to be introduced clinically and is described as the prototype, though other H_2 blockers are more commonly used now.



1. *H_2 blockade* All clinically used H_2 blockers are competitive antagonists of histamine at the H_2 receptors, but with famotidine the antagonism is partly noncompetitive due to stronger binding to the H_2 receptors. These drugs block histamine-induced gastric secretion, cardiac stimulation (prominent only in isolated preparations, especially in guinea pig), uterine relaxation (in rat) and bronchial relaxation (in sheep). Human bronchial muscles express both contractile H_1 and relaxant H_2 receptors. Normally the H_1 response predominates, but H_2 mediated relaxation can be demonstrated after H_1 blockade. As such, H_2 blockers can potentiate histamine-induced bronchospasm. H_2 blockers attenuate fall in BP due to histamine, especially the late phase response seen with high doses. This is due to blockade of relaxant H_2 receptors located directly on vascular smooth muscle. These antagonists are highly selective: have no effect on H_1 mediated responses or on the action of other transmitters/autacoids.

2. *Gastric secretion* The only significant *in vivo* action of H_2 blockers is marked inhibition of gastric secretion. All phases (basal, psychic, neurogenic, gastric) of secretion are suppressed dose-dependently, but the basal nocturnal acid secretion is suppressed more completely. Secretory response to not only histamine but all other stimuli (ACh, gastrin, insulin, alcohol, food) is attenuated. This reflects the permissive role of histamine in amplifying responses to other secretagogues. The volume of gastric juice, pepsin content and intrinsic factor secretion are all reduced, but the most marked effect is on acid secretion. Despite reduction in intrinsic factor secretion, normal vit B_{12} absorption is not interfered: no vit B_{12} deficiency occurs even after prolonged use.

The usual ulcer healing doses produce 60–70% inhibition of 24 hr acid output. The H_2 blockers have antiulcerogenic effect. Gastric ulceration due to stress and drugs (NSAIDs, cholinergic, histaminergic) is prevented. H_2 blockers have no direct effect on gastric or esophageal motility or on lower esophageal sphincter (LES) tone.

Pharmacokinetics Cimetidine is adequately absorbed orally, though bioavailability is 60–80% due to first pass hepatic metabolism. It crosses placenta and reaches milk, but penetration in brain is poor because of its hydrophilic nature. About 2/3 of a dose is excreted unchanged in urine and bile, the rest as oxidized metabolites. The elimination t½ is 2–3 hr, but duration of action is longer, and to some extent dose dependent. Dose reduction is needed in renal failure.

Adverse effects Cimetidine is well tolerated by most patients: adverse effects occur in < 5%. Side effects like headache, dizziness, bowel upset and dry mouth are generally mild. Rapid or high dose i.v. injection can cause confusional state, hallucinations, convulsions, bradycardia, cardiac arrhythmias or cardiac arrest. The CNS effects mostly occur in elderly patients under intensive care given H_2 blocker to prevent stress ulcers. They are more common with cimetidine than with other H_2 blockers.

Cimetidine (but not other H_2 blockers) has antiandrogenic action (displaces dihydrotestosterone from its cytoplasmic receptor), increases plasma prolactin and inhibits degradation of estradiol by liver. High doses given for long periods have produced gynaecomastia, loss of libido, impotence and short-lasting decrease in sperm count.

Transient elevation of plasma aminotransferases occurs, but hepatotoxicity is rare.

Interactions Cimetidine inhibits several cytochrome P-450 isoenzymes and reduces hepatic blood flow. It inhibits the metabolism of many drugs so that they can accumulate to toxic levels, e.g. theophylline, phenytoin, carbamazepine, phenobarbitone, sulfonylureas, metronidazole, warfarin, imipramine, lidocaine, quinidine.

Antacids reduce absorption of all H_2 blockers. When used concurrently a gap of 2 hr should be allowed. Ketoconazole absorption is decreased by H_2 blockers due to reduced gastric acidity.

Dose: For ulcer healing—400 mg BD or 800 mg at bed time orally; maintenance—400 mg at bed time.
For stress ulcer—50 mg/hr i.v. infusion.

CIMETIDINE 200 mg, 400 mg, 800 mg tabs, 200 mg/2 ml inj., LOCK-2 200 mg tab.

Ranitidine This nonimidazole (has a furan ring in place of imidazole ring) H_2 blocker, has several desirable features compared to cimetidine:

- About 5 times more potent than cimetidine. Though its pharmacokinetic profile and t½ of 2–3 hr is similar to cimetidine, a longer duration of action with greater 24 hr acid suppression is obtained clinically because of higher potency.
- No antiandrogenic action, does not increase prolactin secretion or spare estradiol from hepatic metabolism—no effect on male sexual function or gynaecomastia.
- Lesser permeability into the brain: lower propensity to cause CNS effects. In fact, little effect outside g.i.t. has been observed.
- Less marked inhibition of hepatic metabolism of other drugs; drug interactions mostly have no clinical relevance.
- Overall incidence of side effects is lower: headache, diarrhoea/constipation, dizziness have an incidence similar to placebo.

Dose: for ulcer healing 300 mg at bed time or 150 mg BD; for maintenance 150 mg at bed time. Parenteral dose—50 mg i.m. or slow i.v. inj. every 6–8 hr (rapid i.v. injection can cause hypotension), 0.1–0.25 mg/kg/hr by i.v. infusion has been used for prophylaxis of stress ulcers, particularly during prolonged surgery.
For gastrinoma 300 mg 3–4 times a day.

ULTAC, ZINETAC 150 mg, 300 mg tabs; HISTAC, RANITIN, ACILOC, RANTAC 150 mg, 300 mg tabs, 50 mg/2 ml inj.

Famotidine A thiazole ring containing H_2 blocker which binds tightly to H_2 receptors and exhibits longer duration of action despite an elimination t½ of 2.5–3.5 hr. Some inverse agonistic action on H_2 receptors (in the absence of histamine) has been demonstrated. It is 5–8 times more potent than ranitidine. Antiandrogenic action is absent. Because of low affinity for cytochrome P450 and the low dose, drug metabolism modifying propensity is minimal.

The oral bioavailability of famotidine is 40–50%, and it is excreted by the kidney, 70% in the unchanged form. Incidence of adverse effects is low: only headache, dizziness, bowel upset, rarely disorientation and rash have been reported.

Dose: 40 mg at bed time or 20 mg BD (for healing); 20 mg at bed time for maintenance; upto 480 mg/day in ZE syndrome; parenteral dose 20 mg i.v. 12 hourly or 2 mg/hr i.v. infusion.

FAMTAC, FAMONITE, TOPCID 20 mg, 40 mg tabs; FAMOCID, FACID 20, 40 mg tabs, 20 mg/2 ml inj.

Roxatidine The pharmacodynamic, pharmacokinetic and side effect profile of roxatidine is similar to that of ranitidine, but it is twice as

potent and longer acting. It has no antiandrogenic or cytochrome P450 inhibitory action.

Dose: 150 mg at bed time or 75 mg BD; maintenance 75 mg at bed time.

ROTANE, ZORPEX 75 mg, 150 mg SR tabs.

Lafutidine This second generation H_2 blocker developed in Japan is marketed only in Japan and India. In addition to decreasing acid secretion by H_2 blockade, it is claimed to enhance NO production and improve gastric mucosal blood flow, as well as exert gastro-protective effect by increasing mucus production and somatostatin release. However, any clinical implication of these additional actions is not known. Lafutidine is indicated in dyspepsia, peptic ulcer and GERD.

Side effects noted are nausea, vomiting, bowel upset, dizziness.

Dose: 10 mg after breakfast and after dinner.

LAFAXID 10 mg tab, LAFTID, LAFUDAC 5 mg, 10 mg tabs.

Uses

The H_2 blockers are useful in conditions which are improved by suppression of gastric acid secretion. Given in their recommended doses, all H_2 blockers have similar efficacy. Since PPIs produce more complete suppression of acid, are clinically more effective, and are equally well tolerated and safe, they have largely replaced H_2 blockers. However, H_2 blockers are still used for some conditions.

1. *Peptic ulcer* H_2 blockers are seldom used now to heal peptic ulcers, because PPIs are faster acting, produce more complete pain relief, heal larger percentage of ulcers in a shorter time. With H_2 blockers 60–80% duodenal ulcers heal at 4 weeks and 70–90% heal at 8 weeks. Healing rates are lower (50–75% at 8 weeks) for gastric ulcers. For ulcer healing, suppression of nocturnal secretion by single high bed time dose is equally efficacious and physiologically more sound, than the same dose split into two and given morning and evening. Maintenance therapy with bed time low dose H_2 blocker reduces relapse rate in peptic ulcer.

H_2 blockers are not used now for ulcers caused by NSAIDs, as well as those associated with *H. pylori* infection, because PPIs are more effective and heal ulcers, even in those who are not able to stop the NSAID.

2. *Nonulcer dyspepsia* Characterized by abdominal fullness, gas, bloating, pain, nausea and early satiety, it is mostly functional. Both H_2 blockers and PPIs are commonly used in nonulcer dyspepsia, and appear to be equally efficacious. However, many dyspeptic patients respond to placebo as well. Intermittent acid suppressant medication may be used, particularly in those with epigastric pain or heart burn.

3. *Bleeding from stress ulcers and erosive gastritis* Acutely stressful situations like hepatic coma, severe burns and trauma, prolonged surgery, prolonged intensive care, renal failure, asphyxia neonatorum, etc. are associated with gastric erosions and bleeding. Mucosal ischaemia along with acid is causative. Intravenous infusion of H_2 blockers successfully prevents the gastric lesions and haemorrhage as well as promotes healing of erosions that have occurred. PPIs infused i.v. or given through nasogastric tube are equally or more effective for prophylaxis of bleeding. However, once clinically significant bleeding has occurred, continuous i.v. infusion of PPI is more effective.

4. *Gastroesophageal reflux disease (GERD)* The H_2 blockers are indicated only in mild or stage-1 cases of GERD (*see* p. 707).

5. *Prophylaxis of aspiration pneumonia* H_2 blockers given preoperatively (preferably evening before also) reduce the risk of aspiration of acidic gastric contents during anaesthesia and surgery.

6. *Urticaria* H_2 blockers have adjuvant beneficial action in certain cases of urticaria who do not adequately respond to an H_1 antagonist alone.

PROTON PUMP INHIBITORS (PPIs)

Developed a decade after H_2 blockers, this class of potent acid suppressants are one of the most commonly used drugs now.

Omeprazole It is the prototype member of substituted benzimidazoles which inhibit the final common step in gastric acid secretion. The PPIs have overtaken H_2 blockers for acid-peptic disorders. The only significant pharmacological action of omeprazole is dose dependent suppression of gastric acid secretion; without blocking any transmitter receptor. It is a powerful inhibitor of gastric acid, which can totally abolish HCl secretion, both resting as well as that stimulated by food or any of the secretagogues, without much effect on pepsin, intrinsic factor, juice volume and gastric motility.

Omeprazole is inactive at neutral pH, but at pH < 5 it rearranges to two charged cationic forms (a sulphenic acid and a sulphenamide configurations) that react covalently with SH groups of the H^+K^+ATPase enzyme and inactivate it irreversibly, especially when two molecules of omeprazole react with one molecule of the enzyme. After absorption into bloodstream and subsequent diffusion into the parietal cell, it gets concentrated in the acidic canaliculi because the charged forms generated at the acidic pH are unable to diffuse back. Moreover, it gets tightly bound to the enzyme by covalent bonds. These features and the specific localization of H^+K^+ATPase to the apical membrane of the parietal cells confer high degree of selectivity of action to omeprazole and all other PPIs. Acid secretion resumes only when new H^+K^+ATPase molecules are synthesized (reactivation half time 18 hours). It also inhibits gastric mucosal carbonic anhydrase.

Pharmacokinetics All PPIs are administered orally in enteric coated (e.c.) form to protect them from molecular transformation in the acidic gastric juice. The e.c. tablet or granules filled in capsules should not be broken or crushed before swallowing. Oral bioavailability of omeprazole is ~50% due to acid lability. As the gastric pH rises, a higher fraction (up to 3/4) may be absorbed. Bioavailability of all PPIs is reduced by food. They should be taken in empty stomach when only ~10% of proton pumps are active, followed 1 hour later by a meal to activate the H^+K^+ ATPase at a time when plasma concentration of the PPI is maximal. Omeprazole is highly plasma protein bound, rapidly metabolised in liver by CYP2C19 and CYP3A4 (plasma t½ ~1 hr). It also inhibits CYP2C19. The metabolites are excreted in urine. No dose modification is required in elderly or in patients with renal/hepatic impairment. Because of tight binding to its target enzyme—it can be detected in the gastric mucosa long after its disappearance from plasma. As such, inhibition of HCl secretion occurs within 1 hr, reaches maximum at 2 hr, is still half maximal at 24 hr and lasts for 2–3 days. Since only actively acid secreting proton pumps are inhibited, and only few pumps may be active during the brief interval that the PPI is present (all PPIs have 1–2 hours plasma t½), antisecretory action increases on repeated dosing to reach a plateau after 3–4 days. At steady-state all PPIs produce 80–98% suppression of 24 hour acid output with conventional doses. Secretion resumes gradually over 3–4 days after stopping the drug.

Adverse effects PPIs produce minimal adverse effects and are very safe drugs. Nausea, loose stools, headache, abdominal pain, muscle and joint pain, dizziness are complained by 3–5%. Rashes (1.5% incidence), leucopenia and hepatic dysfunction are infrequent.

No harmful effects of PPIs during pregnancy are known. Though manufacturers advise to avoid, PPIs have often been used for GERD during pregnancy.

Accelerated osteoporosis among elderly patients (possibly due to reduced calcium absorption in the absence of gastric acid) has been associated with high-dose long-term use of PPIs for GERD.

Because of marked and long-lasting acid suppression, compensatory hypergastrinemia has been observed, but no increase in gastric tumours has been noted in humans. Few cases of atrophic gastritis have been related to PPI use. Prolonged loss of acid barrier to colonization by ingested bacteria may pose increased risk of respiratory and enteric infections. Though patients have been treated continuously for > 11 years without any problem, it may appear prudent to be apprehensive of prolonged achlorhydria, and if possible, avoid long-term use of PPIs.

Lately, few reports of gynaecomastia and erectile dysfunction (possibly due to reduced testosterone level) after prolonged use of omeprazole have appeared.

Interactions Omeprazole inhibits oxidation of certain drugs: diazepam, phenytoin and warfarin levels may be increased. It interferes with activation of clopidogrel by inhibiting CYP2C19 (*see* p. 678). Reduced gastric acidity decreases absorption of ketoconazole and iron salts. Clarithromycin inhibits omeprazole metabolism and increases its plasma concentration.

OMIZAC, NILSEC 20 mg cap. OMEZ, OCID, OMEZOL 10, 20 mg caps, PROTOLOC 20, 40 mg caps containing enteric coated granules.

Capsules must not be opened or chewed; to be taken in the morning before meals.

OCID, OMEZ 40 mg per amp inj.

Esomeprazole It is the S-enantiomer of omeprazole; claimed to have higher oral bioavailability and to produce better control of intragastric pH than omeprazole in GERD patients because of slower elimination and longer t½. Higher healing rates of erosive esophagitis and better GERD symptom relief have been reported in comparative trials with omeprazole. Side effect and drug interaction profile is similar to the racemic drug.

Dose: 20–40 mg OD; NEXPRO, RACIPER, IZRA 20, 40 mg tabs. RACIPER-IV 40 mg/5 ml inj.

Lansoprazole Somewhat more potent than omeprazole but similar in properties. Inhibition of H^+ K^+ ATPase by lansoprazole is partly reversible. It has higher oral bioavailability, faster onset of action and slightly longer t½ than omeprazole. Dose should be reduced in liver disease. Side effects are similar, but drug interactions appear to be less significant; diazepam and phenytoin metabolism may be reduced.

Ulcer healing dose: 15–30 mg OD; LANZOL, LANZAP, LEVANT, LANPRO 15, 30 mg caps.

Pantoprazole It is similar in potency and clinical efficacy to omeprazole, but is more acid stable and has higher oral bioavailability. Injected i.v., pantoprazole has been particularly employed in bleeding peptic ulcer and for prophylaxis of acute stress ulcers. Affinity for cytochrome P450 is lower than omeprazole or lansoprazole: risk of drug interactions is minimal.

Dose: 40 mg OD; PANTOCID, PANTODAC 20, 40 mg enteric coated tab; PANTIUM, PANTIN 40 mg tab, 40 mg inj for i.v. use.

S-Pantoprazole It is the active single enantiomer, twice as potent as the racemate.

PANPURE, ZOSECTA 20 mg tab.

Rabeprazole This PPI is claimed to cause faster acid suppression. Due to higher pKa, it is more rapidly converted to the active species. However, potency and efficacy are similar to omeprazole. No significant drug interactions have been observed.

Dose: 20 mg OD; ZE syndrome — 60 mg/day.

RABLET, RABELOC, RABICIP, RAZO, HAPPI 10, 20 mg tab, 20 mg/vial inj.

Dexrabeprazole It is the active dextro-isomer of rabeprazole; produces similar acid suppression at half the dose, *i.e.* 10–20 mg daily.

DEXPURE 5, 10 mg tabs.

Ilaprazole This PPI developed in Korea, has been approved for use in India for peptic ulcer, GERD and dyspepsia. Ulcer healing efficacy and tolerability is similar to omeprazole, but dose-to-dose it is twice as potent. It is excreted in urine, both as unchnaged drug and as sulfone metabolite.

Dose: 5–20 mg OD before breakfast or before dinner.

ILATOP, ILACOOL, ILAGATE, ADIZA 5 mg, 10 mg tab.

Uses of PPIs

1. *Peptic ulcer:* PPIs in their recommended doses, e.g. omeprazole 20–40 mg OD are more effective than H_2 blockers. Relief of pain is rapid (within 1–2 days) and excellent. Faster healing has been demonstrated with 40 mg/day than with 20 mg/day. Some duodenal ulcers heal even at 2 weeks and the remaining (over 90%) at 4 weeks. Gastric ulcer generally requires 4–8 weeks. PPIs have achieved healing of ulcers in many patients who did not respond to H_2 blockers. Maintenance therapy with lower doses (e.g. omeprazole 20 mg daily or thrice weekly) can prevent ulcer relapse. PPIs are an integral component of anti-*H. pylori* therapy (*see* p.705–06). PPIs are the drugs of choice for NSAID induced gastric/duodenal ulcers.

Healing may occur despite continued use of the NSAID. However, higher dose or twice daily treatment given for longer periods are generally required. Whenever possible, the NSAID should be discontinued. If that is not possible, it is advisable to switch over to a COX-2 selective NSAID. Maintenance PPI treatment reduces recurrence of NSAID associated ulcer. Ulcer complications like perforation, and bleeding are also reduced.

2. *Bleeding peptic ulcer:* Acid enhances clot dissolution promoting ulcer bleed. Suppression of gastric acid has been found to facilitate clot formation reducing blood loss and rebleed. High dose i.v. PPI therapy (pantoprazole or esomeprazole or rabeprazole 80 mg bolus injection, followed by 8 mg/hr infusion for 3 days) profoundly inhibits gastric acid, and has been shown to reduce rebleeding after therapeutic endoscopy. Even in cases where the bleeding vessel could not be visualized, i.v. followed by oral PPI reduces recurrence of bleeding and need for surgery.

3. *Stress ulcers:* Intravenous pantoprazole/rabeprazole are at least as effective prophylactic (if not more) for stress ulcers as i.v. H_2 blockers (*see* p. 699). Though one metaanalysis has shown PPIs to be more effective, both classes of drugs continue to be used.

4. *Gastroesophageal reflux disease (GERD):* PPIs are the drugs of choice (*see* p. 707). Higher doses than that for peptic ulcer, or twice daily dosing is generally needed.

5. *Zollinger-Ellison syndrome:* It is a gastric hypersecretory state due to 'gastrinoma', a rare tumour secreting gastrin, which presents with difficult to heal gastric/duodenal ulcer(s). High dose oral PPI (60–120 mg/day in 2 doses) is the drug of choice for controlling symptoms. Complete symptomatic relief and healing of ulcers can be achieved by a dose of the PPI which lowers the daily acid output to within normal limits.

Inoperable/metastatic cases have been treated for >6 years with sustained benefit and no serious toxicity. Definitive treatment is resection of the tumour, if possible. Other gastric hypersecretory states like systemic mastocytosis, endocrine adenomas, etc. also respond well.

6. *Aspiration pneumonia:* PPIs are an alternative to H_2 blockers (*see* p. 699) for prophylaxis of aspiration pneumonia due to prolonged anaesthesia.

ANTICHOLINERGICS (SEE CH. 8)

Atropinic drugs reduce the volume of gastric juice without raising its pH unless there is food in stomach to dilute the secreted acid. Stimulated gastric secretion is less completely inhibited. Effective doses (for ulcer healing) of antimuscarinic drugs (atropine, propantheline, oxyphenonium) invariably produce intolerable side effects. Introduction of H_2 blockers and PPIs has sent them into oblivion.

Pirenzepine (*see* p. 129) It is a selective M_1 anticholinergic that was used in Europe for peptic ulcer. Though antimuscarinic side effects were less marked, more effective H_2 blockers and PPIs have rendered it redundant.

PROSTAGLANDIN ANALOGUE

PGE_2 and PGI_2 are produced in the gastric mucosa and appear to serve a protective role by inhibiting acid secretion and promoting mucus as well as HCO_3 secretion (*see* Ch. 13). In addition, PGs inhibit gastrin release, increase mucosal blood flow and probably have an ill-defined "cytoprotective" action. However, their ability to reinforce the mucus layer covering gastric and duodenal mucosa which is buffered by HCO_3^- secreted into this layer by the underlying epithelial cells appears to be the most important.

Natural PGs have very short t½. *Misoprostol* (methyl-PGE_1 ester) is a longer acting synthetic PGE_1 derivative which inhibits acid output. However, reduction in 24 hour acid production is less marked than H_2 blockers because of shorter duration of action (~3 hr.) Ulcer healing rates comparable to cimetidine have been obtained in 4–8 weeks, but misoprostol is poorer in relieving ulcer pain. Some patients may even complain of increased pain during the first week of therapy.

Dose: 200 µg QID;

CYTOLOG 200 µg tab; MISOPROST 100 µg, 200 µg tabs.

Major problems in the use of misoprostol are—diarrhoea, abdominal cramps, uterine bleeding, abortion, and need for multiple daily doses. Patient acceptability is poor.

The primary indication of misoprostol is the prevention and treatment of NSAID associated gastrointestinal injury and blood loss. However, it is seldom employed because PPIs are more effective, more convenient, better tolerated and cheaper.

ANTACIDS

These are basic substances which neutralize gastric acid and raise pH of gastric contents. Peptic activity is indirectly reduced if the pH

rises above 4, because pepsin is secreted as a complex with an inhibitory terminal moiety that dissociates below pH 5: optimum peptic activity is exerted between pH 2 to 4.

Antacids do not decrease acid production; rather, agents that raise the antral pH to > 4 evoke reflex gastrin release → more acid is secreted, especially in patients with hyperacidity and duodenal ulcer; "acid rebound" occurs and gastric motility is increased.

The potency of an antacid is generally expressed in terms of its *acid neutralizing capacity* (ANC), which is defined as number of mEq of 1N HCl that are brought to pH 3.5 in 15 min (or 60 min in some tests) by a unit dose of the antacid preparation. This takes into consideration the rate at which the antacid dissolves and reacts with HCl. This is important because a single dose of any antacid taken in empty stomach acts for 30–60 min only before it is passed into duodenum. Taken with meals antacids may act for at the most 2–3 hr.

Systemic Antacids

Sodium bicarbonate It is water soluble, acts instantaneously, but the duration of action is short. It is a potent neutralizer (1 g → 12 mEq HCl), pH may rise above 7. However, it has several demerits:

(a) Absorbed systemically: large doses will induce alkalosis.
(b) Produces CO_2 in stomach → distention, discomfort, belching, risk of ulcer perforation.
(c) Acid rebound occurs, but is usually short lasting.
(d) Increases Na^+ load: may worsen edema and CHF.

Use of sod. bicarbonate is restricted to casual treatment of heartburn. It provides quick symptomatic relief. Other uses are to alkalinize urine and to treat acidosis.

Sodium citrate Properties similar to sod. bicarbonate; 1 g neutralizes 10 mEq HCl; CO_2 is not evolved.

Nonsystemic Antacids

These are insoluble and poorly absorbed basic compounds; react in stomach to form the corresponding chloride salt. The chloride salt again reacts with the intestinal bicarbonate so that HCO_3^- is not spared for absorption—no acid-base disturbance occurs. However, small amounts that are absorbed have the same alkalinizing effect as $NaHCO_3$.

Mag. hydroxide has low water solubility: its aqueous suspension (milk of magnesia) has low concentration of OH^- ions and thus low alkalinity. However, it reacts with HCl promptly and is an efficacious antacid (1 g → 30 mEq HCl).

MILK OF MAGNESIA 0.4 g/5 ml suspension: 5 ml neutralizes 12 mEq acid.

Magnesium trisilicate has low solubility and reactivity: 1 g can react with 10 mEq acid, but in clinical use only about 1 mEq is neutralized.

About 5% of administered Mg is absorbed systemically—may cause problem if renal function is inadequate. All Mg salts have a laxative action by generating osmotically active $MgCl_2$ in the stomach and through Mg^{2+} ion induced cholecystokinin release.

Aluminium hydroxide gel It is a bland, weak and slowly reacting antacid. On keeping it slowly polymerizes to variable extents into still less reactive forms. Thus, the ANC of a preparation gradually declines on storage. Accordingly, 5 ml of its suspension may neutralize just 1 mEq HCl. As such, little worthwhile acid neutralization is obtained at conventional doses.

The Al^{3+} ions relax smooth muscle. Thus, it delays gastric emptying. Alum. hydrox. frequently causes constipation due to its smooth muscle relaxant and mucosal astringent action.

Small amount of Al^{3+} that is absorbed is excreted by kidney. This is impaired in renal failure—aluminium toxicity (encephalopathy, osteoporosis) can occur.

ALUDROX 0.84 g tab, 0.6 g/10 ml susp.

Magaldrate It is a hydrated complex of hydroxymagnesium aluminate that initially reacts rapidly with acid and releases alum. hydrox. which then reacts more slowly. The freshly released alum. hydrox. is in the unpolymerized more reactive form. Thus, magaldrate cannot be equated to a physical mixture of mag. and alum. hydroxides. It is a good antacid with prompt and sustained neutralizing action. Its ANC is estimated to be 28 mEq HCl/g.

STACID 400 mg tab, 400 mg/5 ml susp.; ULGEL 400 mg with 20 mg simethicone per tab or 5 ml susp.

Calcium carbonate It is a potent and rapidly acting acid neutralizer (1 g → 20 mEq HCl), but ANC of commercial preparations is less and variable due to differing particle size and crystal structure. Though it liberates CO_2 in the stomach at a slower rate than $NaHCO_3$, it can cause distention and discomfort. The Ca^{2+} ions are partly absorbed.

The greatest drawback of $CaCO_3$ as an antacid is that Ca^{2+} ions diffuse into the gastric mucosa—increase HCl production directly by parietal cells as well as by releasing gastrin. Acid rebound occurs.

Milk alkali syndrome In the past, large quantity of milk was prescribed with $CaCO_3$ (or $NaHCO_3$) for peptic ulcer. Such regimen often produced a syndrome characterized by headache, anorexia, weakness, abdominal discomfort, abnormal Ca deposits and renal stones due to concurrent hypercalcaemia and alkalosis. It is rare now.

Antacid combinations A combination of two or more antacids is frequently used. These may be superior to any single agent on the following accounts:

(a) Fast (Mag. hydrox.) and slow (Alum. hydrox.) acting components yield prompt as well as sustained effect.

(b) Mag. salts are laxative, while alum. salts are constipating: combination may annul each other's action and bowel movement may be least affected.

(c) Gastric emptying is least affected; while alum. salts tend to delay it, mag./cal. salts tend to hasten it.

(d) Dose of individual components is reduced; systemic toxicity (dependent on fractional absorption) is minimized.

Some available antacid combinations are:

ACIDIN: Mag. carb. 165 mg, dried alum. hydrox. gel 232 mg, cal. carb. 165 mg, sod. bicarb. 82 mg, with kaolin 105 mg and belladonna herb 30 µg per tab.

ALMACARB: Dried alum. hydrox. gel 325 mg, mag. carb. 50 mg, methyl polysilox. 40 mg, deglycyrrhizinated liquorice 380 mg per tab.

ALLUJEL-DF: Dried alum. hydrox. gel 400 mg, mag. hydrox. 400 mg, methyl polysilox. 30 mg per 10 ml susp.

DIGENE: Dried alum. hydrox. gel 300 mg, mag. alum. silicate 50 mg, mag. hydrox. 25 mg, methylpolysilox. 10 mg per tab.

DIGENE GEL: Mag. hydrox. 185 mg, alum. hydrox. gel 830 mg, sod. carboxymethyl cellulose 100 mg, methylpolysilox. 25 mg per 10 ml susp.

GELUSIL: Dried alum. hydrox. gel 250 mg, mag. trisilicate 500 mg per tab.

GELUSIL LIQUID: Mag. trisilicate 625 mg, alum. hydrox. gel 312 mg per 5 ml susp.

MUCAINE: Alum. hydrox. 290 mg, mag. hydrox. 98 mg, oxethazaine 10 mg per 5 ml susp.

TRICAINE-MPS: Alum. hydrox. gel 300 mg, mag. hydrox. 150 mg, oxethazaine 10 mg, simethicone 10 mg per 5 ml gel.

MAYLOX: Dried alum. hydrox. gel 225 mg, mag. hydrox. 200 mg, dimethicone 50 mg per tab and 5 ml susp.

POLYCROL FORTE GEL: Mag. hydrox. 100 mg, dried alum. hydrox. gel 425 mg, methylpolysilox. 125 mg per 5 ml susp.

Drug interactions By raising gastric pH and by forming complexes, the non-absorbable antacids reduce the absorption of many drugs, especially tetracyclines, iron salts, fluoroquinolones, ketoconazole, H_2 blockers, diazepam, phenothiazines, indomethacin, phenytoin, isoniazid, ethambutol and nitrofurantoin. Stagger their administration by 2 hours. The efficacy of nitrofurantoin is reduced due to alkalinization of urine by the antacid.

Uses Antacids are no longer used for healing peptic ulcer, because they are needed in large and frequent doses, are inconvenient, can cause acid rebound and bowel upset, afford little nocturnal protection and have poor patient acceptability. They are now employed only for intercurrent pain relief, dyspepsia and acidity, mostly self-prescribed by the patients as over-the-counter preparations. Antacids continue to be used for nonulcer dyspepsia and minor episodes of heartburn.

Gastroesophageal reflux Antacids afford faster symptom relief than drugs which inhibit acid secretion, but do not provide sustained benefit. They may be used off-and-on for acid eructation and heartburn.

ULCER PROTECTIVES

Sucralfate It is a basic aluminium salt of sulfated sucrose, which is a drug of its own kind. Sucralfate polymerizes at pH < 4 by cross linking of molecules, assuming a sticky gel-like consistency. It preferentially and strongly adheres to the ulcer base, especially duodenal ulcer, and has been seen endoscopically to remain there for ~ 6 hours. Surface proteins at the ulcer base are precipitated, together with which it acts as a physical barrier preventing acid, pepsin and bile from coming in contact with the ulcer base. Dietary proteins get deposited on this coat, forming another layer.

Sucralfate has no acid neutralizing action, but delays gastric emptying, so that its own stay in stomach is prolonged. Augmented gastric mucosal PG synthesis may supplement physical protective action of sucralfate.

Sucralfate is minimally absorbed after oral administration. Its action is entirely local. It promotes healing of both duodenal and gastric ulcers. Healing efficacy has been found similar to cimetidine at 4 weeks, and may be superior in patients who continue to smoke. However, sucralfate is infrequently used now because of need for 4 large well-timed daily doses and the availability of simpler and more effective H_2 blockers/PPIs.

Dose: The ulcer healing dose of sucralfate is 1 g taken in empty stomach 1 hour before the 3 major meals and at bed time for 4–8 weeks. Antacids should not be taken with sucralfate because its polymerization is dependent on acidic pH.

ULCERFATE, SUCRACE, RECULFATE 1 g tab.

Side effects are few; constipation is reported by 2% patients. It has potential for inducing hypophosphatemia by binding phosphate ions in the intestine. Dry mouth and nausea are infrequent.

Other uses Bile reflux, gastritis and prophylaxis of stress ulcers.

In intensive care units, acid suppressant prophylaxis of stress ulcers (with i.v./intragastric H_2 blocker or PPI) is

almost routinely used now. This practice is considered to contribute to occurrence of pneumonia due to overgrowth of bacteria in the stomach. Intragastric sucralfate administered as a thick suspension provides effective prophylaxis of stress ulcers without acid suppression, and is an alternative to i.v. H_2 blocker/PPI.

As a suspension in glycerol, it has been tried in stomatitis. A topical formulation of sucralfate PEPSIGARD LIGHT GEL is available as a protective for application on burns, bedsores, diabetic/radiation ulcers, excoriated skin, etc.

Interactions Sucralfate adsorbs many drugs. It interferes with the absorption of tetracyclines, fluoroquinolones, cimetidine, phenytoin and digoxin. Antacids given concurrently reduce the efficacy of sucralfate.

Colloidal bismuth subcitrate (CBS; Tripotassium dicitratobismuthate)

It is a colloidal bismuth compound; water soluble but precipitates at pH < 5. It is not an antacid but heals 60% ulcers at 4 weeks and 80–90% at 8 weeks. The mechanism of action of CBS is not clear; probabilities are:

- May increase gastric mucosal PGE_2, mucus and HCO_3^- production.
- May precipitate mucus glycoproteins and coat the ulcer base.
- May detach and inhibit *H. pylori* directly.

Gastritis and nonulcer dyspepsia associated with *H. pylori* are also improved by CBS. The regimen for CBS is 120 mg (as Bi_2O_3) taken ½ hr before 3 major meals and at bedtime for 4–8 weeks. ~~Milk and antacids~~ should not be taken concomitantly.

TRYMO, DENOL 120 mg tab.

Most of the ingested CBS passes in the faeces. Small amounts absorbed are excreted in urine. Side effects are diarrhoea, headache and dizziness. Patient acceptance of CBS is compromised by blackening of tongue, dentures and stools; and by inconvenience of the dosing schedule. Presently, it is used occasionally as a component of triple drug anti-*H. pylori* regimen.

ANTI-*HELICOBACTER PYLORI* DRUGS

H. pylori is a gram negative bacillus uniquely adapted to survival in the hostile environment of stomach. It attaches to the surface epithelium beneath the mucus, possesses high urease activity—produces ammonia which maintains a neutral microenvironment around the bacteria, and promotes back diffusion of H^+ ions. It has been found as a commensal in 20–70% normal individuals, and is now accepted as an important contributor to the causation of chronic gastritis, dyspepsia, peptic ulcer, gastric lymphoma and gastric carcinoma. *H. pylori* infection starts with a neutrophilic gastritis lasting 7–10 days which is usually asymptomatic. Once established, *H. pylori* generally persists for the life of the host. Up to 90% patients of duodenal and gastric ulcer have tested positive for *H. pylori*.

Eradication of *H. pylori* concurrently with PPI therapy of peptic ulcer has been associated with faster ulcer healing and largely prevents ulcer relapse. All *H. pylori* positive ulcer patients should receive *H. pylori* eradication therapy. In the absence of *H. pylori* testing, all cases with failed conventional ulcer therapy and relapse cases must be given the benefit of *H. pylori* eradication.

Antimicrobials that are used clinically against *H. pylori* are: amoxicillin, clarithromycin, tetracycline and metronidazole/tinidazole. However, any single antibiotic is ineffective. Resistance develops rapidly, especially to metronidazole/tinidazole and to clarithromycin, but amoxicillin resistance is infrequent. In tropical countries, metronidazole resistance is more common than clarithromycin resistance. Since bismuth (CBS) is active against *H. pylori* and ~~resis~~tance does not develop to it, combination regimens including bismuth may be used in case of metronidazole and clarithromycin double resistance. Routine use of CBS is precluded by poor patient acceptability. Acid suppression by PPIs enhances effectiveness of anti-*H. pylori* antibiotics, and optimum benefits are obtained when gastric pH is kept >5 for at least 16–18 hours per day. This is a higher degree of round-the-clock acid suppression than is needed for duodenal ulcer healing or for reflux esophagitis. Only twice daily PPI dosing can achieve this degree of acid suppression. The PPIs benefit by altering the acid environment for *H. pylori* as well as by direct inhibitory effect. One of the PPIs is an integral component of all anti-*H. pylori* regimens along with 2 (triple drug) or 3 (quadruple drug) antimicrobials.

Anti-*H. pylori* Regimens			
Proton pump inhibitor	*Amoxicillin*	*Clarithromycin*	*Metronidazole*[$]
One week regimens*			
Omeprazole (20 mg BD) or	1.0 g BD	500 mg BD	—
Esomeprazole (20 mg BD) or	—	250 mg BD	400 mg BD
Lansoprazole (30 mg BD) or	1.0 g BD	—	400 mg BD
Pantoprazole (40 mg BD) or			
Rabeprazole (20 mg BD)			
Omeprazole (20 mg BD)	500 mg TDS	—	400 mg TDS
Two weeks-twice daily regimens			
Omeprazole (20 mg) or	750 mg	—	400 mg
Lansoprazole (30 mg) or	—	250 mg	400 mg
Pantoprazole (40 mg)	750 mg	500 mg	—

* One week regimens adopted from British National Formulary (BNF) Sept. 2016
[$] Tinidazole 500 mg BD may be used alternatively.

A number of 3 drug regimens of 1 or 2 weeks are being used (*see* box). For majority of cases, especially initially, any one of the triple drug one week therapy is recommended. On an average this achieves *H.pylori* eradication in upto 85% cases. The two week triple drug regimens do offer the possibility of higher eradication rate (upto 96%) but they produce more adverse effects, are more expensive and compliance is poor. They should be reserved for patients not achieving complete eradication with 1 week regimens.

The US-FDA approved regimen is:
Lansoprazole 30 mg + Amoxicillin 1000 mg + clarithromycin 500 mg, all given twice daily for 2 weeks.

This has achieved 86–92% eradication rate. Better tolerability of regimens which exclude a nitroimidazole favour using amoxicillin + clarithromycin + PPI, particularly in India where metronidazole resistance is more prevalent. It is advised that patients who in the near past have received a nitroimidazole for another infection should be treated with PPI + amoxicillin + clarithromycin. Similarly, if a patient has received a macrolide antibiotic, the regimen should consist of PPI + metronidazole/tinidazole + amoxicillin.

For large ulcers (> 10 mm in diameter) or those complicated by bleeding/perforation, the PPI should be continued beyond the 2 weeks-triple drug regimen till complete healing occurs.

Quadruple therapy with CBS 120 mg QID + tetracycline 500 mg QID + metronidazole 400 mg TDS + omeprazole 20 mg BD is advocated for eradication failure cases. Another quadruple therapy regimen with PPI + amoxicllin + clarithromycin + metronidazole all twice daily for 2 weeks has been tested in Europe with >90% eradication rate.

All regimens are complex and expensive, side effects are frequent and compliance is poor. Higher failure rates (20–40%) have been reported from India. Also, 5 year recurrence rate of *H. pylori* infection is higher. Three week treatment is being advocated by some. Nevertheless, long-term benefits of anti-*H. pylori* therapy include lowering of ulcer disease prevalence and prevention of gastric carcinoma/lymphoma; but benefits in nonulcer dyspepsia are equivocal.

Some available anti-*H. pylori* kits (one kit to be taken daily in 2 doses)
HP-KIT, HELIBACT, OMXITIN: Omeprazole 20 mg 2 cap + Amoxicillin 750 mg 2 tab + Tinidazole 500 mg 2 tab.
PYLOMOX: Lansoprazole 15 mg 2 cap + Amoxicillin 750 mg 2 tab + Tinidazole 500 mg 2 tab.

LANSI KIT: Lansoprazole 30 mg 1 cap + Amoxicillin 750 mg 1 tab + Tinidazole 500 mg 1 tab (one kit twice a day)
PYLOKIT, HELIGO: Lansoprazole 30 mg 2 cap + Clarithromycin 250 mg 2 cap + Tinidazole 500 mg 2 tab.
LANPROAC: Lansoprazole 30 mg 2 cap + Clarithromycin 250 mg 2 tab + Amoxicillin 750 mg 2 tab.

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Reflux is a very common problem presenting as 'heart-burn', acid eructation, sensation of stomach contents coming back in the foodpipe, especially after a large meal, aggravated by stooping or lying flat. Some cases have an anatomical defect (hiatus hernia) but majority are only functional, wherein there is relaxation of lower esophageal sphincter (LES) in the absence of swallowing. Repeated reflux of acid gastric contents into lower ⅓rd of esophagus causes esophagitis, erosions, ulcers, pain on swallowing, dysphagia, strictures, and increases the risk of esophageal carcinoma.There may also be cough and other extraesophageal complications.

The primary barrier to reflux is the tone of LES which can be altered by several influences:

Inherent tone: of sphincteric smooth muscle.
Hormonal: gastrin increases, progesterone decreases (reflux is common in pregnancy).
Neurogenic: vagus is motor to the sphincter, promotes esophageal peristalsis.
Dietary: fats, alcohol, coffee, chocolates decrease, while protein rich foods increase LES tone.
Drugs: anticholinergics, tricyclic antidepressants, Ca^{2+} channel blockers, nitrates reduce LES tone.
Smoking: relaxes LES.

Delayed gastric emptying and increased intragastric pressure may overcome the LES barrier to reflux. GERD is a wide spectrum of conditions from occasional heartburn (majority of cases) to persistent incapacitating reflux which interferes with sleep and results in esophageal, laryngotracheal and pulmonary complications. Severity of GERD may be graded as:

Stage 1: occasional heartburn (<3 episodes/week), mostly only in relation to a precipitating factor, mild symptoms, no esophageal lesions.

Stage 2: ≥ 3 episodes/week of moderately severe symptoms, nocturnal awakening due to regurgitation, esophagitis present or absent.

Stage 3: Daily/chronic symptoms, disturbed sleep, esophagitis/erosions/stricture/extraesophageal symptoms like laryngitis, hoarseness, dry cough, asthma. Symptoms recur soon after treatment is stopped.

Though GERD is primarily a g.i. motility disorder, acidity of gastric contents is the most important aggressive factor in causing symptoms and esophageal lesions. The functional abnormality is persistent; though short-term remissions do occur. Dietary and other lifestyle measures (light early dinner, raising head end of bed, weight reduction and avoidance of precipitating factors) must be taken.

The goals of treatment in GERD are relief of symptoms, healing of esophageal lesions (if present) and prevention of complications. Treatment is individualized according to severity and stage of the disorder.

The site and mechanism of benefit afforded by different classes of drugs in GERD is depicted in Fig. 47.2.

1. *Proton pump inhibitors (PPIs)* These are the most effective drugs, both for

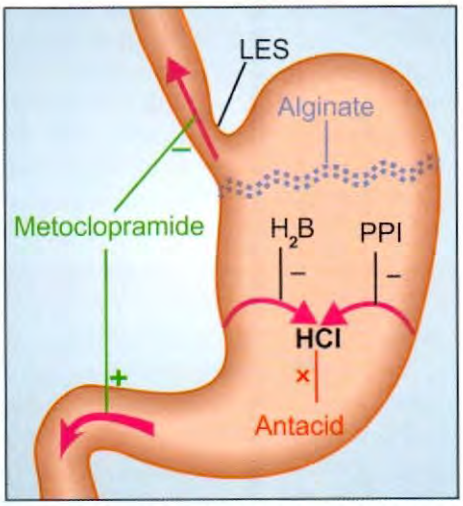


Fig. 47.2: Sites and mechanisms of drug action in gastroesophageal reflux disease.
Metoclopramide increases lower esophageal sphincter (LES) tone and promotes gastric emptying. Proton pump inhibitor (PPI) and H_2 blocker (H_2B) inhibit acid secretion, while antacids neutralize it. Alginate floats on gastric contents and prevents contact of esophageal mucosa with gastric acid

symptomatic relief as well as for healing of esophageal lesions and prevention of complications. Intragastric pH >4 maintained for ~18 hr/day is considered optimal for healing of esophagitis. This level of acid suppression can be consistently achieved only by PPIs. Therefore, PPIs are the drugs of choice for patients with all stages of GERD, particularly stage 2 and 3 cases. Symptom relief is rapid, and 80–90% esophageal lesions heal in 4–8 weeks. Dose titration is needed according to response in individual patients. Some patients, especially stage 2 and 3 cases, need twice daily dosing. Prolonged (often indefinite) therapy is required in chronic cases because symptoms recur a few days after drug stoppage. PPIs have no effect on LES tone.

2. *H_2 blockers* They reduce acidity of gastric contents and have no effect on LES tone. H_2 blockers cause less complete acid suppression than PPIs, *viz* elevate intragastric pH to >4 for less than 8 hours in 24 hours with the conventional doses given twice daily. Adequate symptom relief is obtained only in mild cases; healing of esophagitis may occur in 50–70% patients. H_2 antagonists are indicated for 'on demand' symptom relief when symptoms are occasional or in stage 1 GERD cases. Symptom relief occurs 30–60 min after drug intake and lasts upto 8 hours. They may also be used as alternative to PPIs in stage 2 or 3 cases. The daily dose should be divided into 2–3 portions for better response.

3. *Antacids* Their use in GERD is limited to occasional or intercurrent relief of heartburn because they act within few minutes, but relief may last only 2–3 hours. Antacids are not employed for healing of esophagitis, which they are incapable of.

4. *Sodium alginate* It increases viscosity of gastric contents, forms a thick frothy layer which floats on them like a raft and may prevent contact of acid with esophageal mucosa. It has no effect on LES tone. Combination of alginate with antacids may be used in place of antacids alone, but any benefit is marginal.

REFLUX LIQUID: Sod. alginate 200 mg + alum. hydrox. gel 300 mg + mag. trisilicate 125 mg/10 ml susp; REFLUX FORTE Alginic acid 20 mg + sod. bicarb. 70 mg + alum. hydrox. 300 mg tab; GAVISCON Alginic acid 500 mg + mag. trisilicate 25 mg + alum. hydrox. gel 100 mg + sod. bicarb. 170 mg tab.

5. *Prokinetic drugs* Metoclopramide, mosapride and other prokinetic drugs may relieve regurgitation and heartburn by increasing LES tone, improving esophageal clearance and facilitating gastric emptying, but do not affect gastric acidity or promote healing of esophagitis. Symptom control afforded by prokinetic drugs is much inferior to that by PPIs/H_2 blockers. Their use in GERD has declined. Prokinetic drugs are often coprescribed with PPI/H_2 blocker therapy, but whether this improves outcome is not clear.

PROBLEM DIRECTED STUDY

47.1 A 45-year-old male patient presents with dyspepsia and dull epigastric pain which has been worsening gradually over the last one month. The pain is partly relieved by food, but becomes worse after 2 hours or so. Heartburn and pain which awakens him is often felt at night. Epigastric tenderness is detected on palpation. Upper gastrointestinal endoscopy reveals an ulcer measuring 12 mm X 18 mm in the 1st part of duodenum. His medical records show that he suffered similar episode of pain about 9 months ago. No endoscopy was done, but he was treated with omeprazole 20 mg OD for 6 weeks. Subsequently, nearly 2 months back, he suffered from loose motions and abdominal pain which was treated with a 5 day course of metronidazole + norfloxacin. Facility for *H. pylori* testing is not available. There is no history of NSAID use.

(a) What would be the most appropriate treatment option for him to achieve fast symptom relief, ulcer healing and prevention of further recurrences?

(see Appendix-1 for solution)

Chapter 48 Antiemetic, Prokinetic and Digestant Drugs

Emesis Vomiting occurs due to stimulation of the *emetic (vomiting) centre* situated in the medulla oblongata. Multiple pathways can elicit vomiting (Fig. 48.1). The *chemoreceptor trigger zone (CTZ)* located in the area postrema and the *nucleus tractus solitarius (NTS)* are the most important relay areas for afferent impulses arising in the g.i.t, throat and other viscera. The CTZ is also accessible to blood-borne drugs, mediators, hormones, toxins, etc. because it is unprotected by the blood-brain barrier. Cytotoxic drugs, radiation and other g.i. irritants release 5-HT from enterochromaffin cells which acts on 5-HT_3 receptors present on extrinsic primary afferent neurones (PAN) of the enteric nervous system (ENS). These neurones connect with vagal and spinal visceral afferents to send impulses to NTS and CTZ. Released in large quantity, 5-HT may also spill into circulation and reach CTZ *via* the vascular route. 5-HT may as well be released from platelets by inflammatory mediators. However, 5-HT is not the only mediator of such signals: many peptides, e.g. substance P and other messengers are also involved.

The CTZ and NTS express a variety of receptors, e.g. histamine H_1, dopamine D2, serotonin 5-HT_3, cholinergic M, neurokinin NK_1 (activated by substance P), cannabinoid CB_1 and opioid μ receptors through which the emetic signals are relayed and which could be targets of antiemetic drug action.

The vestibular apparatus generates impulses when body is rotated or equilibrium is disturbed or when ototoxic drugs act. These impulses reach the vomiting centre mainly relayed from the cerebellum and utilize muscarinic as well as H_1 receptors. Various unpleasant sensory stimuli such as bad odour, ghastly sight, severe pain as well as fear, recall of an obnoxious event, anticipation of an emetic stimulus (repeat dose of cisplatin) cause nausea and vomiting through higher centres.

Nausea is accompanied by reduced gastric tone and peristalsis. In the emetic response fundus and body of stomach, esophageal sphincter and esophagus relax, glottis closes, while duodenum and pyloric stomach contract in a retrograde manner. Rhythmic contractions of diaphragm and abdominal muscles then compress the stomach and evacuate its contents *via* the mouth. Conditions that inhibit gastric emptying predispose to vomiting.

EMETICS

These are drugs used to evoke vomiting.

1. *Act on CTZ* : Apomorphine
2. *Act reflexly and on CTZ* : Ipecacuanha

Vomiting needs to be induced only when an undesirable substance (poison) has been ingested. Powdered mustard suspension or strong salts solution may be used in emergency. They act reflexly by irritating the stomach.

Apomorphine It is a semisynthetic derivative of morphine; acts as a dopaminergic agonist on the CTZ. Injected i.m./s.c. in a dose of 6 mg, it promptly (within 5 min) induces vomiting. It should not be used if respiration is depressed, because it has inherent respiratory and CNS depressant actions.

Apomorphine has a therapeutic effect in parkinsonism, but is not used due to side effects.

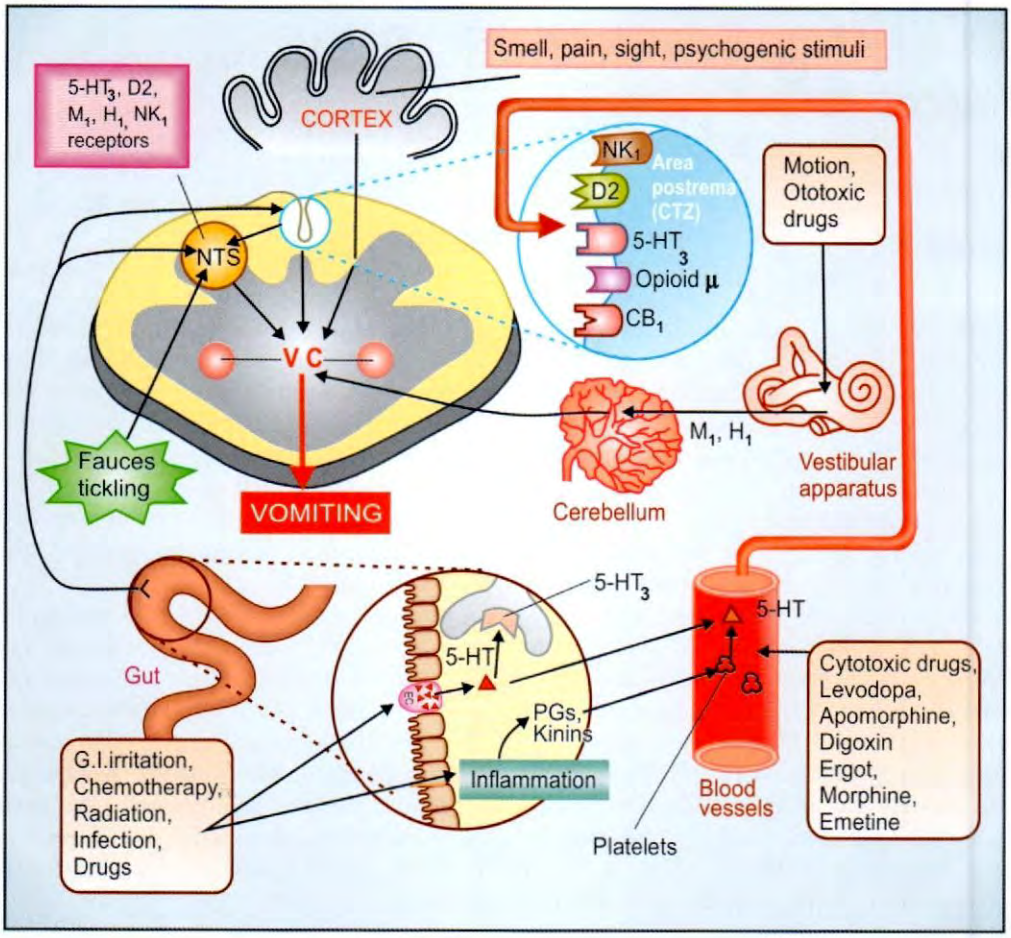


Fig. 48.1: Major central and visceral structures involved in emesis and the neurohumoral receptors mediating the emetic response
NTS–Nucleus tractus solitarius; VC–Vomiting centre; CTZ—Chemoreceptor trigger zone; 5-HT_3–5-HT_3 receptor; H_1–Histamine H_1 receptor; D2–Dopamine D2 receptor; M_1–Muscarinic M_1 receptor; NK_1–Neurokinin$_1$ receptor; CB_1–Cannabinoid 1 receptor

Ipecacuanha The dried root of *Cephaelis ipecacuanha* contains emetine and is used as *syrup ipecac* (15–30 ml in adults, 10–15 ml in children) for inducing vomiting. It is less dependable than parenteral apomorphine and takes 15 min or more for the effect, but is safer; has been used as a household remedy. It acts by irritating gastric mucosa as well as through CTZ.

All emetics are contraindicated in:

(a) Corrosive (acid, alkali) poisoning: there is risk of perforation and further injury to esophageal mucosa.

(b) CNS stimulant drug poisoning: because convulsions may be precipitated.

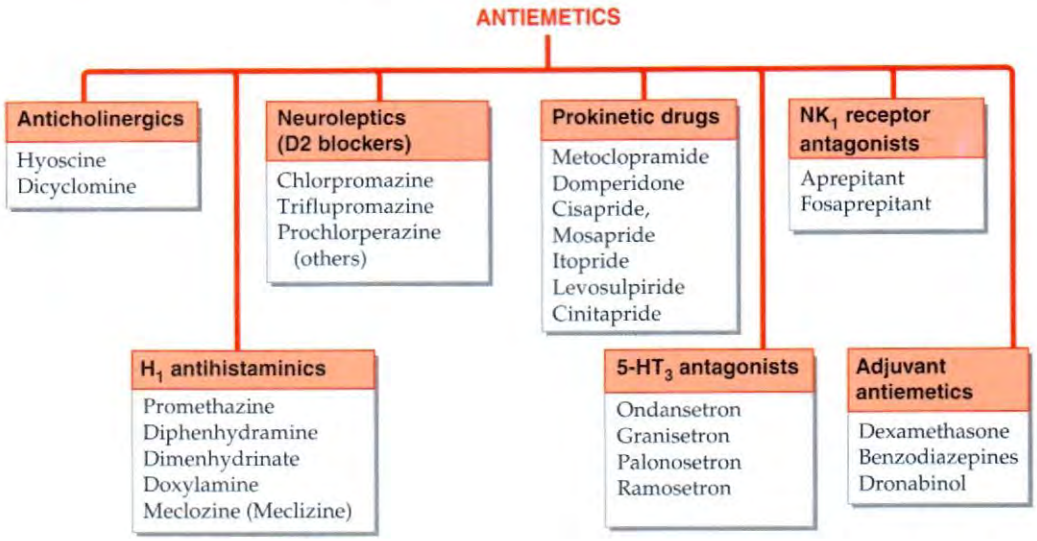
(c) Kerosine (petroleum) poisoning: there is risk of aspiration of the liquid (due to low viscosity) and chemical pneumonia.

(d) Unconscious patient: may aspirate the vomitus, because laryngeal reflex is likely to be impaired.

(e) Morphine or phenothiazine poisoning: because emetics may fail to act.

ANTIEMETICS

These are drugs used to prevent or suppress vomiting.



ANTICHOLINERGICS (*See* Ch. 8)

Hyoscine (0.2–0.4 mg oral, i.m.) is the most effective drug for motion sickness. However, it has a brief duration of action; produces sedation, dry mouth and other anticholinergic side effects. Hyoscine is suitable only for short brisk journies. Antiemetic action is exerted probably by blocking conduction of nerve impulses across a cholinergic link in the pathway leading from the vestibular apparatus to the vomiting centre and has poor efficacy in vomiting of other etiologies.

A transdermal patch containing 1.5 mg of hyoscine, to be delivered over 3 days has been developed. Applied behind the pinna, it suppresses motion sickness while producing only mild side effects.

Dicyclomine (10–20 mg oral) has been used for prophylaxis of motion sickness and for morning sickness (*see* p. 129). It has been cleared of ~~teratogenic~~ potential.

H_1 ANTIHISTAMINICS (*See* Ch. 11)

Some antihistaminics are antiemetic. They are useful mainly in motion sickness and to a lesser extent in morning sickness, postoperative and some other forms of vomiting. Their antiemetic effect appears to be based on anticholinergic, antihistaminic, weak antidopaminergic and sedative properties.

Promethazine, diphenhydramine, dimenhydrinate These drugs afford protection from motion sickness for 4–6 hours, but produce sedation and dryness of mouth. ~~Driving~~ is not advisable after taking these anti-motion sickness drugs. By their central anticholinergic action they block the extrapyramidal side effects of metoclopramide while supplementing its antiemetic action. Promethazine is a phenothiazine; has weak central antidopaminergic action as well. Combination of these antihistaminics with other antiemetics has been used in chemotherapy-induced nausea and vomiting (CINV).

Promethazine theoclate (AVOMINE 25 mg tab.) This salt of promethazine has been specially promoted as an antiemetic, but the action does not appear to be significantly different from promethazine HCl.

Doxylamine It is a sedative H_1 antihistaminic with prominent anticholinergic activity. Marketed in combination with pyridoxine, it is specifically promoted in India for 'morning sickness' (vomiting of early pregnancy), although such use is not made in UK and many other countries.

After over 2 decades of worldwide use of a combination product of doxylamine for morning sickness, some reports of foetal malformation appeared and the product was withdrawn in 1981. Subsequent studies have both supported and refuted its teratogenic potential. Though the US-FDA and CSM in UK found no credible evidence of increase in birth defects, they did not rule out the possibility. The product remained suspended in these countries, probably to avoid litigation, but not due to safety or efficacy concerns. Recently, the American College of Obstetricians and Gynecologists have recommended a combination of doxylamine + pyridoxine as first line treatment of morning sickness, and it is FDA approved.* However, it is still not used in U.K.

Oral absorption of doxylamine is slow, and its t½ is 10 hr. The side effects are drowsiness, dry mouth, vertigo and abdominal upset. *Dose:* 10–20 mg at bed time; if needed additional doses may be given in morning and afternoon.

DOXINATE, GRAVIDOX, VOMNEX, NOSIC 10 mg with pyridoxine 10 mg tab.

Meclozine (meclizine) It is less sedative, less anticholinergic and longer-acting; protects against sea sickness for nearly 24 hours.

DILIGAN: meclozine 12.5 mg + nicotinic acid 50 mg tab;

PREGNIDOXIN: meclozine 25 mg + caffeine 20 mg tab.

Cinnarizine It is an antivertigo drug (*see* p. 183) having antimotion sickness property. It probably acts by inhibiting influx of Ca^{2+} from endolymph into the vestibular sensory cells which mediates labyrinthine reflexes.

Motion sickness Antiemetics with anticholinergic-antihistaminic property are the first choice drugs for *motion sickness*. Antidopaminergic and anti-HT_3 drugs are less effective. All antimotion sickness drugs act better when taken ½–1 hour before commencing journey. Once sickness has started, it is more difficult to control; higher doses/parenteral administration may be needed.

Morning sickness The antihistaminics are suspected to have teratogenic potential, but there is no conclusive proof. Nevertheless, it is better to avoid them for morning sickness. Most cases of morning sickness can be managed by reassurance and dietary adjustment. If an antiemetic has to be used, dicyclomine, promethazine, prochlorperazine or metoclopramide may be prescribed in low doses.

NEUROLEPTICS (*See* Ch. 32)

The older neuroleptics (phenothazines, haloperidol) are potent antiemetics and sedative. They act by blocking D2 receptors in the CTZ; antagonize apomorphine induced vomiting. Many of them have additional antimuscarinic as well as H_1 antihistaminic property. They have broad spectrum antiemetic action effective in:

(a) Drug induced and postoperative nausea and vomiting (PONV).
(b) Disease induced vomiting: gastroenteritis, uraemia, liver disease, migraine, etc.
(c) Malignancy associated and cancer chemotherapy (mildly emetogenic) induced vomiting.
(d) Radiation sickness vomiting (less effective).
(e) Morning sickness: should not be used except in hyperemesis gravidarum.

Neuroleptics are less effective in motion sickness: the vestibular pathway does not involve dopaminergic link.

Most of these drugs produce significant degree of sedation. Hypotension may also occur, especially on parenteral administration. Acute muscle dystonia may occur after a single dose, especially in children and girls. The antiemetic dose is generally much lower than antipsychotic doses. These agents should not be administered until the cause of vomiting has been diagnosed; otherwise specific treatment of conditions like intestinal obstruction, appendicitis, etc. may be delayed due to symptom relief.

Prochlorperazine This D2 blocking phenothiazine is a labyrinthine suppressant, has selective antivertigo and antiemetic actions. It is highly effective when given by injection in vertigo associated vomiting, and to some extent in CINV. Prochlorperazine is used as an antiemetic, but not as antipsychotic. Muscle dystonia and other extrapyramidal side effects are the most important limitations. Dystonic reactions are

* Slaughter SR et al. FDA approval of doxylamine-pyridoxine therapy for use in pregnancy; N Engl J Med **370:** 1081-83, 2014.

more common in children, especially after i.m. injection (*see* p. 471). Parenteral use in children is not recommended. Mouth dissolving tab. may be used in vomiting.

Dose: 5–10 mg BD/TDS oral, 12.5–25 mg by deep i.m. injection.

STEMETIL 5 mg tab, 5 mg mouth dissolving tab, 12.5 mg in 1 ml amp., NAUSETIL 5 mg tab, 12.5 mg/ml inj.

PROKINETIC DRUGS

These are drugs which promote gastrointestinal transit and speed gastric emptying by enhancing coordinated propulsive motility. This excludes traditional cholinomimetics and anti-ChEs which produce tonic and largely uncoordinated contraction.

Metoclopramide

Metoclopramide, a substituted benzamide, is chemically related to procainamide, but has no pharmacological similarity with it. Introduced in early 1970s as a 'gastric hurrying' agent, it is a commonly used antiemetic. Metoclopramide acts in the g.i.t. as well as in CNS.

GIT: Metoclopramide has more prominent effect on upper g.i.t.; increases gastric peristalsis while relaxing the pylorus and the first part of duodenum. This speeds up gastric emptying, especially if it was slow. Lower esophageal sphincter (LES) tone is increased and gastroesophageal reflux is opposed. It also increases intestinal peristalsis to some extent, but has no significant action on colonic motility and on gastric secretion.

CNS Metoclopramide is an effective antiemetic. Acting on the CTZ it blocks apomorphine induced vomiting. The gastrokinetic action may contribute to the antiemetic effect. However, it has no chlorpromazine (CPZ) like antipsychotic property, though it does share the extrapyramidal and prolactin secretion augmenting actions of CPZ.

Mechanism of action: Metoclopramide acts through both dopaminergic and serotonergic receptors (*see* Fig. 48.2)

(a) *D2 antagonism* Dopamine (acting through D2 receptors) is an inhibitory transmitter in the g.i.t. It normally acts to delay gastric emptying when food is present in the stomach. It also appears to cause gastric dilatation and LES relaxation attending nausea and vomiting. Metoclopramide blocks D2 receptors and has an opposite effect—hastening gastric emptying and enhancing LES tone by augmenting ACh release. However, clinically this action is secondary to that exerted through $5HT_4$ receptors.

The central antidopaminergic (D2) action of metoclopramide on CTZ is clearly responsible for its antiemetic property. Other manifestations of D2 blockade are antagonism of apomorphine induced vomiting, CPZ like extrapyramidal effects and hyperprolactinaemia.

(b) *$5\text{-}HT_4$ agonism* Metoclopramide acts in the g.i.t. to enhance ACh release from myenteric motor neurones. This results from $5\text{-}HT_4$ receptor activation on primary afferent neurones (PAN) of the ENS, which in turn activate the excitatory interneurones (Fig. 48.2). The *gastric hurrying* and *LES tonic* effects of metoclopramide are mainly due to this action which is synergised by bethanechol and attenuated by atropine.

(c) *$5\text{-}HT_3$ antagonism* At high concentrations metoclopramide can block $5\text{-}HT_3$ receptors present on inhibitory myenteric interneurones and in the NTS/CTZ. The peripheral action can augment ACh release in the gut, but appears to be minor. The central anti $5\text{-}HT_3$ action appears to be significant only when large doses are used to control CINV.

Pharmacokinetics Metoclopramide is rapidly absorbed orally, enters brain, crosses placenta and is secreted in milk. It is partly conjugated in liver and excreted in urine within 24 hours; $t_{1/2}$ is 3–6 hours. Orally it acts in ½–1 hr, but within 10 min after i.m. and 2 min after i.v. injection. Action lasts for 4–6 hours.

Interactions The rate of absorption of some drugs, e.g. aspirin, diazepam, digoxin may be altered by the gastric hurrying action of metoclopramide.

By blocking DA receptors in basal ganglia, it abolishes the therapeutic effect of levodopa.

Adverse effects Metoclopramide is generally well tolerated.

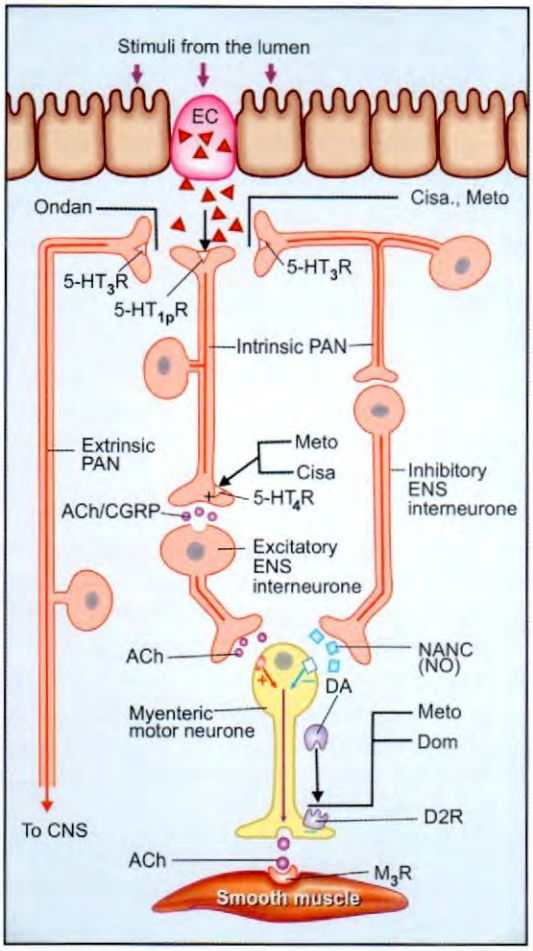


Fig. 48.2: Schematic depiction of seronergic (5-HT) regulation of peristaltic reflex, and sites of action of prokinetic drugs.

Distention and other luminal stimuli trigger 5-HT release from the enterochromaffin cells (EC) located in the enteric mucosa. This stimulates intrinsic and extrinsic primary afferent neurones (PAN) of the enteric nervous system (ENS) through the peripheral variant of 5-HT$_1$ receptor (5-HT$_{1P}$R) and 5-HT$_3$ receptor (5-HT$_3$R). The extrinsic PAN convey impulses to the CNS *via* vagus and dorsal root ganglia and participate in the causation of vomiting and abdominal pain when stimulation is strong. Ondansetron (Ondan) acts partly by blocking activation of extrinsic PAN through 5-HT$_3$R.

The intrinsic PAN interact with excitatory and inhibitory interneurones of the ENS to mediate both contraction (of proximal gut muscles) and relaxation (of distal gut muscles) to coordinate the peristaltic reflex, respectively through release of acetylcholine (ACh)/calcitonin gene related peptide (CGRP) and nonadrenergic–noncholinergic (NANC) transmitter, which is mainly nitric oxide (NO). Cisapride (Cisa.) and metoclopramide (Meto.) activate the prejunctional 5-HT$_4$ receptors (5-HT$_4$R) located on the terminals of the intrinsic PAN and promote contractile activity by enhancing ACh/CGRP release. The weak 5-HT$_3$ blocking action of Cisa. and Meto., in addition, reduces activity in the inhibitory interneurone (minor action).

Domperidone (Dom) and Meto also block the action of dopamine (DA) on prejunctional D2 receptor (D2R) which normally inhibits ACh release from the myenteric motor neurone, and thus augment smooth muscle contraction elicited through muscarinic M$_3$ receptor (M$_3$R)

Sedation, dizziness, loose stools, muscle dystonias (especially in children) are the main side effects. Long-term use can cause parkinsonism, galactorrhoea and gynaecomastia, but it should not be used to augment lactation. No harmful effects are known when used during pregnancy. Though the amount secreted in milk is small, but suckling infant may develop loose motions, dystonia, myoclonus.

Dose: 10 mg (children 0.2–0.5 mg/kg) TDS oral or i.m. For CINV 0.3–2 mg/kg slow i.v./i.m.

PERINORM, MAXERON, REGLAN, SIGMET, 10 mg tab; 5 mg/5 ml syr; 10 mg/2 ml inj.; 50 mg/10 ml inj.

Uses

1. *Antiemetic:* Metoclopramide is an effective and popular drug for many types of vomiting—postoperative, drug induced, disease associated (especially migraine), radiation sickness, etc, but is less effective in motion sickness. Though ondansetron is preferred, metoclopramide continues to be used for prophylaxis and treatment of vomiting induced by emetogenic anticancer drugs (cisplatin, etc.). Promethazine, diphenhydramine, diazepam or lorazepam injected i.v. along with metoclopramide supplement its antiemetic action and reduce the attending dystonic reactions. Dexamethasone i.v. also augments the efficacy of metoclopramide.
2. *Gastrokinetic:* To accelerate gastric emptying:
   (a) When emergency general anaesthesia has to be given and the patient has taken food less than 4 hours before.
   (b) To relieve postvagotomy or diabetic gastroparesis associated gastric stasis.

   However, clinical efficacy is moderate.

3. *Dyspepsia* and other functional g.i. disorders: symptomatic relief may obtained. Metoclopramide may succeed in stopping persistent hiccups.
4. *Gastroesophageal reflux disease (GERD)* Metoclopramide may benefit milder cases of GERD, but is much less effective than PPIs/H_2 blockers (*see* p. 708).

Domperidone It is a D2 receptor antagonist, chemically related to haloperidol, but pharmacologically related to metoclopramide. The antiemetic and prokinetic actions have a lower ceiling (less efficacious). Unlike metoclopramide, its prokinetic action is based only on D2 receptor blockade in upper g.i.t., and is not attenuated by atropine. Domperidone crosses blood-brain barrier poorly. Accordingly, extrapyramidal side effects are rare, but hyperprolactinaemia can occur. The antiemetic action is exerted mainly through CTZ which is not protected by blood-brain barrier. Because of poor entry into CNS, it does not block the therapeutic effect of levodopa in parkinsonism, but counteracts its dose-limiting emetic action.

Domperidone is absorbed orally, but bioavailability is only ~15% due to first pass metabolism. It is completely biotransformed and metabolites are excreted in urine. Plasma t½ is 7.5 hr.

Domperidone produces few side effects. Dry mouth, loose stools, headache, rashes, galactorrhoea are generally mild. Cardiac arrhythmias have developed on rapid i.v. injection.

Domperidone is primarily used as an antiemetic for mild-to-moderate cases of postoperative, drug and disease induced nausea and vomiting, but is not effective in severe cases. It is also not useful in motion sickness and is not advised for morning sickness. Efficacy in CINV is low.

Dose: 10–40 mg (Children 0.3–0.6 mg/kg) TDS.

DOMSTAL, DOMPERON, NORMETIC 10 mg tab, 1 mg/ml susp, MOTINORM 10 mg tab, 1 mg/ml drops.

Cisapride This benzamide derivative is a prokinetic with little antiemetic property, because it lacks D2 receptor antagonism. Effects of cisapride on gastric motility resemble metoclopramide, i.e. gastric emptying is accelerated, LES tone is improved and esophageal peristalsis is augmented. It restores and facilitates motility throughout the g.i.t., including colon (metoclopramide/domperidone do not accelerate colonic transit). The prokinetic action is exerted mainly through 5-HT_4 agonism which promotes ACh release from myenteric neurones, aided by weak 5-HT_3 antagonism which suppresses inhibitory transmission in myenteric plexus. Enteric neuronal activation *via* 5-HT_4 receptor also promotes cAMP-dependent Cl^- secretion in the colon, increasing water content of stools. Thus, cisapride often produces loose stools by enhancing colonic motility and secretion. It is devoid of action on CTZ, and does not produce extrapyramidal symptoms or hyperprolactinaemia.

Safety of cisapride was challenged by reports of serious ventricular arrhythmias and death, mainly among patients who concurrently took CYP3A4 inhibitors like azole antifungals, macrolide antibiotics, antidepressants, HIV protease inhibitors, etc. At high concentrations, cisapride blocks delayed rectifying K^+ channels in heart—prolongs Q-Tc interval and predisposes to *torsades de pointes*/ventricular fibrillation. Following such reports, cisapride was suspended from marketing in most countries several years back, but was available in India till it was banned in March 2011.

Mosapride A subsequently introduced congener of cisapride with similar gastrokinetic and LES tonic action due to 5-HT_4 agonistic (major) and 5-HT_3 antagonistic (minor) action in the myenteric plexus. Like cisapride, it has no clinically useful antiemetic action and does not produce extrapyramidal or hyperprolactinaemic side effects due to absence of D2 blocking property. Side effects are loose motions, abdominal pain, headache, dizziness and insomnia.

Preclinical studies showed that mosapride may not have the potential to prolong Q-T interval and carry risk of arrhythmias. However, after general use some reports of Q-T prolongation and arrhythmias, including *torsades de pointes* have appeared. Like cisapride, its plasma concentration is elevated by erythromycin and other CYP3A4 inhibitors increasing the risk of Q-T prolongation. Though, it has not been banned, it may not be as safe as considered earlier. Indications of mosapride are—nonulcer dyspepsia, diabetic gastroparesis, GERD (as adjuvant to PPIs), and some cases of chronic constipation. However, efficacy is not impressive.

Dose: 5 mg (elderly 2.5 mg) TDS.

KINETIX 5 mg tab, MOZA, MOZASEF, MOPRIDE 2.5 mg, 5 mg tabs; MOZA MPS: 5 mg + methylpolysiloxane 125 mg tab.

Itopride Another substituted benzamide produced in Japan and marketed in few countries,

but not in UK or USA, as a prokinetic drug. It has D2 antidopaminergic and anti-ChE (ACh potentiating) activity, but very low affinity for 5-HT_4 receptor. Thus, the basis of prokinetic action may be different from that of cisapride and mosapride. In healthy volunteers it was found unlikely to cause cardiac arrhythmias. This may be due to its low affinity for cardiac 5-HT_4 receptors which have been implicated in the adverse cardiac effects of cisapride.

Itopride is metabolized mainly by flavin monooxygenases and not by CYP450 isoenzymes. Thus, unlike cisapride and mosapride, it is devoid of drug interactions with CYP3A4 inhibitors (macrolides, azoles, etc.) resulting in cardiac arrhythmias. Side effects of itopride are diarrhoea, abdominal pain, headache. Galactorrhoea and gynaecomastia occur infrequently. No extrapyramidal effects are reported.

Indications of itopride are similar to those of other prokinetic drugs. In small comparative trials, its efficacy in relieving symptoms of dyspepsia has been rated similar to or better than domperidone and mosapride.

Dose: 50 mg TDS before meals.

GANATON, ITOFLUX, ITOKINE, ITOPRID 50 mg tab.

Levosulpiride This substituted benzamide blocks central as well as peripheral D2 receptors and has atypical antipsychotic (*see* p. 468), prokinetic and antiemetic properties. Because it acts both centrally as well as in the gut, levosulpiride has been used mainly for symptomatic relief of several functional gastrointestinal disorders, e.g. dyspepsia, nausea, bloating, GERD, irritable bowel syndrome, etc.

Dose: 25 mg TDS to 75 mg BD as SR tab.

LESURIDE, NEXIPRIDE 25 mg tab, 75 mg tab, 25 mg/2 ml inj.

Cinitapride It is a benzamide gastrokinetic drug developed in Spain and marketed in Spain, Mexico, Argentina and India. Cinitapride acts by inhibiting 5-HT_3 and dopamine D2 receptors, as well as by stimulating 5-HT_4 receptors in the myenteric plexus. It is indicated in functional g.i. disorders like non-ulcer dyspepsia, delayed gastric emptying and GERD, but only limited clinical data is available about its efficacy and safety. It is claimed to afford partial to complete relief of symptoms like epigastric pain, belching, reflux, early satiety, dysphagia, nausea and vomiting in upto 80 patients of dyspepsia. However, comparative value with other prokinetic drugs has not been adequately evaluated. Common side effects are drowsiness, diarrhoea, muscle dystonias of head, neck and tongue. Mental confusion and allergic reactions can occur. Driving is not advised after taking cinitapride. However, no Q–T prolongation or risk of arrhythmia has been observed, even on taking it with ketoconazole. Atropinic drugs may reduce its efficacy.

Dose: 1 mg TDS 15 min before meals, or 3 mg OD as extended release (ER) tablet.

CINTAPRO, KINPRIDE, CIN MOVE 1 mg tab, 3 mg ER tab.

5-HT_3 ANTAGONISTS

Ondansetron It is the prototype of a distinct class of antiemetic drugs developed to control cancer chemotherapy/radiotherapy induced vomiting, and later found to be highly effective in PONV and disease/drug associated vomiting as well. Ondansetron blocks the depolarizing action of 5-HT exerted through 5-HT_3 receptors on vagal afferents in the g.i.t. as well as in NTS and CTZ. Cytotoxic drugs/radiation produce nausea and vomiting by causing cellular damage, which releases mediators including 5-HT from intestinal mucosa → activation of vagal afferents in the gut resulting in transmission of emetogenic impulses to the NTS and CTZ. Ondansetron blocks emetogenic impulses mainly at their peripheral origin in the g.i.t. and at their central relay. It does not block dopamine receptors. Vomiting induced by apomorphine or motion sickness is not suppressed. A minor 5-HT_4 antagonistic action has also been shown, but seems to have no clinical relevance.

Pharmacokinetics: Oral bioavailability of ondansetron is 60–70% due to first pass metabolism. It is hydroxylated by CYP1A2,

CYP2D6 and CYP3A, followed by glucuronide and sulfate conjugation. No clinically significant drug interactions have been noted. It is eliminated in urine and faeces, mostly as metabolites; t½ is 3–5 hrs, and duration of action is 8–12 hrs (longer at higher doses).

Dose and efficacy: For cisplatin and other highly emetogenic drugs—8 mg i.v. by slow injection over 15 min ½ hr before chemotherapeutic infusion, followed by 2 similar doses 4 hour apart. Single 24 mg i.v. dose on first day has also been used. To prevent delayed emesis 8 mg oral is given twice a day for 3–5 days. For PONV 4–8 mg i.v. given before induction is repeated 8 hourly. For less emetogenic drugs and for radiotherapy, an oral dose of 8 mg is given 1–2 hr prior to the procedure and repeated twice 8 hrly. Ondansetron is effective in 60–80% cases. This level of efficacy is similar to or better than high doses of metoclopramide, but it does not cause dystonias or sedation like the latter. However, many patients obtain only partial relief, and adjuvant drugs are now mostly used along with it to improve chances of complete response.
EMESET, VOMIZ, OSETRON, EMSETRON 4, 8 mg tabs, 2 mg/ml inj in 2 ml and 4 ml amps. ONDY, EMESET 2 mg/5 ml syrup.

In patients who do not obtain optimum protection by ondansetron alone, addition of dexamethasone, promethazine/diazepam or both, dexamethasone + NK_1 antagonist aprepitant enhances antiemetic efficacy. Adjuvant drugs are more often required for delayed phase vomiting that occurs on the second to fifth day of cisplatin therapy, in some, but not all patients.

Ondansetron alone is less effective in delayed vomiting than in acute vomiting which occurs within 24 hours of cisplatin dose in all patients.

Other types of vomiting: Efficacy of 5-HT_3 antagonists in prevention and treatment of PONV is now well established. Since this vomiting is multifactorial in origin, many other classes of antiemetic drugs are also protective. In comparative trials, superiority of ondansetron in terms of efficacy as well as lack of side effects and drug interactions has been demonstrated over metoclopramide and phenothiazines. Administered before surgery ondansetron (4–8 mg i.v.) repeated after 4 hours has become the first choice antiemetic at many centres.

Vomiting occurring as side effect of drugs or due to drug overdosage, g.i. disorders, uraemia and neurological injuries is also suppressed. However, efficacy in motion sickness is poor. Due to lack of safety data, ondansetron (also other 5-HT_3 antagonists) should be used during pregnancy only when unavoidable, such as in hyperemesis gravidarum.

Side effects: Ondansetron is generally well tolerated: the only common side effects are headache and dizziness. Mild constipation and abdominal discomfort occur in few patients. Hypotension, bradycardia, chest pain and allergic reactions are reported, especially after i.v. injection.

Granisetron It is 10 times more potent than ondansetron and probably more effective during the repeat cycle of chemotherapy. The weak 5-HT_4 blockade seen with ondansetron has not been detected in granisetron. Its plasma t½ is longer (8–12 hrs) and it needs to be given only twice on the day of chemotherapy. Side effect profile is similar to ondansetron.

Dose: 1–3 mg diluted in 20–50 ml saline and infused i.v. over 5 min before chemotherapy, repeated after 12 hr. For less emetogenic regimen 2 mg oral 1 hr before chemotherapy or 1 mg before and 1 mg 12 hr after it. For PONV 1 mg diluted in 5 ml and injected i.v. over 30 sec before starting anaesthesia or 1 mg orally every 12 hours.
GRANICIP, GRANISET 1 mg, 2 mg tabs; 1 mg/ml inj. (1, 3 ml amps).

Palonosetron It is the longest acting 5-HT_3 blocker having the highest affinity for 5-HT_3 receptors. Efficacy against acute phase CINV is comparable to ondansetron, but it is more effective in suppressing delayed vomiting occurring between 2nd to 5th days, probably because of its longer duration of action (elimination t½ is 40 hours). It is the only drug of this class approved by US-FDA for delayed CINV. Moreover, antiemetic efficacy is maintained during repeat cycles of chemotherapy.

Palonosetron is metabolized in liver as well as in kidney, mainly by CYP2D6, but also by CYP3A4 and CYP1A2. Side effects are headache, fatigue, dizziness, abdominal pain. Additive Q-T prolongation can occur when given with moxifloxacin, erythromycin, anti-psychotics,

antidepressants, etc. Rapid i.v. injection has caused blurring of vision. A mouth dissolving tablet containing 0.5 mg palonosetron has been approved for use in CINV.

Dose: 250 µg by slow i.v. injection 30 min before chemotherapy. Do not repeat before 7 days.

For PONV 75 µg i.v. as a single injection just before induction.

PALONOX 0.25 mg/ml inj, PALZEN 0.25 mg/50 ml inj.

Ramosetron It is a potent 5-HT_3 antagonist developed in Japan and marketed only in few Southeast Asian countries. The general properties are similar to ondansetron. It is used for CINV in a dose of 0.3 mg injected i.v. before chemotherapy, and repeated once daily. For low emetogenic chemotherapy, it can be given orally in a dose of 0.1 mg once daily. Ramosetron 0.3 mg i.v. is as effective as ondansetron 8 mg i.v. in preventing PONV. Since it has shown potential to normalize disturbed colonic function, ramosetron is also indicated for diarrhoea-predominant irritable bowel syndrome.

NOZIA 0.1 mg tab, 0.3 mg in 2 ml amp.

NK_1 RECEPTOR ANTAGONISTS

Realizing that activation of neurokinin (NK_1) receptor in CTZ and NTS by substance P released due to emetogenic chemotherapy and other stimuli plays a role in the causation of vomiting, selective antagonists of this receptor have been produced, and are being used as antiemetic.

Aprepitant It is a recently introduced selective, high affinity NK_1 receptor antagonist that blocks the emetic action of substance P, with little effect on 5 HT_3 and D2 or other receptors. Gastrointestinal motility is not affected. Oral aprepitant (125 mg + 80 mg + 80 mg over 3 days) combined with standard i.v. ondansetron + dexamethasone regimen significantly enhanced the antiemetic efficacy to protect upto 90% patients against high emetogenic cisplatin based chemotherapy. Greater additional protection (>70% cases protected *vs* only 40–50% protected without apprepitant) was afforded against delayed vomiting than against acute vomiting. It was particularly useful in patients undergoing multiple cycles of chemotherapy. Adjuvant benefit of aprepitant has also been demonstrated in cyclophosphamide based moderately emetogenic chemotherapy. A single (40 mg) oral dose of aprepitant has been found equally effective as ondansetron in PONV as well.

Aprepitant is well absorbed orally. It penetrates blood-brain barrier to act on central NK_1 receptors. It is metabolized in liver, mainly by CYP3A4. Metabolites are eliminated *via* bile in faeces and in urine; t½ is 9–13 hours, but clearance is reduced with increase in dose. Inducers and inhibitors of CYP3A4 are likely to interact with aprepitant. Dose of dexamethasone and warfarin needs to be reduced. Aprepitant should not be given with Q-T interval prolonging drugs like cisapride.

Tolerability of aprepitant is good. Adverse effects of combined regimen were similar to those produced by ondansetron + dexamethasone without aprepitant. Symptoms attributed to aprepitant are weakness, fatigue, flatulence and rearely rise in liver enzymes.

Dose: For CINV—125 mg before chemotherapy + 80 mg each on 2nd and 3rd day (all oral) along with i.v. ondansetron + dexamethasone.

For PONV—40 mg (single dose) oral before abdominal or other surgery.

APRECAP, APRESET, APRELIFE, EMPOV 125 mg (one cap) + 80 mg (2 caps) kit.

Fosaprepitant It is a parenterally administered prodrug of aprepitant.

ADJUVANT ANTIEMETICS

Corticosteroids (e.g. dexamethasone 8–20 mg i.v. before chemotherapy) can partly alleviate nausea and vomiting due to moderately emetogenic chemotherapy, but are more often employed to augment the efficacy of other primary antiemetic drugs like metoclopramide and ondansetron against highly emetogenic regimens. Corticosteroids enhance efficacy against both acute and delayed emesis. Dexamethasone 8 mg/day oral from 2–5th day of chemotherapy helps to alleviate delayed vomiting. The basis of the effect is not known; appears to be due to their anti-inflammatory action. They also serve to reduce certain side effects of the primary antiemetic.

Benzodiazepines The weak antiemetic property of BZDs is primarily based on the sedative action. Diazepam or lorazepam (oral/i.v.) given before chemotherapy as adjuvant to metoclopramide or ondansetron, help by relieving the psychogenic component, anticipatory vomiting and produce amnesia for the unpleasant procedure. They also suppress the dystonic side effects of metoclopramide.

Cannabinoids Δ^9 Tetrahydrocannabinol (Δ^9 THC) is the active principle of the hallucinogen *Cannabis indica* that possesses antiemetic activity against moderately emetogenic chemotherapy. It probably acts through the CB_1 subtype of cannabinoid receptors located on neurones in the CTZ and/or the vomiting centre itself.

Dronabinol is pure Δ^9 THC produced synthetically or extracted from *Cannabis*. In a dose of 5–10 mg/m^2 BSA orally (repeated as required) it can be used as an alternative antiemetic for moderately emetogenic chemotherapy in patients who cannot tolerate other antiemetics or are unresponsive to them. The hallucinogenic, disorienting and other central sympathomimetic effects (described on p. 480) are produced, and some subjects may experience a 'high', which may lead to addiction. The CNS actions limit the use of dronabinol to few nonresponsive patients. Its antiemetic action can be supplemented by dexamethasone.

Dronabinol is an appetite stimulant as well. It has been used in lower doses to improve feeding in cachectic/AIDS patients.

DIGESTANTS

These are substances intended to promote digestion of food. A number of proteolytic, amylolytic and lipolytic enzymes are marketed in combination formulations and are vigorously promoted for dyspeptic symptoms, and as appetite stimulants or health tonics. They are occasionally beneficial, only when elaboration of enzymes in g.i.t. is deficient. Their routine use in tonics and appetite improving mixtures is irrational.

1. *Pepsin* May be used along with HCl in gastric achylia due to atrophic gastritis, gastric carcinoma, pernicious anaemia, etc.

2. *Papain* It is a proteolytic enzyme obtained from raw papaya. Its efficacy after oral ingestion is doubtful.

3. *Pancreatin* It is a mixture of pancreatic enzymes obtained from hog and pig pancreas. It contains amylase, trypsin and lipase, and is indicated in chronic pancreatitis or other exocrine pancreatic deficiency states. Fat and nitrogen content of stools may be reduced and diarrhoea/steatorrhoea may be prevented. It has to be used as enteric coated tablets or capsules to protect the enzymes from being themselves digested in the stomach by pepsin. Nausea, diarrhoea and hyperuricaemia are the occasional side effects.

4. *Diastase and Takadiastase* These are amylolytic enzymes obtained from the fungus *Aspergillus oryzae*. They have been used in pancreatic insufficiency, but efficacy is equivocal.

Preparations

ARISTOZYME: Fungal diastase 50 mg, pepsin 10 mg, simethicone 50 mg cap and per 5 ml liquid.

DIGEPLEX: Diastase 62.5 mg, pepsin 20 mg per 10 ml after dissolving the tablet in sorbitol base provided.

ENTOZYME: Fungal diastase 50 mg, pepsin 10 mg per 5 ml syr.

LUPIZYME: Pepsin 125 mg, fungal diastase 18.75 mg, thiamine 2 mg, riboflavine 1 mg, pyridoxine 1.5 mg, vit B_{12} 1 µg, nicotinamide 15 mg per cap and per 5 ml syr.

PANZYNORM: Pancreatin 100 mg, bile ext. 40 mg, dry stomach ext. 110 mg tab.

UNIENZYME: Fungal diastase 20 mg, papain 30 mg, simethicone 50 mg, nicotinamide 25 mg, activated charcoal 75 mg tab.

VITAZYME: Fungal diastase 40 mg, cinnamon oil 0.25 mg, caraway oil 0.5 mg, cardamom oil 0.5 mg per 10 ml liq.

Enzyme preparations containing an antispasmodic or a laxative and fixed dose combinations of pancreatine or pancrelipase containing amylase, protease and lipase with any other enzyme are banned in India.

Methyl polysiloxane (Dimethyl polysiloxane, Simethicone, Dimethicone) It is a silicone polymer, a viscous amphiphilic liquid which reduces surface tension and collapses froth, 'antifoaming agent'. It is not absorbed from g.i.t. and is pharmacologically inert. Added to antacid, digestant and antireflux preparations (*see* above), it is briskly promoted as a remedy for 'gas', a very common gastric complaint. It is also claimed to coat and protect ulcer surface, to aid dispersion of antacids in gastric contents, and to prevent gastroesophageal reflux. However clinical efficacy is equivocal.
Dose: 40–120 mg 3 to 4 times a day.
DIMOL 40 mg tab. (single ingredient).

GALLSTONE DISSOLVING DRUGS

Laparoscopic cholecystectomy is the treatment of choice for gallstones, but medical therapy is an option in patients with small cholesterol (CH) stones who are unwilling or unfit for surgery.

CH remains dissolved in bile with the help of bile salts (salts of cholic acid and chenodeoxycholic acid conjugated with glycine and taurine) because bile salts are highly amphiphilic. A high CH : bile salt ratio favours crystallization of CH in bile; these crystals act as nidi for stone formation. *Chenodeoxycholic acid* (Chenodiol) and *Ursodeoxycholic acid* (Ursodiol) decrease CH content of bile, enabling solubilization of CH from the stone surface.

Chenodiol is not used now, because it is less effective, frequently causes diarrhoea, can raise plasma LDL-CH and carries risk of liver damage.

Ursodiol It is the hydroxy epimer of chenodiol, which is more effective and needs to be given at lower doses. Administered orally, ursodiol is well absorbed, gets conjugated in liver with glycine and taurine, and is excreted in bile. Thereafter, it largely undergoes enterohepatic circulation and has a long plasma t½ of ~ 4 days. It promptly reduces CH secretion into bile and promotes solubilization of biliary CH by liquid crystal formation. Ursodiol also inhibits intestinal CH absorption. Plasma LDL-CH level is not raised. It can achieve complete dissolution of biliary CH stones in upto 50% cases when given for 6–24 months. It is more liketly to succeed in patients who have a functioning gallbladder with multiple small floating gall stones.

Diarrhoea and rise in hepatic transaminase level is infrequent, and ursodiol is much better tolerated than clenodiol. However, gatric mucosal resistance may be impaired predisposing to ulceration.

Dose: 450–600 mg daily in 2–3 divided doses after meals; UDIHEP 150 mg tab, URSOCOL 150, 300 mg tabs, 450 mg SR cap.

Dissolution of gallstones is a very slow process: patient compliance is often poor. Once treatment is discontinued after stone dissolution, recurrences are common, because bile returns to its CH supersaturated state. Repeat courses may have to be given.

SECTION 11

☞ PROBLEM DIRECTED STUDY

48.1 A 4-year-old girl is brought to the hospital emergency. The parents are very alarmed by her condition that has developed over the past one hour, when she started making bizarre faces. The neck has become rigid and head has tilted to one side. The teeth are clinched and she is not speaking. The eyes are staring in one direction and there are intermittent purposeless movements of the upper limbs. The parents inform that she had vomited twice in the morning and was taken to a local doctor, who had given her an injection. The vomiting had stopped, but after about 2 hours of the injection she developed the above symptoms.

(a) What is the most likely cause of her symptoms? Could it be due to the injection given to her? If so, which drug could have caused it?

(b) How should this patient be treated?

(see Appendix-1 for solution)

Chapter 49 Drugs for Constipation and Diarrhoea

LAXATIVES (Aperients, Purgatives, Cathartics)

These are drugs that promote evacuation of bowels. A distinction is sometimes made according to the intensity of action.

(a) *Laxative or aperient*: milder action, elimination of soft but formed stools.

(b) *Purgative or cathartic*: stronger action resulting in more fluid and forceful evacuation.

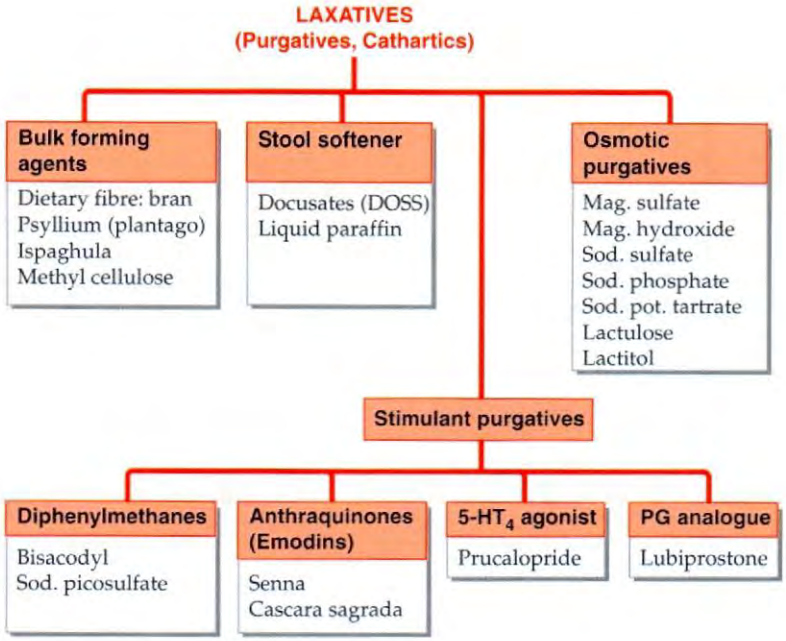
Many drugs in low doses act as laxative and in larger doses as purgative. The distinction, thus is vague.

MECHANISM OF ACTION

All purgatives increase the water content of the faeces by:

(a) A hydrophilic or osmotic action, retaining water and electrolytes in the intestinal lumen—increase volume of colonic content and make it easily propelled.

(b) Acting on intestinal mucosa, decrease net absorption of water and electrolyte; intestinal transit is enhanced indirectly by the fluid bulk.



(c) Increasing propulsive activity as primary action—allowing less time for absorption of salt and water as a secondary effect.

For some of the drugs, controversy continues as to whether they increase water content of stools as the primary action or it is a consequence of increased motility, because the amount of water absorbed largely depends on transit time. However, certain purgatives do increase motility through an action on the myenteric plexuses. Laxatives modify the fluid dynamics of the mucosal cell and may cause fluid accumulation in gut lumen by one or more of following mechanisms:

(a) Inhibiting Na^+K^+ATPase of *villous cells*—impairing electrolyte and water absorption.
(b) Stimulating adenylyl cyclase in *crypt cells*—increasing water and electrolyte secretion.
(c) Enhancing PG synthesis in mucosa which increases secretion.
(d) Increasing NO synthesis which enhances secretion and inhibits non-propulsive contractions in colon.
(e) Structural injury to the absorbing intestinal mucosal cells.

BULK PURGATIVES

Dietary fibre: bran Dietary fibre consists of unabsorbable cell wall and other constituents of vegetable food—cellulose, lignins, gums, pectins, glycoproteins and other polysaccharides. Bran is the residual product of flour industry which consists of ~40% dietary fibre. It absorbs water in the intestines, swells, increases water content of faeces—softens it and facilitates colonic transit. Osmotically active products may be formed in the colon by bacterial degradation of pectins, gums, etc. which act to retain water. Dietary fibre supports bacterial growth in colon which contribute to the faecal mass. Certain dietary fibres (gums, lignins, pectins) bind bile acids and promote their excretion in faeces → degradation of cholesterol in liver is enhanced → plasma LDL-cholesterol may be somewhat lowered.

Increased intake of dietary fibres is the most appropriate method for prevention of functional constipation, particularly if the diet is deficient in fibre. It is the first line approach for most patients of simple constipation. Dietary fibre is also useful when straining at stools has to be avoided.

Drawbacks: Bran is generally safe, but it is unpalatable, large quantity (20–40 g/day) needs to be ingested. It has been included in some breakfast cereals, biscuits, etc. Full effect requires daily intake for at least 3–4 days. It does not soften faeces already present in colon or rectum. As such, bran is useful for prevention of constipation, but not for treating already constipated subjects. Flatulence may occur.

Bran should not be used in patients with gut ulcerations, adhesions, stenosis and when faecal impaction is a possibility. Symptoms of irritable bowel syndrome (IBS) may be worsened by bran and other insoluble fibres.

Psyllium (Plantago) **and Ispaghula** They contain natural colloidal mucilage which forms a bulky gelatinous mass by absorbing water. It is largey fermented in colon: increases bacterial mass and softens the faeces. Refined ispaghula husk 3–8 g is freshly mixed with cold milk, fruit juice or water and taken once or twice daily. It acts in 1–3 days. It should not be swallowed dry (may cause esophageal impaction). Prolonged intake of ispaghula and other soluble fibres reduces rectosigmoid intraluminal pressure and helps to relieve symptoms of IBS, including pain, constipation as well as diarrhoea. Symptoms of chronic diverticulosis may also be relieved.

Ispaghula husk (refined): ISOGEL (27 g/ 30 g), NATURE CARE (49 g/100 g), FYBOGEL (3.5 g/5.4 g) powder FIBRIL (3.4 g/11 g) powder;
Psyllium hydrophilic mucilloid: ISOVAC (65 g/100 g) granules.

Methylcellulose A semi-synthetic, colloidal, hydrophilic derivative of cellulose that remains largely unfermented in colon. A dose of 4–6 g/day is satisfactory in most individuals.

Bulk forming agents can improve stool consistency in patients with colostomy. Generous amounts of water must be taken with all bulk forming agents. The choice among different bulking agents is a matter of personal preferences.

STOOL SOFTENER

Docusates (Dioctyl sodium sulfosuccinate: DOSS) It is an anionic detergent, softens the stools by net water accumulation in the lumen by an action on the intestinal mucosa. It emulsifies the colonic contents and increases penetration of water into the faeces. By a detergent action, it can disrupt the mucosal barrier and enhance absorption of many nonabsorbable drugs, e.g. liquid paraffin—should not be combined with it. It is a mild laxative; especially indicated when straining at stools must be avoided.

Dose: 100–400 mg/day; acts in 1–3 days.

CELLUBRIL 100 mg cap; LAXICON 100 mg tab, DOSLAX 150 mg cap.

As enema 50–150 mg in 50–100 ml;

LAXICON 125 mg in 50 ml enema.

Cramps and abdominal pain can occur. It is bitter; liquid preparations may cause nausea. Hepatotoxicity is feared on prolonged use.

Liquid paraffin It is a viscous liquid; a mixture of petroleum hydrocarbons, that was introduced as a laxative at the turn of 19th century. Millions of gallons have passed through the intestinal pipeline since then. It is pharmacologically inert. Taken for 2–3 days, it softens stools, retards water absorption and is said to lubricate hard scybali by coating them.

Dose: 15–30 ml/day—oil as such or in emulsified form.

Disadvantages

(a) It is bland but very unpleasant to swallow because of oily consistency.

(b) Small amount passes into the intestinal mucosa—is carried into the lymph → may produce foreign body granulomas in the intestinal submucosa, mesenteric lymph nodes, liver and spleen.

(c) While swallowing it may trickle into lungs—cause lipid pneumonia.

(d) Carries away fat soluble vitamins with it into the stools: deficiency may occur on chronic use.

(e) Leakage of the oil past anal sphincter may embarrass.

(f) May interfere with healing in the anorectal region

Thus, it should be used only occasionally.

CREMAFFIN: Liquid paraffin 3.75 ml, milk of magnesia 11.25 ml/15 ml emulsion, AGAROL: Liquid paraffin 4.8 ml with glycine and sorbitol in 15 ml aqueous emulsion.

STIMULANT PURGATIVES

These are powerful purgatives: often produce griping. The mechanism of action is not clearly known. Some of them directly increase gut motility by acting on myenteric plexus neurones. However, the more important made of action appears to be accumulation of water and electrolytes in the gut lumen by altering absorptive and secretory activity of the mucosal cell. They inhibit Na^+K^+ATPase at the basolateral membrane of villous cells, thereby transport of Na^+ and accompanying water into the interstitium is reduced. Secretion is enhanced by activation of cAMP in crypt cells (*see* Fig. 49.1) as well as by increased PG synthesis. The laxative action of bisacodyl and cascara is shown to be partly dependent upon increased NO synthesis or action in the colon.

Larger doses of stimulant purgatives can cause excess purgation resulting in fluid and electrolyte imbalance. Hypokalaemia can occur on regular intake. Routine and long-term use must be discouraged, because it can produce colonic atony. They can reflexly stimulate gravid uterus, therefore are contraindicated during pregnancy. Subacute or chronic intestinal obstruction is another contraindication.

Diphenylmethanes

Bisacodyl Administered orally, this synthetic diphenylmethane purgative is absorbed in the intestine and excreted in bile to undergo partial enterohepatic circulation. After activation in the intestine by deacetylation, it irritates colonic mucosa to increase fluid secretion, as well as stimulate enteric neurones to promote peristaltic movements.

One or two semiformed motions occur after 6–8 hours. Optimum doses vary considerably among individuals. The average dose is:

Bisacodyl 5–10 mg oral at bed time; 10 mg (adult), 5 mg (child) suppository in morning. DULCOLAX 5 mg tab; 10 mg (adult), 5 mg (child) suppository: CONLAX 5 mg, 10 mg suppository.

Orally, this dose may be ineffective in some individuals, but produces fluid evacuations and cramps in others. Morphological alterations in

the colonic mucosa have been observed; the mucosa becomes more leaky. The suppository may cause rectal inflammation.

Allergic reactions—skin rashes, fixed drug eruption and Stevens-Johnson syndrome have been reported.

Sodium picosulfate: Another diphenylmethane related to bisacodyl. It is hydrolysed by colonic bacteria to the active form, which then acts locally to irritate the mucosa and activate myenteric neurones. Bowel movement generally occurs after 6–12 hours of oral dose. Along with mag. citrate solution, it has been used to evacuate the colon for colonoscopy and colonic surgery.

Dose: 5–10 mg at bed time. Indications and side effects are similar to bisacodyl.

CREMALAX, LAXICARE 10 mg tab; PICOFIT 5 mg/5 ml syr.

Anthraquinones

These are plant products used in household/traditional medicine for centuries.

Senna is obtained from leaves and pods of certain *Cassia sp.*, while *Cascara sagrada* is the powdered bark of the buck-thorn tree. These and a number of other plant purgatives contain anthraquinone glycosides, also called *emodins*. Senna is most popularly used. The glycosides are not active as such. Unabsorbed in the small intestine, they are passed to the colon where bacteria liberate the active *anthrol* form, which either acts locally or is absorbed into circulation—excreted in bile to act on small intestine. Thus, they take 6–8 hours to produce action. Taken by lactating mothers, the amount secreted in milk is sufficient to cause purgation in the suckling infant.

The purgative action and uses of anthraquinones are quite similar to those of diphenylmethanes. Taken at bed time—a single, soft but formed evacuation generally occurs in the morning. Cramps and excessive purging occur in some individuals. The active principle stimulates the myenteric plexus to increase peristalsis and decrease segmentation. They also promote secretion and inhibit salt and water absorption in the colon.

Skin rashes, fixed drug eruption are the occasional adverse effects.

Regular use for 4–12 months causes colonic atony and mucosal pigmentation (melanosis).

Sennosides (Cal. salt): GLAXENNA 11.5 mg tab; PURSENNID 18 mg tab; SOFSENA 12 mg tab.

Prucalopride It is a selective 5-HT_4 receptor agonist marketed in Europe, UK and Canada for the treatment of chronic constipation in women, when other laxatives fail to provide adequate relief. It activates prejunctional 5-HT_4 receptors on intrinsic enteric neurones (*see* Fig. 48.2) to enhance release of the excitatory transmitter ACh, thereby promoting propulsive contractions in ileum and more prominently in colon. Colonic transit and stool frequency is improved in constipation-predominant IBS.

A 5-HT_4 receptor partial agonist *tegaserod* with similar action on colon was introduced few years back, but was withdrawn soon after when postmarketing surveillance showed that it increased the risk of edema, heart attack and stroke. These adverse consequences were ascribed to its interaction with 5-$HT_{1B/1D}$ receptors in addition to 5-HT_4 receptors. Prucalopride has shown low affinity for 5-$HT_{1B/1D}$ receptor, as well as for cardiac K^+ channels. As such, it appears to be free of cardiovascular risk. No Q-T prolongation has been noted during clinical trial. Side effects are headache, dizziness, fatigue, abdominal pain and diarrhoea, which generally subside during use.

Dose: 2 mg OD, elderly start with 1 mg OD.

Prucalopride has been cleared for clinical trial in India.

Lubiprostone This PG analogue developed recently, represents a new strategy in the treatment of constipation-predominant IBS and in idiopathic chronic constipation. Lubiprostone is an EP_4 receptor agonist which activates mucosal Cl^- channels by stimulating guanylyl-cyclase C. It produces Cl^- rich intestinal fluid and accelerates colonic transit. Refractoriness to its beneficial effects in chronic constipation does not appear to develop even after prolonged use. It also delays gastric emptying. Only a small fraction of the administered dose is absorbed. The most common side effect is nausea; others are dyspepsia and diarrhoea. Lubiprostone is recommended only in patients who have not improved adequately by other measures, including laxatives of at least two classes. It is expensive.

Dose: 24 µg BD with meals.

LUBOWEL 8 µg, 24 µg caps.

OSMOTIC PURGATIVES

Solutes that are not absorbed in the intestine retain water osmotically, increase fluidity of stools and distend the bowel—increasing peristalsis indirectly.

Magnesium ions release cholecystokinin which augments motility and secretion, contributing to purgative action of Mag. salts. All inorganic salts used as osmotic (saline) purgatives have similar action—differ only in dose, palatability and risk of systemic toxicity.

- Mag. sulfate (Epsom salt): 5–15 g; bitter in taste, may nauseate.
- Mag. hydroxide (as 8% W/W suspension—milk of magnesia) 30 ml; bland in taste; frequently used both as purgative and as antacid.
- Sod. sulfate (Glauber's salt): 10–15 g; bad in taste.
- Sod. phosphate: 6–12 g, taste not unpleasant.
- Sod. pot. tartrate (Rochelle salt): 8–15 g, relatively pleasant tasting.

The salts taken in above mentioned doses, dissolved in 150–200 ml of water, produce 1–2 fluid evacuations within 1–3 hours with mild cramping; cause nearly complete emptying of bowels. Smaller doses may have a milder laxative action.

Mag. salts are contraindicated in renal insufficiency, while Sod. salts should not be given to patients of CHF and other Sod. retaining states. Repeated use of saline purgatives can cause fluid and electrolyte imbalance.

Saline purgatives are infrequently used now for the treatment of constipation because they are inconvenient/unpleasant, produce watery stools and after-constipation. However, they may be employed when constipation is to be relieved urgently and for preparation of bowel before surgery, colonoscopy; in food/drug poisoning and as after-purge in the treatment of tapeworm infestation.

Lactulose It is a semisynthetic disaccharide of fructose and lactose which is neither digested nor absorbed in the small intestine, therefore retains water. Lactulose is broken down in the colon by bacteria to osmotically more active and weakly acidic products. In a dose of 10–30 g taken with plenty of water, it produces soft formed stools in 8–24 hours. Flatulence and flatus is common, cramps occur in few. Some patients feel nauseated by its peculiar sweet taste.

In patients with hepatic encephalopathy, lactulose causes reduction of blood NH_3 concentration by 25–50%. The acidic breakdown products of lactulose lower the pH of stools which is unfavourable to NH_3 producing bacteria. Ammonia produced by bacteria in colon is converted to ionized NH_4^+ salts that are not absorbed. For this purpose 20 g TDS or more may be needed. Loose motions are produced at this dose.

LACSAN, MTLAC 10 g/15 ml liq. DUPHALAC, LIVO-LUK 6.67 g/10 ml liq, LOOZ 10 g/15 ml soln.

Lactitol It is a disaccharide sugar alcohol with properties similar to lactulose. Lactitol is neither absorbed nor digested in ileum, but gets fermented by colonic bacteria into osmotically active and weakly acidic products. Water content of faeces is increased while its pH is lowered. Thus, it discourages NH_3 producing colonic bacteria and reduces NH_3 absorption to be helpful in hepatic encephalopathy. The laxative efficacy of lactitol is comparable to that of lactulose, but its palatability and patient acceptability is claimed to be better. Side effects are distention, flatulence, cramps, dyspepsia, nausea and vomiting.

Lactitol is indicated as an alternative to lactulose for the treatment of constipation and hepatic encephalopathy.

Dose: 15–30 ml of syrup containing 10 g/15 ml.

LACTIHEP, GUTCLEAR, EVA-Q: Lactitol 10 g/15 ml syr, 10 g granules sachet; CADILOSE GREEN GRANULES: Lactitol 10 g + ispaghula husk 3.5 g/15 g sachet.

CHOICE AND USE OF PURGATIVES

The primary indication of laxatives is prevention and treatment of acute as well as chronic constipation. However, they are contraindicated in:

- A patient of undiagnosed abdominal pain, colic or vomiting.
- Organic (secondary) constipation due to stricture or obstruction in bowel, hypothyroidism, hypercalcaemia, malignancies and certain drugs, e.g.—opiates, sedatives, anticholinergics including antiparkinsonian, antidepressants and antihistaminics, oral iron, clonidine, verapamil and laxative abuse itself.

The primary cause should be treated in these cases. Valid indications of laxatives are:

1. *Functional constipation* Constipation is infrequent production of hard stools requiring straining to pass, or a sense of incomplete evacuation. A stool frequency of once in 2 days

to 2–3 times per day is considered normal by different individuals. Constipation is a symptom rather than a disease. Various aspects of the patient's lifestyle may contribute:

(a) Misconception about the normal/necessary frequency, amount or consistency of stools.
(b) Inadequate fibre in diet, less fluid intake.
(c) Lack of exercise, sedentary nature of work.
(d) Irregular bowel habits, rushing out for job.

Proper assessment of the causative factor in the patient and its correction by high fibre diet, adequate fluids, physical exercise and regular bowel habits, leaves only a minority of cases to be treated by drugs.

Constipation may be spastic or atonic.

(i) *Spastic constipation* (irritable bowel): The stools are hard, rounded, stone like and difficult to pass. The first choice laxative is ispaghula or any of the soluble fibres taken over weeks/months. Stimulant purgatives are contraindicated.

(ii) *Atonic constipation* (sluggish bowel): mostly due to advanced age, debility or laxative abuse. Non-drug measures like plenty of fluids, exercise, regular habits and reassurance should be tried. If these measures do not work, a bulk forming agent or osmotic laxatives like lactulose or mag. hydroxide may be prescribed. Stimulant laxatives like bisacodyl or senna should be used only in patients with unsatisfactory response or those with poor compliance to the above.

2. *Bedridden patients* (myocardial infarction, stroke, fractures, postoperative): bowel movement may be sluggish and constipation can be anticipated.

To prevent constipation: Give bulk forming agents on a regular schedule; docusates, lactulose and liquid paraffin are alternatives.

To treat constipation: Enema (soap-water/glycerine) is preferred; bisacodyl or senna may be used orally.

Methylnaltrexone It is an opioid antagonist (primarily μ receptor) that does not penetrate blood-brain barrier, but acts on opioid receptors in the gut. Methylnaltrexone has been used to counteract opioid analgesic induced constipation in cancer/palliative care patients without blocking the analgesic action.

3. *To avoid straining at stools* (hernia, cardiovascular disease, eye surgery) and in perianal afflictions (piles, fissure, anal surgery) it is essential to keep the faeces soft. One should not hesitate to use adequate dose of a bulk forming agent, lactulose or docusates.

4. *Preparation of bowel for surgery, colonoscopy, abdominal X-ray* The bowel needs to be emptied of the contents including gas. Saline purgative, bisacodyl or senna may be used.

5. *After certain anthelmintics* (especially for tapeworm) Saline purgative or senna may be used to flush out the worm and the anthelmintic drug.

Fixed dose combinations of an anthelmintic (other than piperazine) with a purgative is banned in India, as are laxatives with enzyme preparations.

6. *Food/drug poisoning* The idea is to drive out the unabsorbed irritant/poisonous material from the intestines. Only saline purgatives are satisfactory.

The choice of a purgative depends on the latency of action and type of stools desired. This is given in Table 49.1.

Some combined preparations

AGAROL: Liquid paraffin 9.5 ml, phenolphthalein 400 mg, agar 60 mg per 30 ml emulsion.
CREMAFFIN: Milk of magnesia 11.25 ml, liq. paraffin 3.75 ml per 15 ml emulsion.
JULAX: Bisacodyl 10 mg, casanthranol 10 mg dragees.
PURSENNID-IN (with DOS): Purified senna ext. (cal salt) 18 mg, docusates 50 mg tab.

Purgative abuse Purgatives are often self prescribed and taken without consulting a physician. Some individuals are obsessed with

Table 49.1: Type of stools and latency of action of purgatives employed in usually recommended doses

Soft, formed faeces (take 1–3 days)	*Semifluid stools (take 6–8 hrs)*	*Watery evacuation (within 1–3 hrs)*
Bulk forming	Bisacodyl	Saline purgatives
Docusates	Sod. picosulfate	
Liquid paraffin	Senna	
Lactulose		

using purgatives regularly. This may be the reflection of a psychological problem. Others use a purgative casually, obtain thorough bowel evacuation, and by the time the colon fills up for a proper motion (2–3 days) they get convinced that they are constipated and start taking the purgative regularly. Chronic use of stimulant purgatives must be discouraged. Once the purgative habit forms, it is difficult to break. Drawbacks of purgative abuse are:

1. Fluid and electrolyte imbalance, especially hypokalaemia.
2. Steatorrhoea, malabsorption syndrome.
3. Protein losing enteropathy.
4. Spastic colitis.

TREATMENT OF DIARRHOEAS

Diarrhoea is too frequent, often too precipitate passage of poorly formed stools. It can range from an acute self-limiting episode to severe chronic illness. Diarrhoea is defined by WHO as 3 or more loose or watery stools in a 24 hour period. In pathological terms, it occurs due to passage of excess water in faeces.This may be due to:

- Decreased electrolyte and water absorption.
- Increased secretion by intestinal mucosa.
- Increased luminal osmotic load.
- Inflammation of mucosa and exudation into lumen.

Diarrhoeal diseases constitute a major cause of morbidity and mortality worldwide; especially in developing countries. It is more prevalent among children. According to current UNICEF data, 1400 young children die every day worldwide due to diarrhoea. The Ministry of Health has estimated that 13 children die of diarrhoea every hour in India, and that there were >100,000 under 5 yr deaths in 2015 due to diarrhoea. Recurrent or protracted diarrhoea is also a major cause of protein-calorie malnutrition in developing countries.

Relevant pathophysiology

Water and electrolytes are absorbed as well as secreted in the intestine. Jejunum is freely permeable to salt and water which are passively absorbed secondary to nutrient (glucose, amino acids, etc.) absorption. In the ileum and colon, Na^+K^+ATPase mediated active salt absorption occurs, primarily in the mature cells lining the villous tips, water follows isoosmotically. In addition *glucose facilitated Na^+ absorption* takes place in the ileum by Na^+-glucose cotransporter; one Na^+ ion is transported along with each molecule of glucose absorbed. This mechanism remains intact even in severe diarrhoeas.

Absorption of Cl^- and HCO_3^- is passive (paracellular) as well as by exchange of HCO_3^- for Cl^- (transcellular). Bicarbonate is absorbed also by the secretion of H^+ (similar to that in proximal tubule of kidney) and Na^+ accompanies it. K^+ is excreted in faecal water by exchange with Na^+, as well as by secretion into mucus and in desquamated cells. The osmotic load of luminal contents plays an important role in determining final stool water volume. When nonabsorbable solutes (e.g. lactulose) are present, and in disaccharidase deficiency (which occurs during starvation), the stool water is increased. Inhibition of Na^+K^+ATPase and structural damage to mucosal cell (by Rota virus) causes diarrhoea by reducing absorption.

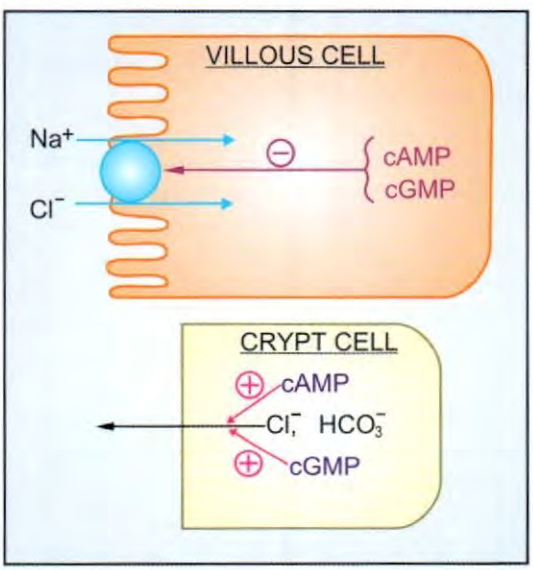


Fig. 49.1: Action of cyclic nucleotides on electrolyte transport of intestinal mucosal cells. In crypt cells cAMP plays the dominant role

Intracellular cyclic nucleotides are important regulators of absorptive and secretory processes (Fig. 49.1). Stimuli enhancing cAMP or cGMP cause net loss of salt and water, both by inhibiting NaCl absorption in villous cells and by promoting Cl^- secretion (Na^+ accompanies) in the crypt cells which are primarily secretory. Many bacterial toxins, e.g. cholera toxin, exotoxin elaborated by *Enterotoxigenic E. coli* (ETEC), *Staph. aureus, Salmonella,* etc. activate adenylyl cyclase which enhances secretion that reaches its peak after 3–4 hours and persists until the stimulated cells are shed in the normal turnover, i.e. 36 hours after a single exposure. Concurrent inhibition of absorption adds to the rate of salt and water loss. Prostaglandins (PGs) and intracellular Ca^{2+} also stimulate the secretory process. All acute enteric infections produce secretory diarrhoea. The heat stable toxin (ST) of ETEC, *Clostridium difficile* and *E. histolytica* cause accumulation of cGMP which also stimulates anion secretion (though it is less potent than cAMP) and inhibits Na^+ absorption.

Diarrhoea associated with carcinoid (secreting 5-HT) and medullary carcinoma of thyroid (secreting calcitonin) is mediated by cAMP. Excess of bile acids also cause diarrhoea by activating adenylyl cyclase.

Traditionally, hypermotility of bowel has been ascribed a crucial role in diarrhoea. However, changes in intestinal motility are now thought to be of secondary importance and motility changes may be due to fluid accumulation in the lumen. Decreased segmenting activity in the intestine may promote diarrhoea by allowing less time for the absorptive processes.

Principles of management

Rational management of diarrhoea depends on establishing the underlying cause and instituting specific therapy (only if necessary), since most acute diarrhoeas are self-limiting. Majority of enteropathogens are taken care of by motility and other defence mechanisms of the gut. Therapeutic measures may be grouped into:

(a) Treatment of fluid depletion, shock and acidosis.
(b) Maintenance of nutrition.
(c) Drug therapy.

The relative importance of each measure is governed by the severity and nature of diarrhoea.

REHYDRATION

The priority measure in acute diarrhoea is to prevent and reverse salt and water depletion. In majority of cases, this is the only measure needed. Rehydration can be done orally or i.v.

Intravenous rehydration It is needed only when fluid loss is severe, i.e. > 10% body weight (if not promptly corrected, it will lead to shock and death), or if patient is losing > 10 ml/kg/hr, or is unable to take enough oral fluids due to weakness, stupor or vomiting. The recommended composition of i.v. fluid (Dhaka fluid) is:

NaCl	85 mM = 5 g	in 1 L of water or 5% glucose solution.
KCl	13 mM = 1 g	
$NaHCO_3$	48 mM = 4 g	

This provides 133 mM Na^+, 13 mM K^+, 98 mM Cl^- and 48 mM HCO_3^-. Ringer lactate (Na^+ 130, Cl^- 109, K^+ 4, lactate 28 mM) can be used alternatively.

Volume equivalent to 10% BW should be infused over 2–4 hours; the subsequent rate of infusion is matched with the rate of fluid loss. In most cases, oral rehydration can be instituted after the initial volume replacement.

Oral rehydration Advent of oral rehydration therapy (ORT) is considered a major advance of recent times. If the fluid loss is mild (5–7% BW) or moderate (7.5–10% BW) ORT can be instituted from the very beginning.

Rationale of ORS composition Oral rehydration is possible if glucose is added with salt. It capitalizes on the intactness of glucose coupled Na^+ absorption, even when other mechanisms have failed or when intestinal secretion is excessive, because the secreted fluid lacks glucose and cannot be reabsorbed. The principles governing composition of oral rehydration salt/solution (ORS) are:

(a) It should be isotonic or somewhat hypotonic, i.e. total osmolarity 200–310 mOsm/L (diarrhoea fluids are approximately isotonic with plasma, which is ~290 mOsm/L).
(b) The molar ratio of glucose should be equal to or somewhat higher than Na^+ (excess glucose will be utilized in absorbing Na^+ present in the intestinal secretions), but not exceed 110 mM.
(c) Enough K^+ (15–25 mM) and bicarbonate/citrate (8–12 mM) should be provided to make up the losses in stool.

The WHO recommended a standard formula in 1984 which provided Na^+ 90 mM, K^+ 20 mM, Cl^- 80 mM, citrate (base) 10 mM, glucose 110 mM and had a total osmolarity of 310 mOsm/L. Trisod. citrate was included in place of sod. bicarbonate because bicarbonate containing powder caked and developed a brown colour due to formation of furfural compounds with glucose, and had a short shelf life.

The above formula given to children with noncholera diarrhoea often produced periorbital edema due to excess Na^+ absorption. Based on the Na^+ content of ETEC stools, many paediatricians favoured 60 mM Na^+ and 90 mM glucose ORS.

New formula WHO-ORS In 2002 a new formula low Na^+ low glucose ORS was released by the WHO. A combined analysis of studies using this low osmolarity ORS has revealed that stool volume is reduced by 20% and incidence of vomiting by 30% compared to the older formula ORS. It also permits faster water absorption, precludes risk of hypernatremia and is cheaper. The new formula ORS has proven as effective and as safe in cholera as well.

The WHO and UNICEF have recommended replacement of standard (310 mOsm/L) ORS formula by the new (245 mOsm/L)/formula.

New formula WHO-ORS			
Content		*Concentrations*	
NaCl	2.6 g	Na^+	— 75 mM
KCl	1.5 g	K^+	— 20 mM
Trisod. citrate	2.9 g	Cl^-	— 65 mM
Glucose	13.5 g	Citrate	— 10 mM
Water	1 L	Glucose	— 75 mM
Total osmolarity 245 mOsm/L			

(available as ORETRAL-A, ELECTROBION, ELECTRAL 21 g sachet for 1000 ml; WALYTE, RELYTE 4.2 g sachet for 200 ml).

Potassium is an important constituent of ORS, since in most acute diarrhoeas K^+ loss is substantial. The base (bicarbonate, citrate, lactate) is added to correct acidosis due to alkali loss in stools. The base may independently promote Na^+ and water absorption. Though base-free ORS has been found to be equally effective in rehydrating, correction of acidosis is slower. Some experts consider base to be a nonessential constituent of ORS, but if present it may be beneficial, especially in severe cases with overt acidosis.

Administration of ORT Patients are encouraged to drink ORS at ½–1 hourly intervals. Initially 5–7.5% BW volume equivalent is given in 2–4 hours (5 ml/kg/hr in children). Thirst due to volume depletion provides an adequate driving force. Subsequently it may be left to demand, but should at least cover the rate of loss in stools. In a weak child who refuses to drink ORS at the desired rate, it can be given by intragastric drip. Restoring hydration within 6 hours should be aimed.

ORT is not designed to stop diarrhoea, but to restore and maintain hydration, electrolyte and pH balance until diarrhoea ceases, mostly spontaneously. It is the best and not a second choice approach to i.v. hydration.

Non-diarrhoeal uses of ORT

(a) Postsurgical, postburn and post-trauma maintenance of hydration and nutrition (in place of i.v. infusion).
(b) Heat stroke.
(c) During changeover from intravenous to enteral alimentation.

Zinc in pediatric diarrhoea Recent studies have shown that administration of zinc along with low osmolarity ORS reduces the duration and severity of acute diarrhoea episodes in children below 5 years of age. Continued zinc supplementation (20 mg/day for 6–60 months age; 10 mg/day for 0–6 month age) for 10–14 days following the diarrhoea episode also reduces recurrences of diarrhoea for the next 2–3 months. Accordingly, the WHO jointly with UNICEF and USAID have recommended that all children with acute diarrhoea should be given zinc supplementation along

with ORS and continued for the next 10–14 days. The Indian Academy of Pediatrics has endorsed the WHO recommendation and the Govt. of India has initiated providing zinc in addition to ORS through its National Rural Health Mission.

The mechanism of benefit of zinc in diarrhoea is not known. *In vitro* studies have suggested that zinc could reduce fluid secretion in the intestine by indirectly inhibiting cAMP dependent Cl^- transport across the mucosa through an action on the basolateral membrane K^+ channels. It could also strengthen the immune response and help regeneration of intestinal epithelium.

Zinc can be administered to children by dissolving zinc sulfate dispersible tablets.

ULSEEL (50 mg Zn) Cap (for adults)

ZIORAL 10 mg and 20 mg (Zn) dispersible tabs for infants and children respectively.

MAINTENANCE OF NUTRITION

Contrary to traditional view, patients of diarrhoea should not be starved. Fasting decreases brush border disaccharidase enzymes and reduces absorption of salt, water and nutrients. Starving can lead to malnutrition if diarrhoea is prolonged or recurrent. Feeding during diarrhoea has been shown to increase intestinal digestive enzymes and cell proliferation in mucosa. Simple foods like breast milk or ½ strength buffalo milk, boiled potato, cooked rice, fruit juices, chicken soup, banana, sago, etc. should be given as soon as the patient can eat. Avoiding fats, high fibre foods and alcohol generally improves patient comfort.

DRUG THERAPY

1. Antimicrobials in diarrhoea

One or more antimicrobial agent is almost routinely prescribed to most patients of diarrhoea. However, empiric use of antibiotics in all cases of acute diarrhoea is not justified, because:

- Bacterial pathogen is responsible for only a fraction of cases.
- Even in bacterial diarrhoea, antimicrobials alter the course of illness only in selected cases.
- Antimicrobials may prolong the carrier state.

Acute diarrhoea patients can be broadly placed in one of the two categories:

(a) *Noninvasive diarrhoea* Abundant watery diarrhoea lacking mucus or blood, usually dehydrating with frequent vomiting, periumbilical cramps, but little or no fever. These symptoms indicate small intestine to be the source of diarrhoea, which is generally caused by adhesive but noninvasive enterotoxigenic bacteria such as cholera, ETEC, *Salmonella enteritidis, Staph. aureus, Bacillus cereus* or by rota virus and other viruses which stimulate massive secretion by activating cAMP in intestinal mucosal cell. ORS and not antimicrobials is the main therapy.

(b) *Invasive diarrhoea* Slightly loose, smaller volume stools, frequently with mucus and/or blood, abdominal cramps, urgency, mild dehydration, usually attended with fever, but not vomiting. These symptoms are indicative of colonic involvement, mucosal invasion, generally caused by enteroinvasive organisms like *Shigella*, enteropathogenic *E. coli* (EPEC), *Campy. jejuni, Salmonella typhimurium, Yersinia enterocolitica, E. histolytica, Clostri. difficile.* Antimicrobials are needed in most of these.

A. *Antimicrobials are of no value* In diarrhoea due to *noninfective causes*, such as:

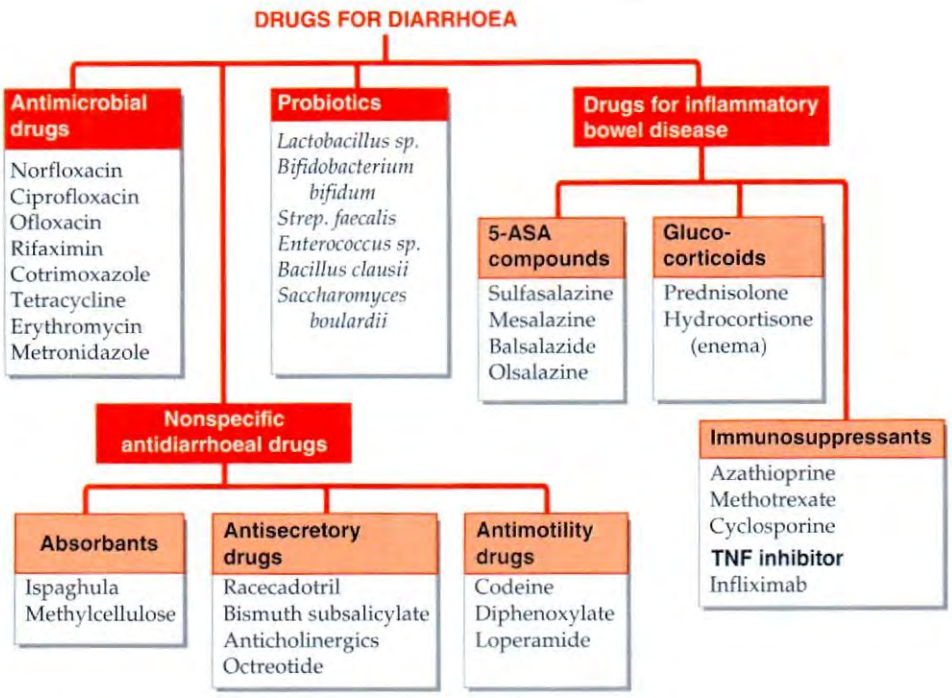
- Irritable bowel syndrome (IBS)
- Coeliac disease
- Pancreatic enzyme deficiency
- Tropical sprue (except when there is secondary infection)
- Thyrotoxicosis.

Rotavirus is an important pathogen of acute diarrhoea, especially in children. Along with other diarrhoea causing viruses, it is not amenable to chemotherapy.

B. *Antimicrobials are useful in severe disease:*

(1) *Salmonella* food poisoning is generally a self-limiting disease not requiring antimicrobials. However, antibiotics have been widely used, but should be restricted to severe illness or that in infants/elderly or immunocompromized patients. Ciprofloxacin or azithromycin or i.v. ceftriaxone may be employed when needed.

(2) Travellers' diarrhoea: mostly due to ETEC, *Campylobacter* or virus: ciprofloxacin,



norfloxacin, doxycycline or cotrimoxazole reduce the duration of diarrhoea and total fluid needed only in severe cases.

Rifaximin It is a minimally absorbed oral rifamycin (related to rifampin) active against *E. coli* and many other gut pathogens. It is approved by US-FDA for the empiric treatment of travellers' diarrhoea and is frequently used in India now in a dose of 400 mg TDS for 3 days. A review of data from controlled trials using rifaximin 200 mg TDS for 3 days has rated it to be superior to placebo, and as effective as ciprofloxacin in reducing duration of travellers' diarrhoea, irrespective of whether the causative pathogen was identified or not. It has also been used in diarrhoeal phase of IBS as well as for prophylaxis before and after gut surgery. A higher strength (550 mg) tablet is marketed for reducing the risk of hepatic encephalopathy recurrence by suppressing NH_3 forming gut bacteria. Patients with complaints of bloating, flatulence and flatus have reported subjective relief while taking rfaximin 400 mg BD, probably due to suppression of gas producing colonic bacteria.

The tolerability profile of rifaximin is similar to placebo. Side effects are flatulence, abdominal pain, defecation urgency and headache. Because of poor absorption, systemic toxicity is not expected.

Dose: For empiric treatment of diarrhoea 200–400 mg TDS for 3 days; for prevention of hepatic encephalopathy 550 mg TDS.

RIFAGUT, TORFIX, RACFAX 200, 400 mg tabs, RIXIMIN 200, 400, 550 mg tabs.

(3) Invasive diarrhoea: Severe cases with blood and mucus in stools, fever, cramps caused by EPEC, *Shigella*, non-typhoid *Salmonella*, *Yersinia enterocolitica*, etc. need to be treated empirically with ciprofloxacin, ofloxacin, norfloxacin, cotrimoxazole or doxycycline for symptomatic relief as well as for eradicating the pathogen.

C. Antimicrobials are useful in all cases:

- Cholera: Though only fluid replacement is life saving, tetracyclines reduce stool volume to nearly half. Cotrimoxazole is an alternative, especially in children. Lately, multidrug resistant cholera strains have arisen. These can be treated with norfloxacin/ciprofloxacin. Ampicillin and erythromycin are also effective.

- *Campylobacter jejuni:* Norfloxacin and other fluoroquinolones eradicate the organism from the stools and control diarrhoea. Erythromycin is fairly effective and is the preferred drug in children.
- *Clostridium difficile:* produces antibiotic associated pseudomembranous enterocolitis. The drug of choice for this superinfection is metronidazole, while vancomycin given orally is an alternative. The offending antibiotic must be stopped.
- Diarrhoea associated with bacterial growth in blind loops/diverticulitis may be treated with tetracycline or metronidazole.
- Amoebiasis, Giardiasis } metronidazole, diloxanide furoate, are effective drugs (*see* Ch. 62).

2. Probiotics in diarrhoea

These are microbial cell preparations, either live cultures or lyophillised powders, that are intended to restore and maintain healthy gut flora or have other health benefits. Diarrhoeal illnesses and antibiotic use are associated with alteration in the population, composition and balance of gut microflora. Recolonization of the gut by non-pathogenic, mostly lactic acid forming bacteria and yeast is believed to help restore this balance. Organisms most commonly used are—*Lactobacillus sp.*, *Bifidobacterium*, *Streptococcus faecalis*, *Enterococcus sp.* and the yeast *Saccharomyces boulardii*, etc.

Several reviews and metaanalysis of clinical trials have suggested that probiotics significantly reduce antibiotic-associated diarrhoea, particularly *C. difficile* diarrhoea, acute infective diarrhoea and risk of traveller's diarrhoea. Such studies also note that most of the randomised placebo controlled trials have been carried out in health-care hospital setting in developed countries, while data from community based studies carried out in resource-poor countries is minimal. Several probiotic strains, either alone or in combination, have been used in different trials, but the protective effect has been more or less similar, though collation of such data is difficult.

There is some evidence of adjunctive benefit of probiotics in mild-to-moderate cases of ulcerative colitis, when added to the primary therapy. Probiotics are reported to afford subjective relief in bloating and flatulence. While probiotics appear to be useful adjuncts to conventional therapy of acute infectious diarrhoea, and are loudly promoted as well as frequently prescribed, convincing evidence of their efficacy is lacking. This prevents them from being accepted as a standard component of diarrhoea therapy. Stronger evidence of efficacy has emerged against antibiotic-associated diarrhoea, but there is no justification yet for routine use of probiotics along with antibiotics. Natural curd/yogurt is an abundant source of lactic acid producing organisms, which can serve as probiotic.

For all practical purposes, probiotics are safe. Infections and acidosis caused by probiotics are very rare, though caution may be prudent in immunocompromized patients.

ECONORM, STIBS: *Saccharomyces boulardii* 250 mg sachet.

DAROLAC: *Lactobacillus,B. longam, S. boulardii* 1.25 billion live cells/sachet. One sachet to be taken suspended in water, milk, fruit juice.

BIFILAC: *Lactobacillus* 50 M (million), *Streptococcus faecalis* 30 M, *Clostridium butyricum* 2M, *Bacillus mesentericus* 1M per cap/sachet.

BIFILIN: *Lactobacillus sp*, 1 billion (B) *Bifidobacterium bifidum* 1B, *Streptococcus thermophillus* 0.25B, *Saccharomyces boulardii* 0.25B cap and sachet.

ACTIGUT: *Lactobacillus sp.*, *Bifidobacterium sp.* cap.
ENTEROGERMINA: *Bacillus clausii* 2 billion spores/5 ml oral amp.

3. Nonspecific antidiarrhoeal drugs

These drugs can be grouped into:

A. Absorbants and adsorbants
B. Antisecretory drugs
C. Antimotility drugs

A. Absorbants *Absorbants* are colloidal bulk forming substances like ispaghula, methyl cellulose, carboxy methyl cellulose which absorb water and swell. They modify the consistency and frequency of stools and give an impression of improvement, but do not reduce the water and electrolyte loss. They are of value in selected conditions like diarrhoea phase of IBS, and to increase the consistency of faeces in colostomy patients. Ispaghula and other bulk forming colloids are useful in both constipation and diarrhoea phases of IBS and reduce abdominal pain as well. Substances that do not ferment in colon are preferred for diarrhoea.

Adsorbants like kaolin, pectin, attapulgite are believed to adsorb bacterial toxins in the gut and coat/protect the mucosa. They were ones very popular ingredients of diarrhoea remedies, but are now banned in India, because there is no objective proof of their efficacy.

B. Antisecretory drugs

Racecadotril This recently introduced prodrug is rapidly converted to *thiorphan,* an enkephalinase inhibitor. It prevents degradation of endogenous enkephalins (ENKs) which are mainly δ opioid receptor agonists. Racecadotril decreases intestinal hypersecretion, without affecting motility (motility appears to be regulated through μ receptors) by lowering mucosal cAMP due to enhanced ENK action. It is indicated in the short-term treatment of acute secretory diarrhoeas. In contrast to loperamide or diphenoxylate, it is not contraindicated in children. The elimination t½ as thiorphan is 3 hr. Side effects are nausea, vomiting, drowsiness, flatulence.

Dose: 100 mg (children 1.5 mg/kg) TDS for not more than 7 days.

CADOTRIL, RACIGYL 100 mg cap, 15 mg sachet; REDOTIL 100 mg cap. ZEDOTT, ZOMATRIL 100 mg tab, 10 mg and 30 mg sachet and dispersible tab.

Bismuth subsalicylate Taken as suspension (60 ml 6 hourly) it is thought to act by decreasing PG synthesis in the intestinal mucosa, thereby reducing Cl^- secretion. It has some prophylactic value in travellers' diarrhoea (probably due to weak antibacterial action as well), but it is rather inconvenient to carry and take.Though quite popular in USA, it is not used in India and UK.

Anticholinergics Atropinic drugs can reduce bowel motility and secretion, but have poor efficacy in secretory diarrhoeas. They may benefit nervous/drug (neostigmine, metoclopramide) induced diarrhoeas and provide some symptomatic relief in dysenteries, diverticulitis.

Octreotide This somatostatin analogue (*see* p. 260) has a long plasma t½ (90 min) as well as potent antisecretory/antimotility action on the gut. It has been used to control diarrhoea in carcinoid and vasoactive intestinal peptide (VIP) secreting tumours, and for refractory diarrhoea in AIDS patients, but needs to be given by s.c. injection.

Opioids In addition to their well recognized antimotility action, opioids reduce intestinal secretion. Loperamide has been clearly shown to reduce secretion, probably through specific opioid receptors, but does not affect mucosal cAMP or cGMP levels.

C. Antimotility drugs

These are opioid drugs which increase tone and segmenting activity of the bowel, reduce propulsive movements and diminish intestinal secretions while enhancing absorption. They afford only symptomatic relief in diarrhoea. The major action appears to be mediated through μ opioid receptors located on enteric neuronal network, but direct action on intestinal smooth muscle and secretory/absorptive epithelium has also been demonstrated. The δ receptors are believed to promote absorption and inhibit secretion, while the μ receptors enhance absorption and decrease propulsive movements. Overall they increase resistance to luminal transit and allow more time for the absorptive processes. Colonic mass-peristalsis is suppressed. No tolerance develops to their constipating action.

Codeine (*see* p. 502) This opium alkaloid has prominent constipating action at a dose of 60 mg TDS. Codeine also has central effects, including low but significant dependence producing liability, because of which it is not used for diarrhoea now.

Diphenoxylate (2.5 mg) + *atropine* (0.025 mg): LOMOTIL tab and in 5 ml liquid.

Dose: 5–10 mg, followed by 2.5–5 mg 6 hourly.

Diphenoxylate is a synthetic opioid, chemically related to pethidine and used exclusively as constipating agent. The antidiarrhoeal action is most prominent, but because it is absorbed systemically and crosses blood-brain barrier—CNS effects do occur. Atropine is added in subpharmacological dose to discourage abuse by taking several tablets. Abuse liability is rated low, and overdose will produce disturbing atropinic side effects. It has caused respiratory depression, paralytic ileus and toxic megacolon in children, because of which it is contraindicated below 6 years of age. Loperamide has largely superseded it.

Loperamide This opiate analogue has major peripheral μ opioid agonistic and additional weak anticholinergic property. As a constipating agent it is much more potent than codeine. Because of poor water solubility—little is absorbed from the intestines. Entry into brain is negligible—CNS effects are rare and occur only with high doses. Loperamide has no analgesic action or abuse liability. The duration of action is longer (12 hr) than codeine and diphenoxylate.

In addition to its opiate like action on motility, loperamide also inhibits intestinal secretion. Direct interaction with calmodulin may be responsible

for the antidiarrhoeal action. Faecal continence is improved by enhancement of anal sphincter tone.

Adverse effects Abdominal cramps and rashes are the most common side effects. Paralytic ileus, toxic megacolon with abdominal distension is a serious complication in young children—fatalities have occurred, probably due to absorption of toxins from the intestines. Loperamide is contraindicated in children < 4 yr. However, it appears to be the most effective and most suitable antimotility antidiarrhoeal drug for adults.

Dose: 4 mg followed by 2 mg after each motion (max. 10 mg in a day); 2 mg BD for chronic diarrhoea.

IMODIUM, LOPESTAL, DIARLOP: 2 mg tab, cap.

Liquid formulation has been withdrawn to prevent use in young children.

The utility of antimotility drugs in diarrhoea is limited to symptomatic relief in noninvasive diarrhoea, mild traveller's diarrhoea, and when diarrhoea is exhausting; also for idiopathic diarrhoea in AIDS patients. They improve patient comfort by reducing stool frequency and urgency. Low doses may be used for chronic diarrhoea in IBS, but higher doses must be avoided. Their use is a short-term measure only.

Antimotility drugs are contraindicated in acute diarrhoea due to invasive organisms (*Shigella*, EPEC, EH, etc.), because they can be disastrous by increasing the risk of systemic invasion. Careful use may be made in mild IBD when loose motions and urgency are interfering with daily activities, but antimotility drugs are contraindicated in severe disease, since they may raise intraluminal pressure.

Antimotility drugs can be used to induce deliberate short-term constipation, e.g. after anal surgery, and to reduce the volume, fluidity and bag cleaning frequency in ileostomy/colostomy patients.

4. Drugs for inflammatory bowel disease (IBD)

IBD is a chronic relapsing inflammatory disease of the ileum, colon, or both, that may be associated with systemic manifestations. It is idiopathic, but appears to have an important immune component triggered by a variety of factors. The two major types of IBD are ulcerative colitis (UC) and Crohn's disease (CrD).

Ulcerative colitis It involves only the colon starting from the anal canal. The disease may remain restricted to the rectum or extend proximally in a contiguous manner to variable extent upto caecum. The lesions are mucosal and may be diffuse or confluent.

Crohn's disease In CrD lesions are patchy and transmural; may involve any part of the g.i.t. from mouth to the anus. Majority of patients have ileocaecal disease upto ascending colon, but in some it may be restricted to the small intestine, while in others to the colon. Because the lesions are transmural, complications like perforation, abscess, fistula, strictures, etc. occur. CrD is less amenable to medical therapy than is UC. Though UC and CrD are distinct clinical entities, few patients have features of both and cannot be clearly categorized into UC or CrD.

Extraintestinal manifestations like fever, oral ulceration, arthritis, dermatitis, hepatitis, uveitis, etc. may accompany both UC and CrD in upto 50% cases. The drugs used in UC and CrD are the same, but their roles and efficacy do differ. Drugs used in IBD can be grouped into:

- 5-Amino salicylic acid (5-ASA) compounds
- Corticosteroids
- Immunosuppressants
- TNFα inhibitors

Sulfasalazine (Salicylazosulfapyridine) It is a compound of 5-aminosalicylic acid (5-ASA) with sulfapyridine linked through an azo bond, and has a specific therapeutic effect in IBD.



5-ASA Azo bond Sulfapyridine

SULFASALAZINE

Having low solubility, sulfasalazine is poorly absorbed from the ileum. The azo bond is split by colonic bacteria to release 5-ASA and sulfapyridine. The former exerts a local antiinflammatory effect, the mechanism of which is not clear. Though 5-ASA inhibits both COX and LOX, decreased PG and LT production appears to play a minor role in the therapeutic effect. Inhibition of cytokine, PAF, TNFα and nuclear transcription factor (NFκB) generation seems to be more important. Migration of inflammatory

cells into bowel wall is interfered and mucosal secretion is reduced, affording symptomatic relief only in UC (because sulfasalazine releases 5-ASA in colon). Given during active phase of the disease sulfasalazine reduces number of stools, abdominal cramps and fever, but is less effective than corticosteroids. Alone, it is suitable for mild to moderate exacerbation only. A dose of 3–4 g/day induces remission over a few weeks in many patients of UC, but relapses are common after stoppage. Maintenance therapy with 1.5–2 g/day has been found to postpone relapse in many, but not all cases. The primary value of sulfasalazine is in maintaining remission in UC, while corticosteroids are reserved to treat acute exacerbations.

Though sulfasalazine and other 5-ASA compounds have been used in colon-restricted CrD, recent metaanalysis of clinical trials and observational studies have concluded that the 5-ASA drugs neither help in inducing remission in active CrD nor in maintaining it. The current treatment guidelines *do not recommend use of 5-ASA compounds in CrD.*

The beneficial effect of sulfasalazine in UC is clearly not due to any antibacterial action (bowel flora remains largely unaffected). The sulfapyridine moiety only serves to carry 5-ASA to the colon without being absorbed proximally. However, most of the released sulfapyridine is absorbed in the colon and is responsible for adverse effects like rashes, fever, joint pain, haemolysis and blood dyscrasias. Mild anaemia often persists during sulfasalazine therapy. Nausea, vomiting, headache and malaise are other frequent dose related side effects. Upto 1/3rd patients suffer intolerable adverse effects. Oligozoospermia and male infertility is reported. Sulfasalazine interferes with folate absorbtion. Folic acid supplementation should always be given during its use. Since other 5-ASA compounds produce fewer side effects, sulfasalazine is infrequently used now.

Sulfasalazine has also been used as a disease modifying drug in rheumatoid arthritis. The absorbed sulfapyridine moiety appears to be responsible for the therapeutic effect (*see* p. 228).

SALAZOPYRIN, SAZO-EN 0.5 g tab.

Mesalazine (Mesalamine) Both, mesalazine and mesalamine, are the official names given to 5-ASA. Realizing that 5-ASA is the active moiety in UC, but is not effective orally because of inability to reach the large bowel (it is absorbed in the small intestine), it has been formulated as a delayed release preparation or has been coated with pH sensitive acrylic polymer. The pattern of release over the length of jejunum, ileum and colon differs among the different formulations. The coated formulation (ASACOL, MESACOL) delivers 5-ASA to the distal small bowel and colon. A daily dose of 2.4 g has been found to improve over 50% patients of UC. Less than half of the 5-ASA released from these preparations is absorbed systemically, acetylated in the liver and excreted in urine. Like sulfasalazine, the primary use of mesalazine is in preventing relapse of UC. It may also be employed to treat mild-to-moderate exacerbations or as adjunct to corticosteroid in more severe active disease. It is not useful in either inducing or in maintaining remission in CrD.

MESACOL 400 mg, 800 mg tab, 0.5 g suppository; ASACOL, TIDOCOL 400 mg tab; ETISA 500 mg sachet.

Adverse effects Coated mesalazine is much better tolerated than sulfasalazine. Many patients who donot tolerate the latter, tolerate mesalazine. Side effects noted are nausea, diarrhoea, abdominal pain and headache, but are mild and less frequent. Serious adverse effects are fever, itching and leucopenia. Rashes and hypersensitivity reactions are rare. Bone marrow depression and decreased sperm count has not occurred. Mesalazine has nephrotoxic potential, because 30–40% of 5-ASA is released in the ileum and is absorbed. It is contraindicated in renal and hepatic impairment.

Drug interactions Coated mesalazine may enhance the gastric toxicity of glucocorticoids and hypoglycaemic action of sulfonylureas. Interaction with coumarins, furosemide, spironolactone, methotrexate and rifampicin are possible.

5-ASA enema Another mode of delivery of 5-ASA to colon is to administer it by a retention enema: 4 g enema once or twice daily is effective in distal ulcerative colitis and proctitis, including some refractory cases. 5-ASA enema is not useful for maintenance of remission.
MESACOL ENEMA 4 g/60 ml.

Olsalazine It consists of two molecules of 5-ASA coupled together by azo bond. Olsalazine is poorly absorbed in the ileum, the azo bond is split in the colon to provide 5-ASA locally. No separate carrier moiety is needed. Olsalazine is probably the most reliable preparation for delivery of 5-ASA to the colon. However, it often aggravates diarrhoea initially by decreasing transit time for gut contents and increasing secretions.

Balsalazide This is 5-ASA linked to 4-aminobenzoyl-β-alanine as the carrier which, unlike sulfapyridine, is inert. The 5-ASA is released in the colon, and the carrier is poorly absorbed. It can be used as a safer alternative to sulfasalazine.
Dose: 1.5 g BD to 2.25 g TDS.
COLOREX 750 mg cap and per 5 ml syr., INTAZIDE, BALACOL 750 mg tab.

Corticosteroids Prednisolone (40–60 mg/day) or equivalent dose of another glucocorticoid is highly effective in controlling symptoms as well as in inducing remission in both UC and CrD. Glucocorticoids are the drugs of choice for moderately severe exacerbations and in patients who do not respond to 5-ASA compounds. In responsive patients symptomatic relief usually starts within 3–7 days and remission is induced in 2–3 weeks. In more severe disease with extraintestinal manifestations and for rapid relief therapy may be initiated with i.v. methyl prednisolone 40–60 mg 12 to 24 hourly for few days. Hydrocortisone enema, or foam (ENTOFOAM 10%) can be used for topical treatment of proctitis and distal ulcerative colitis, but is less effective than oral treatment. Corticosteroids are generally used for short term; tapered over 8–12 weeks and discontinued after remission is induced. Because of the high dosage requirement even short term therapy with glucocorticoids is mostly attended by significant side effects, which should be managed symptomatically. Mesalazine started during steroid therapy is continued to prevent relapses. Corticosteroids are neither effective nor suitable for maintaining remission either in UC or CrD.

A sizeable percentage of severe IBD patients either relapse on stoppage of the steroid (*steroid-dependent*) or do not respond to it (*steroid-resistant*). Specific immunosuppressant drugs are strongly indicated in such IBD patients, and are now frequently prescribed. They also serve to avoid long-term steroid therapy which carries hazards.

Immunosuppressants *(see Ch. 64, 65)*

Immunosuppressants have now come to play an important role in the long-term management of IBD, especially CrD. About 60% patients with CrD and substantial number of UC patients require immunosuppressive therapy. However, risks of chronic immunosuppression must be weighed in each patient before instituting therapy with these drugs. Because of long latency of response, they are not suitable for acute flareups of the disease, but have good remission maintaining and steroid-sparing property.

Azathioprine This purine antimetabolite is the most effective and most commonly used immunosuppressant in IBD. *6-Mercaptopurine* (into which azathioprine is converted in the body) can be used in its place. Azathioprine or 6-MP are indicated in steroid-dependent, streroid-resistant and relatively severe cases of IBD, as well as for those who experience frequent flareups. Although, azathioprine and 6-MP have good remission maintaining property, their remission inducing activity is delayed and not dependable. The current guidelines donot recommend thiopurine monotherapy for inducing remission in IBD. Thiopurines have their own adverse effect potential, but the same is rated lower than that of prolonged steroid therapy. Some patients experience higher bone marrow toxicity of azathioprine and 6-MP due to genetic abnormality of one of its metabolizing enzymes TPMT. Such patients cannot be treated with these drugs.

Dose: Azathioprine 1.5–2.5 mg/kg/day, 6-MP 1–1.5 mg/kg/day for IBD.

Methotrexate This dihydrofolate reductase inhibitor with immunosuppressant and anti-inflammatory property is a 2nd line drug in IBD; may be needed particularly in CrD. It acts faster than azathioprine and has remission inducing property as well. The doses effective in IBD are higher than those needed for rheumatoid arthritis, and have been shown to suppress TNFα expression in macrophages and monocytes. Weekly parenteral therapy is needed, since absorption and efficacy of methotrexate by oral route is poor in IBD. Toxicity therefore is higher. Thus, methotrexate has a role only in severe CrD and in patients not responsive to or not tolerating azathioprine. Efficacy in UC is poor.

Cyclosporine This potent immunosuppressant is occasionally used in severe UC patients who do not improve with corticosteroid therapy. In this setting, i.v. cyclosporine usually controls symptoms in 7–10 days, and can be used as 'bridge' therapy for 2–3 months till azathioprine takes effect. Though, cyclosporine has remission maintaining effect in UC and CrD, it is not preferred for this purpose because of its renal toxicity and poor efficacy in IBD by the oral route.

TNFα inhibitors

Infliximab It is chimeric anti-TNFα antibody (*see* p. 230) that is indicated in severe active CrD, fistulating CrD and severe UC which has not improved with i.v. corticosteroids and immunosuppressants, or when the latter are inappropriate. Infused i.v. every 2–8 weeks, it decreases acute flareups and helps in fistula closure. Response occurs in 2–4 weeks. Therapy is continued till response is maintained. Infliximab produces substantial toxicity, including acute reactions, formation of antibodies and lowering of resistance to infections. Thus, it is only a reserve drug for selected patients with refractory disease.

Adalimumab and some other TNFα inhibitors are also being used in severe and refractory IBD.

NOTE: Drugs Controller General of India has banned the following category of antidiarrhoeal drugs:

1. Containing adsorbants like Kaolin, pectin, attapulgite, activated charcoal, etc.
2. Containing phthalylsulfathiazole, succinylsulfathiazole, sulfaguanidine, neomycin, streptomycin, dihydrostreptomycin.
3. *For pediatric use* containing diphenoxylate, loperamide, atropine, belladonna, hyosciamine, halogenated hydroxyquinolines.
4. Fixed dose combinations of antidiarrhoeals with electrolytes.
5. Fixed dose combination of loperamide with furazolidone.
6. Fixed dose combination of antidiarrhoeals with antihistaminics.

☞ PROBLEM DIRECTED STUDY

49.1 A 35-year-old man has come with complaint of acute onset diarrhoea. The stools are relatively small volume, liquid but not watery, frothy and are preceded by griping pain in abdomen. Foul smelling wind, urgency, eructation and mild fever are the other complaints. He has passed 4 loose motions in the past 8 hours and there is no appetite. He admits to have eaten spicy snacks last evening at a road side stall. Physical examination reveals body temperature 101°F, no signs of dehydration, but diffuse abdominal tenderness. A tentative diagnosis of enteroinvasive diarrhoea is made.

(a) Does this patient require rehydration therapy?
(b) Should an antibiotic be prescribed? If so, which antibiotic would be appropriate?
(c) Should an antimotility-antidiarrhoeal drug be coprescribed to reduce the number of stools?
(d) Should any other symptomatic drug be given to him?

(see Appendix-1 for solution)

SECTION 12

ANTIMICROBIAL DRUGS

Chapter 50 Antimicrobial Drugs: General Considerations

Antimicrobial drugs are the greatest contribution of the 20th century to therapeutics. Their advent changed the outlook of the physician about the power drugs can have on diseases. They are one of the few class of drugs which can cure, and not just palliate disease. Their importance is magnified in the developing countries, where infective diseases predominate. As a class, they are one of the most frequently used as well as misused drugs.

Drugs in this class differ from all others in that they are designed to inhibit/kill the infecting organism and to have no/minimal effect on the recipient. This type of therapy is generally called *chemotherapy* which has come to mean 'treatment of systemic infections with specific drugs that selectively suppress/kill the infecting microorganism without significantly affecting the host.' The basis of selective microbial toxicity is the action of the drug on a component of the microbe (e.g. bacterial cell wall) or metabolic processes (e.g. folate synthesis) that is not found in the host, or high affinity for certain microbial biomolecules (e.g. trimethoprim for bacterial dihydrofolate reductase). Due to analogy between the malignant cell and the pathogenic microbes, treatment of neoplastic diseases with drugs is also called 'chemotherapy'.

Antibiotics These are substances produced by microorganisms, which selectively suppress the growth of or kill other microorganisms at very low concentrations. This definition excludes other natural substances which also inhibit microorganisms but are produced by higher forms (e.g. antibodies) or even those produced by microbes but are needed in high concentrations (ethanol, lactic acid, H_2O_2).

Chemotherapeutic agent Initially this term was restricted to synthetic compounds, but since many antibiotics and their analogues have now been synthesized, this criterion has become irrelevant; both synthetic and microbiologically produced drugs need to be included together. It would be more meaningful to use the term *Antimicrobial agent* (AMA) to designate synthetic as well as naturally obtained drugs that attenuate microorganisms.

The *history* of chemotherapy may be divided into 3 phases.

(a) The period of empirical use: of 'mouldy curd' by Chinese on boils, chaulmoogra oil by the Hindus in leprosy, chenopodium by Aztecs for intestinal worms, mercury by Paracelsus (16th century) for syphilis, cinchona bark (17th century) for fevers.

(b) Ehrlich's phase of dyes and organometallic compounds (1890–1935): With the discovery of microbes in the later half of 19th century and that they are the cause of many

diseases; Ehrlich toyed with the idea that if certain dyes could selectively stain microbes, they could also be selectively toxic to these organisms. He tried methylene blue, trypan red, etc. He developed the arsenicals—*atoxyl* for sleeping sickness, *arsphenamine* in 1906 and neoarsphenamine in 1909 for syphilis. He coined the term 'chemotherapy' because he used drugs of known chemical structure (that of most other drugs in use at that time was not known) and showed that selective attenuation of infecting parasite was a practical proposition.

(c) The modern era of chemotherapy was ushered by Domagk in 1935 by demonstrating the therapeutic effect of *Prontosil*, a sulfonamide dye, in pyogenic infection. It was soon realized that the active moiety was paraamino benzene sulfonamide, and the dye part was not essential. Sulfapyridine (M & B 693) was the first sulfonamide to be marketed in 1938.

The phenomenon of *antibiosis* was demonstrated by Pasteur in 1877: growth of anthrax bacilli in urine was inhibited by air-borne bacteria. Fleming (1929) found that a diffusible substance was elaborated by *Penicillium* mould which could destroy *Staphylococcus* on the culture plate. He named this substance *penicillin* but could not purify it. Chain and Florey followed up this observation in 1939 which culminated in the clinical use of penicillin in 1941. Because of the great potential of this discovery in treating war wounds, commercial manufacture of penicillin soon started.

In the 1940s, Waksman and his colleagues undertook a systematic search of Actinomycetes as source of antibiotics and discovered *streptomycin* in 1944. This group of soil microbes proved to be a treasure-house of antibiotics and soon tetracyclines, chloramphenicol, erythromycin and many others followed. All three groups of scientists, Domagk, Fleming-Chain-Florey and Waksman received the Nobel Prize for their discoveries.

Over the past 50 years emphasis has shifted from searching new antibiotic producing organisms to developing semisynthetic derivatives of older antibiotics with more desirable properties or differing spectrum of activity. Few novel synthetic AMAs, e.g. fluoroquinolones, oxazolidinones have also been produced.

CLASSIFICATION

Antimicrobial drugs can be classified on the basis of many characteristics:

A. Chemical structure

1. *Sulfonamides and related drugs*: Sulfadiazine and others, Sulfones—Dapsone (DDS), Paraaminosalicylic acid (PAS).
2. *Diaminopyrimidines:* Trimethoprim, Pyrimethamine.
3. *Quinolones:* Nalidixic acid, Norfloxacin, Ciprofloxacin, Prulifloxacin, etc.
4. *β-Lactam antibiotics:* Penicillins, Cephalosporins, Monobactams, Carbapenems.
5. *Tetracyclines:* Oxytetracycline, Doxycycline, etc.
6. *Nitrobenzene derivative:* Chloramphenicol.
7. *Aminoglycosides:* Streptomycin, Gentamicin, Amikacin, Neomycin, etc.
8. *Macrolide antibiotics:* Erythromycin, Clarithromycin, Azithromycin, etc.
9. *Lincosamide antibiotics:* Lincomycin, Clindamycin.
10. *Glycopeptide antibiotics:* Vancomycin, Teicoplanin.
11. *Oxazolidinone:* Linezolid.
12. *Polypeptide antibiotics:* Polymyxin-B, Colistin, Bacitracin, Tyrothricin.
13. *Nitrofuran derivatives:* Nitrofurantoin, Furazolidone.
14. *Nitroimidazoles:* Metronidazole, Tinidazole, etc.
15. *Nicotinic acid derivatives:* Isoniazid, Pyrazinamide, Ethionamide.
16. *Polyene antibiotics:* Nystatin, Amphotericin-B, Hamycin.
17. *Azole derivatives:* Miconazole, Clotrimazole, Ketoconazole, Fluconazole.
18. *Others:* Rifampin, Spectinomycin, Sod. fusidate, Cycloserine, Viomycin, Ethambutol, Clofazimine, Griseofulvin.

B. Type of organisms against which primarily active

1. *Antibacterial:* Penicillins, Aminoglycosides, Erythromycin, Fluoroquinolones, etc.
2. *Antifungal*: Griseofulvin, Amphotericin B, Ketoconazole, etc.
3. *Antiviral:* Acyclovir, Amantadine, Zidovudine, etc.
4. *Antiprotozoal:* Chloroquine, Pyrimethamine, Metronidazole, Diloxanide, etc.
5. *Anthelmintic:* Mebendazole, Pyrantel, Niclosamide, Diethyl carbamazine, etc.

C. Spectrum of activity

Narrow-spectrum	*Broad-spectrum*
Penicillin G	Tetracyclines
Streptomycin	Chloramphenicol
Erythromycin	

The initial distinction between narrow and broad-spectrum antibiotics is no longer clearcut. Drugs with all ranges of intermediate band width, e.g. extended spectrum penicillins, newer cephalosporins, aminoglycosides, fluoroquinolones are now available. However, the terms 'narrow-spectrum' and 'broad-spectrum' are still popular.

D. Type of action

Primarily bacteriostatic

Sulfonamides	Erythromycin
Tetracyclines	Clindamycin
Chloramphenicol	Linezolid
	Ethambutol

Primarily bactericidal

Penicillins	Cephalosporins
Aminoglycosides	Vancomycin
Polypeptides	Fluoroquinolones
Rifampin	Metronidazole
Isoniazid	Cotrimoxazole
Pyrazinamide	

Some primarily static drugs may become cidal at higher concentrations (as attained in the urinary tract), e.g. erythromycin, nitrofurantoin. On the other hand, some cidal drugs, e.g. cotrimoxazole, streptomycin may just be static under certain circumstances.

E. Natural sources of antibiotics

Fungi

Penicillin	Griseofulvin
Cephalosporin	

Bacteria

Polymyxin B	Tyrothricin
Colistin	Aztreonam
Bacitracin	

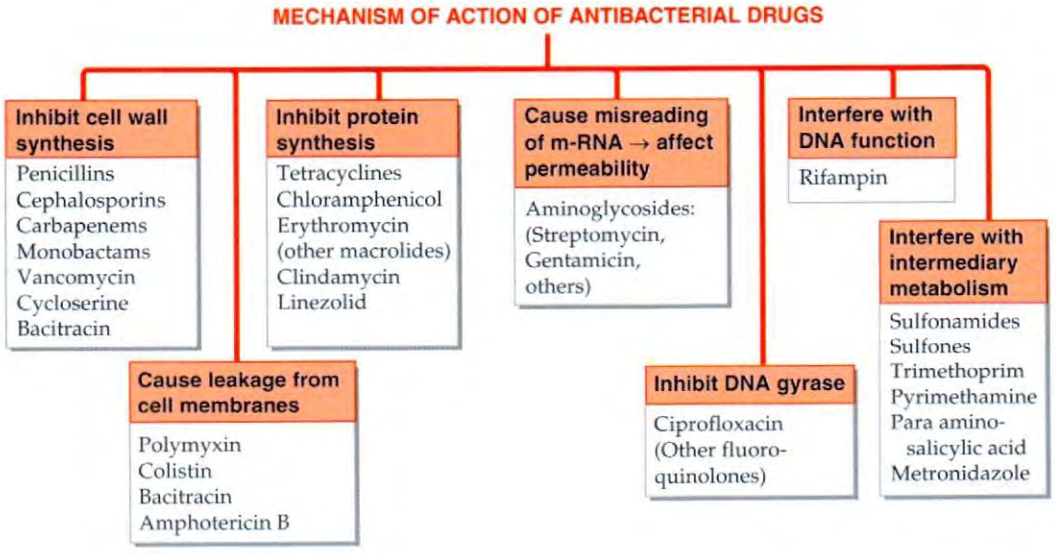
Actinomycetes

Aminoglycosides	Macrolides
Tetracyclines	Polyenes
Chloramphenicol	

PROBLEMS THAT ARISE WITH THE USE OF AMAs

1. Toxicity

(a) *Local irritancy*: This is exerted at the site of administration. Gastric irritation, pain and



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abscess formation at the site of i.m. injection, thrombophlebitis of the injected vein are the complications. Practically all AMAs, especially erythromycin, tetracyclines, certain cephalosporins and chloramphenicol are irritants.

(b) *Systemic toxicity:* Almost all AMAs produce dose related and predictable organ toxicities. Characteristic toxicities are exhibited by different AMAs.

Some have a *high therapeutic index*—doses up to 20-fold range may be given without apparent damage to host cells. These include penicillins, some cephalosporins and erythromycin.

Others have a *lower therapeutic index*—doses have to be individualized and toxicity watched for, e.g.:

Aminoglycosides	: 8th cranial nerve and kidney toxicity.
Tetracyclines	: liver and kidney damage, antianabolic effect.
Vancomycin	: hearing loss, kidney damage.
Chloramphenicol	: bone marrow depression.

Still others have a *very low therapeutic index*—use is highly restricted to conditions where no suitable alternative is available, e.g.:

Polymyxin B	: neurological and renal toxicity.
Amphotericin B	: kidney, bone marrow and neurological toxicity.

2. Hypersensitivity reactions

Practically all AMAs are capable of causing hypersensitivity reactions. These are unpredictable and unrelated to dose. The whole range of reactions from rashes to anaphylactic shock can be produced. The more commonly involved AMAs in hypersensitivity reactions are—penicillins, cephalosporins, sulfonamides, fluoroquinolones.

3. Drug resistance

It refers to unresponsiveness of a microorganism to an AMA, and is akin to the phenomenon of tolerance seen in higher organisms.

Natural resistance Some microbes have always been resistant to certain AMAs. They lack the metabolic process or the target site which is affected by the particular drug. This is generally a group or species characteristic, e.g. gram-negative bacilli are normally unaffected by penicillin G; aerobic organisms are not affected by metronidazole; while anaerobic bacteria are not inhibited by aminoglycoside antibiotics, or *M. tuberculosis* is insensitive to tetracyclines. This type of resistance does not pose a significant clinical problem.

Acquired resistance This refers to development of resistance by an organism (which was sensitive before) due to the use of an AMA over a period of time. This can happen with any microbe and is a major clinical problem. However, development of resistance is dependent on the microorganism as well as on the drug. Some bacteria are notorious for rapid acquisition of resistance, e.g. staphylococci, coliforms, tubercle bacilli. Others like *Strep. pyogenes* and spirochetes have not developed significant resistance to penicillin despite its widespread use for > 60 years. Gonococci quickly developed resistance to sulfonamides, but only slowly and low-grade resistance to penicillin. However, in the past 50 years, highly penicillin resistant gonococci producing penicillinase have appeared.

Resistance may be developed by mutation or gene transfer.

Mutation It is a stable and heritable genetic change that occurs spontaneously and randomly among microorganisms. Any sensitive population of a microbe contains a few mutant cells which require higher concentration of the AMA for inhibition. These are selectively preserved and get a chance to proliferate when the sensitive cells are eliminated by the AMA. Thus, in time it would appear that a sensitive strain has been replaced by a resistant one, as happens when a single antitubercular drug is used. This is called *vertical transfer* of resistance; is relatively slow and usually of lower grade. Mutation and resistance may be:

- *Single step:* A single gene mutation may confer high degree of resistance. It emerges rapidly, e.g. enterococci to streptomycin.
- *Multistep:* A number of gene modifications are involved; sensitivity decreases gradually in a stepwise manner. Resistance to erythromycin, tetracyclines and chloramphenicol is developed by many organisms in this manner.

Gene transfer (infectious resistance) The resistance causing gene is passed from one organism to the other; is called *horizontal transfer* of resistance. Rapid spread of resistance can occur by this mechanism and high level resistance to several antibiotics (multidrug resistance) can be acquired concurrently.

(i) *Conjugation* Sexual contact through the formation of a bridge or sex pilus is common among gram-negative bacilli of the same or another species. This may involve chromosomal or extrachromosomal (plasmid) DNA. The gene carrying the 'resistance' or 'R' factor is transferred only if another 'resistance transfer factor' (RTF) is also present. Conjugation frequently occurs in the colon where a large variety of gram-negative bacilli come in close contact. Even nonpathogenic organisms may transfer R factor to pathogenic organisms, which may become widespread by contamination of food or water. Chloramphenicol resistance of typhoid bacilli, streptomycin resistance of *E. coli*, and many others have been traced to this mechanism.

(ii) *Transduction* It is the transfer of gene carrying resistance through the agency of a bacteriophage. The R factor is taken up by the phage and delivered to another bacterium which it infects. Certain instances of penicillin, erythromycin and chloramphenicol resistance have been found to be phage mediated.

(iii) *Transformation* A resistant bacterium may release the resistance carrying DNA into the medium and this may be imbibed by another sensitive organism—becoming unresponsive to the drug. This mechanism is probably not clinically significant.

Resistance once acquired by any of the above mechanisms becomes prevalent due to the *selection pressure* of a widely used AMA, i.e. presence of the AMA provides opportunity for the resistant subpopulation to thrive in preference to the sensitive population.

Resistant organisms can broadly be of the following three types:

(a) *Drug tolerant* The target biomolecule of the microorganism loses affinity for a particular AMA, e.g. resistant *Staph. aureus* and *E. coli* develop a RNA polymerase that does not bind rifampin, certain penicillin-resistant pneumococcal strains have altered penicillin binding proteins. Mutational target site modification is an important mechanism of fluoroquinolone and macrolide resistance. Another mechanism is acquisition of an alternative metabolic pathway, e.g. certain sulfonamide resistant bacteria switch over to utilizing preformed folic acid in place of synthesizing it from PABA taken up from the medium.

(b) *Drug destroying* The resistant microbe elaborates an enzyme which inactivates the drug, e.g.

- β-lactamases are produced by staphylococci, *Haemophilus*, gonococci, etc. which inactivate penicillin G. The β-lactamases may be present in low quantity but strategically located periplasmically (as in gram-negative bacteria) so that the drug is inactivated soon after entry, or may be elaborated in large quantities (by gram-positive bacteria) to diffuse into the medium and destroy the drug before entry.
- Chloramphenicol acetyl transferase is acquired by resistant *E. coli, H. influenzae* and *S. typhi*.
- Many of the aminoglycoside-resistant coliforms have been found to produce enzymes which adenylate/acetylate/phosphorylate specific aminoglycoside antibiotics.

(c) *Drug impermeable* Many hydrophilic antibiotics gain access into the bacterial cell through specific channels formed by proteins called 'porins', or need specific transport mechanisms. These porins may be lost by the resistant strains, e.g. concentration of some aminoglycosides and tetracyclines in the resistant gram-negative bacterial strains has been found to be much lower than that in their sensitive counterparts when both were exposed to equal concentrations of the drugs. Similarly, the low degree penicillin-resistant gonococci are less permeable to penicillin G; chloroquine-resistant *P. falciparum* accumulates less chloroquine. The bacteria may also acquire plasmid directed

inducible energy dependent efflux proteins in their cell membrane which pump out tetracyclines. Active efflux-based resistance has been detected for erythromycin and fluoroquinolones as well.

Cross resistance Acquisition of resistance to one AMA conferring resistance to another AMA, to which the organism has not been exposed, is called cross resistance. This is more commonly seen between chemically or mechanistically related drugs, e.g. resistance to one sulfonamide means resistance to all others, and resistance to one tetracycline means insensitivity to all others. Such cross resistance is often complete. However, resistance to one aminoglycoside may not extend to another, e.g. gentamicin-resistant strains may respond to amikacin. Sometimes unrelated drugs show partial cross resistance, e.g. between tetracyclines and chloramphenicol, between erythromycin and lincomycin.

Prevention of drug resistance It is of utmost clinical importance to curb development of drug resistance. Measures are:

(a) No indiscriminate and inadequate or unduly prolonged use of AMAs should be made. This would minimize the selection pressure and resistant strains will get less chance to preferentially propagate. For acute localized infections in otherwise healthy patients, symptom-determined shorter courses of AMAs are advocated.

(b) Prefer rapidly acting and selective (narrow-spectrum) AMAs whenever possible; broad-spectrum drugs should be used only when a specific one cannot be determined or is not suitable.

(c) Use combination of AMAs whenever prolonged therapy is undertaken, e.g. tuberculosis, SABE, HIV-AIDS.

(d) Infection by organisms notorious for developing resistance, e.g. *Staph. aureus, E. coli, M. tuberculosis, Proteus,* etc. must be treated intensively.

4. Superinfection (Suprainfection)

This refers to the appearance of a new infection as a result of antimicrobial therapy.

Use of most AMAs causes some alteration in the normal microbial flora of the body. The normal flora contributes to host defence by elaborating substances called *bacteriocins* which inhibit pathogenic organisms. Further, ordinarily, the pathogen has to compete with the normal flora for nutrients, etc. to establish itself. Lack of competition may allow even a normally nonpathogenic component of the flora (e.g. *Candida*), which is not inhibited by the drug to predominate and invade. More complete the suppression of body flora, greater are the chances of developing superinfection. Thus, it is commonly associated with the use of broad/extended-spectrum antibiotics, such as tetracyclines, chloramphenicol, ampicillin, newer cephalosporins; especially when combinations of these are employed. Tetracyclines are more liable than chloramphenicol and ampicillin is more liable than amoxicillin to cause superinfection diarrhoeas, because of incomplete absorption in ileum higher amounts reach the lower bowel and cause greater suppression of colonic bacteria.

Superinfections are more common when host defence is compromised.

Sites involved in superinfection are those that normally harbour commensals, i.e. oropharynx; intestinal, respiratory and genitourinary tracts; occasionally skin.

Superinfections are generally more difficult to treat. The organisms frequently involved in superinfections, diseases caused and drugs for treating them are:

Conditions predisposing to superinfections

- Corticosteroid therapy
- Leukaemias and other malignancies, especially when treated with anticancer drugs (these drugs are also immunosuppressants and decrease WBC count)
- Acquired immunodeficiency syndrome (AIDS)
- Agranulocytosis
- Diabetes, disseminated lupus erythematosus
- Old age

(a) *Candida albicans:* monilial diarrhoea, thrush, vulvovaginitis; treat with nystatin or clotrimazole.

(b) Resistant staphylococci: enteritis; treat with cloxacillin or vancomycin/linezolid.

(c) *Clostridium difficile*: pseudomembranous enterocolitis; mostly associated with the use of clindamycin, tetracyclines, aminoglycosides, ampicillin, etc. It is more common after colorectal surgery. The organism produces an enterotoxin which damages gut mucosa forming plaques; metronidazole and vancomycin are the drugs of choice.

(d) *Proteus*: Urinary tract infection, enteritis; treat with a cephalosporin or gentamicin.

(e) *Pseudomonas*: Urinary tract infection, enteritis; treat with ticarcillin, piperacillin, ceftazidime, cefoperazone or gentamicin.

To minimize superinfections:

- Use specific (narrow-spectrum) AMA whenever possible.
- Do not use antimicrobials to treat trivial, self-limiting or untreatable (viral) infections.
- Do not unnecessarily prolong antimicrobial therapy.

5. Nutritional deficiencies

Some of the B complex group of vitamins and vit K synthesized by the intestinal flora is utilized by man. Prolonged use of antimicrobials which alter this flora may result in vitamin deficiencies.

Neomycin causes morphological abnormalities in the intestinal mucosa, which can produce steatorrhoea and malabsorption syndrome.

6. Masking of an infection

A short course of an AMA may be sufficient to treat one infection but only briefly suppress another one contacted concurrently. The other infection will be masked initially, only to manifest later in a severe form. Examples are:

- Syphilis masked by the use of a single dose of penicillin which is sufficient to cure gonorrhoea.
- Tuberculosis masked by a short course of streptomycin given for a minor respiratory infection.

CHOICE OF AN ANTIMICROBIAL AGENT

After having established the need for using a systemic AMA in a patient by assessing that the condition is due to a treatable (mostly bacterial) infection, and that it is not likely to resolve by itself or by local measures (antiseptics, drainage of pus, etc) only, one has to choose a particular AMA from the large number available. The choice depends on the particulars of the patient, the infecting organism and the drug.

Patient factors

1. *Age* may affect kinetics of many AMAs, and certain AMAs produce age-related effects. Conjugation and excretion of chloramphenicol is inefficient in the newborn: larger doses produce *gray baby syndrome*. Sulfonamides displace bilirubin from protein binding sites—can cause kernicterus in the neonate because their blood-brain barrier is more permeable. The t½ of aminoglycosides is prolonged in the elderly and they are more prone to develop VIII nerve toxicity. Tetracyclines deposit in the developing teeth and bone—discolour and weaken them—are contraindicated below the age of 6 years.

2. *Renal and hepatic function* Cautious use and modification of the dose of an AMA (with low safety margin) becomes necessary when the organ of its disposal is defective (*see* box).

3. *Local factors* The conditions prevailing at the site of infection greatly affect the action of AMAs.

(a) Presence of pus and secretions decrease the efficacy of most AMAs, especially sulfonamides and aminoglycosides. Drainage of the abscess reduces the population of the causative bacteria, suppresses anaerobes by exposure to oxygen, and improves diffusion of the antibiotic into the abscess.

Antimicrobials needing dose reduction/ avoidance in renal failure

Reduce dose even in mild failure	
Aminoglycosides	Amphotericin B
Cephalosporins	Ethambutol
Vancomycin	Flucytosine
Reduce dose only in moderate-severe failure	
Metronidazole	Carbenicillin
Cotrimoxazole	Fluoroquinolones
Aztreonam	Clarithromycin
Meropenem	Imipenem
Drugs to be avoided	
Nalidixic acid	Tetracyclines
Nitrofurantoin	(except doxycycline)

Antimicrobials in liver disease

Drugs to be avoided	
Erythromycin estolate	Tetracyclines
Pyrazinamide	Nalidixic acid
	Pefloxacin
Dose reduction needed	
Chloramphenicol	Isoniazid
Metronidazole	Rifampin
Clindamycin	

(b) Presence of necrotic material or foreign body including catheters, implants and prosthesis makes eradication of infection practically impossible. Bacteria adhering to foreign surfaces create a biofilm around them and grow very slowly, rendering them difficult to reach and less vulnerable to the antibiotic.

(c) Haematomas foster bacterial growth; tetracyclines, penicillins and cephalosporins get bound to the degraded haemoglobin in the haematoma.

(d) Lowering of pH at the site of infection reduces activity of macrolide and aminoglycoside antibiotics.

(e) Anaerobic environment in the centre of an abscess impairs bacterial transport processes which concentrate aminoglycosides in the bacterial cell, rendering them less susceptible.

(f) Penetration barriers at certain sites may hamper the access of the AMA to the site, such as in subacute bacterial endocarditis (SABE), endophthalmitis, prostatitis. However, trimethoprim and fluoroquinolones attain high concentration in prostate due to ion trapping.

4. *Earlier drug exposure* History of previous exposure to an AMA should be obtained. If an AMA has caused allergic reaction—it has to be avoided in that patient, e.g. drug of choice for syphilis in a patient allergic to penicillin is tetracycline. β-lactams, sulfonamides, fluoroquinolones and nitrofurantoin frequently cause allergy. Tuberculosis patients who have been treated previously are liketly to harbour resistant bacilli.

5. *Impaired host defence* Integrity of host defence plays a crucial role in overcoming an infection. Pyogenic infections occur readily in neutropenic patients, while if cell-mediated immunity is impaired (e.g. AIDS), infections by low grade pathogens and intracellular organisms abound. In an individual with normal host defence, a bacteriostatic AMA may achieve cure; while intensive therapy with cidal drugs is imperative in those with impaired host defence (conditions given on p. 744) or when the organisms are protected by a barrier—as in SABE. Even then complete eradication of the organism may not occur.

6. *Pregnancy* All AMAs should be avoided in the pregnant woman because of risk to the foetus. Penicillins, many cephalosporins and erythromycin are safe, while safety data on most others is not available. Therefore, manufacturers label 'contraindicated during pregnancy'. Tetracyclines are clearly contraindicated. They carry risk of acute yellow atrophy of liver, pancreatitis and kidney damage in the mother, as well as cause teeth and bone deformities in the offspring. Aminoglycosides can cause foetal ear damage. Animal studies indicate increased risk to the foetus, especially with fluoroquinolones, cotrimoxazole, chloramphenicol, sulfonamides and nitrofurantoin. Though metronidazole has not been found teratogenic, its mutagenic potential warrants caution in its use during pregnancy.

7. *Genetic factors* Primaquine, nitrofurantoin, sulfonamides, chloramphenicol and fluoroquinolones carry the risk of producing haemolysis in G-6-PD deficient patient.

Organism-related considerations

Each AMA has a specific effect on a limited number of microbes. Successful chemotherapy must be rational and demands a diagnosis. However, most of the time, definitive bacteriological diagnosis is not available before initiating treatment. Bacteriological testing takes time, is expensive and appropriate samples of infected material for bacteriology may not be obtainable. Empirical therapy has to be instituted and has been demonstrated to be beneficial in many situations. A clinical diagnosis should first be made, at least tentatively, and the likely pathogen guessed.

The following line of action may be taken:

1. *Clinical diagnosis itself directs choice of the AMA* The infecting organism and its sensitivity pattern are by-and-large known, e.g. syphilis, chancroid, diphtheria, tetanus, plague, cholera, trachoma, thrush, tuberculosis, lobar pneumonia, leprosy, amoebiasis, herpes simplex, etc.

2. *A good guess can be made* from the clinical features and local experience about the type of organism and its sensitivity, e.g. tonsillitis, otitis media, boils, vaginitis, urethritis; the most appropriate specific AMA should be prescribed and the response watched for. A Gram stained smear examination of infected material may help to aid the choice.

3. *Choice to be based on bacteriological/diagnostic examination* No guess can be made about the infecting organism or its sensitivity, e.g. bronchopneumonia, empyema, meningitis, osteomyelitis, urinary tract infection, wound infection, etc. In these situations, an AMA should be selected on the basis of culture and sensitivity tests or other suitable diagnostic tests, e.g. antigen/antibody tests, PCR, etc); but this may not be always possible.

(a) *Bacteriological/diagnostic services are not available:* empirical therapy to cover all likely organisms with a broad-spectrum drug like fluoroquinolone, tetracycline or a combination such as gentamicin + a cephalosporin may be used (with metronidazole or clindamycin if anaerobes are suspected). Further therapy is modified on the basis of clinical response; but hasty and arbitrary changes in the selection of AMA should be avoided.

(b) *Bacteriological /diagnostic services are available, but treatment cannot be delayed:* as in serious infections like meningitis, septicaemias, etc., specimens for bacteriological examination should be collected and empirical therapy started provisionally as in (a). In case of inadequate response, the AMA should be changed later in the light of bacteriological findings.

(c) *Bacteriological services are available and treatment can be delayed for a few days:* as in chronic urinary tract infection; it is better to wait for the culture and sensitivity report; start definitive therapy thereafter.

Bacteriological sensitivity testing This is generally done by disk-agar diffusion method using standardized concentrations of antibiotics based on clinically attained plasma concentrations of these. As such, they provide only qualitative results, which may serve as indicators, and cannot be blindly extrapolated to the clinical situation in every patient and for every organism. Broth cultures with *break-point* concentration (concentration that demarcates between sensitive and resistant bacteria) of antibiotics probably yield more reliable results. Break-point concentrations are to be related to clinically attainable serum concentrations of the antibiotic.

Minimum inhibitory concentration (MIC), i.e the lowest concentration of an antibiotic which prevents visible growth of a bacterium after 24 hours incubation in microwell culture plates using serial dilutions of the antibiotic is more informative. Lately, the disk-diffusion method has been refined to provide a quantitative estimate of the inhibitory action of an AMA and its MIC. In this test called the *Epsilometer test* (E-test) a rectangular test strip impregnated with ascending concentrations of the AMA is placed on an inoculated agar plate and the bacterial growth is observed after a specific period, depending on the organism. The curved line separating the clear zone from the zone with bacterial growth divides the strip at the MIC value of concentration.

Minimum bactericidal concentration (MBC) of the antibiotic is determined by subculturing from tubes with no visible growth. If the organism is killed, no growth will occur; but if it was only inhibited in the parent culture—it will grow on subculturing in antibiotic-free medium. MBC is the concentration of the antibiotic which kills 99.9% of the bacteria. A small difference between MIC and MBC indicates that the antibiotic is primarily bactericidal, while a

large difference indicates bacteriostatic action. MBC is not used to guide selection of antibiotics in clinical practice.

Postantibiotic effect (PAE) After a brief exposure if the organism is placed in antibiotic-free medium, it starts multiplying again, but after a lag period which depends on the antibiotic as well as the organism. This lag period in growth resumption is known as 'postantibiotic effect' (PAE) and is the time required for reattainment of logarithmic growth. It is generally calculated from the difference in time required to attain 10 fold increase in bacterial count in the culture for antibiotic exposed and unexposed tubes. The *in vivo* PAEs are generally much longer than the *in vitro* PAEs. A long and dose-dependent PAE has been noted with fluoroquinolones, aminoglycosides and rifampin.

Drug factors

When any one of a number of AMAs could be used to treat an infection, choice among them is based upon specific properties of these AMAs:

1. *Spectrum of activity:* For definitive therapy, a narrow-spectrum drug which selectively affects the concerned organism is preferred, because it is generally more effective than a broad-spectrum AMA, and is less likely to disturb the normal microbial flora. However, for empirical therapy, often a broad-spectrum drug has to be used to cover all likely pathogens.

2. *Type of activity:* Many infections in patients with normal host defence respond equally well to bacteriostatic and bactericidal AMAs. But several acute infections resolve faster with a cidal than a static drug, because the cidal drug directly reduces the number of bacteria at the site of infection, while the static drug only prevents increase in their number. Many bactericidal drugs exert prolonged post-antibiotic effect (PAE) so that maintenance of drug level continuously above the MIC is not essential. With bacteriostatic AMAs the bacteria start multiplying quickly when drug level falls below the MIC, resulting in relapse of infection.

A bactericidal antibiotic is clearly superior to bacteriostatic one in treating patients with impaired host defence, life-threatening infections, infections at less accessible sites (SABE) or when carrier state is possible (e.g. typhoid).

3. *Sensitivity of the organism:* Assessed on the basis of MIC values (if available) and consideration of PAE.

4. *Relative toxicity:* Obviously, a less toxic antibiotic is preferred, e.g. a β-lactam over an aminoglycoside or erythromycin over clindamycin.

5. *Pharmacokinetic profile:* For optimum action the antibiotic has to be present at the site of infection in sufficient concentration for an adequate length of time. This depends on their pharmacokinetic characteristics. Most antibiotics are given at 2 to 4 half-life intervals—thus attaining therapeutic concentrations only intermittently. For many organisms, aminoglycosides, fluoroquinolones and metronidazole produce '*concentration-dependent killing*', i.e. inhibitory effect depends on the ratio of peak concentration to the MIC. The same daily dose of gentamicin produces better action when given as a single dose than if it is divided into 2–3 portions. On the other hand, β-lactams, glycopeptides and macrolides produce '*time-dependent killing*', i.e. antimicrobial action depends on the length of time the concentration remains above the MIC; division of daily dose improves the effect. However, the doses should be so spaced that the surviving organisms again start multiplying and a cidal action is exerted.

Penetration to the site of infection also depends on the pharmacokinetic properties of the drug. A drug which penetrates better and attains higher concentration at the site of infection is likely to be more effective. The fluoroquinolones have excellent tissue penetration—attain high concentrations in soft tissues, lungs, prostate, joints, etc. Ciprofloxacin and rifampin have very good intracellular penetration. Cefuroxime, ceftriaxone, chloramphenicol, ciprofloxacin attain high CSF concentration. On the other hand, penicillins and aminoglycosides penetrate poorly into CSF unless meninges

are inflamed. Ampicillin, cephalosporins and erythromycin attain high biliary concentration.

6. *Route of administration:* Many AMAs can be given orally as well as parenterally, but aminoglycosides, penicillin G, ticarcillin, many cephalosporins, vancomycin, etc. have to be given by injection only. For less severe infections, an oral antibiotic is preferable; but for serious infections, e.g. meningitis, spreading cellulitis, septicaemias, a parenteral antibiotic would be more reliable.

7. *Evidence of clinical efficacy:* Relative value of different AMAs in treating an infection is decided on the basis of comparative clinical trials. Optimum dosage regimens and duration of treatment are also determined on the basis of such trials. Reliable clinical trial data, if available, is the final guide for choice of the antibiotic.

8. *Cost:* Less expensive drugs are to be preferred.

COMBINED USE OF ANTIMICROBIALS

More than one AMA are frequently used concurrently. This should be done only with a specific purpose and not blindly in the hope that if one is good, two should be better and three should cure almost any infection. The objectives of using antimicrobial combinations are:

1. To achieve synergism Every AMA has a specific effect on selected microorganisms. Depending on the drug pair as well as the organism involved, either synergism (supra-additive effect), additive action, indifference or antagonism may be observed when two AMAs belonging to different classes are used together.

Synergism may manifest in terms of decrease in the MIC of one AMA in the presence of another, or the MICs of both may be lowered. If the MIC of each AMA is reduced to 25% or less, the pair is considered synergistic, 25–50% of each is considered additive and more than 50% of each indicates antagonism. Thus, a synergistic drug sensitizes the organisms to the action of the other member of the pair. This may also manifest as a more rapid lethal action of the combination than either of the individual members resulting in faster cure of the infection. Synergistic prolongation of PAE has also been demonstrated for combinations of β-lactams with an aminoglycoside, and by addition of rifampin to a variety of antibiotics.

Every combination is unique; the same drugs may be synergistic for one organism but antagonistic for another. However, general guidelines are:

(a) Two bacteriostatic agents are often additive, rarely synergistic, i.e. combination of tetracyclines, chloramphenicol, erythromycin, etc. A sulfonamide used with trimethoprim is a special case where supraadditive effect is obtained because of sequential block in folate metabolism of certain bacteria (Ch. 51). The combination often exerts cidal action, while the individual components are only static.

(b) Two bactericidal drugs are frequently additive and sometime synergistic if the organism is sensitive to both, e.g.:

- Penicillin/ampicillin + streptomycin/gentamicin or vancomycin + gentamicin for enterococcal SABE. Penicillins by acting on the cell wall may enhance the penetration of the aminoglycoside into the bacterium.
- Ticarcillin + gentamicin for *Pseudomonas* infection, especially in neutropenic patients.
- Ceftazidime + ciprofloxacin for *Pseudomonas* infected orthopedic prosthesis.
- Rifampin + isoniazid in tuberculosis.

In the above cases, the combination produces faster cure and reduces the chances of relapse by more complete eradication of the pathogen.

(c) Combination of a bactericidal with a bacteriostatic drug may be synergistic or antagonistic depending on the organism. In general:

(i) If the organism is highly sensitive to the cidal drug—response to the combination is equal to the static drug given alone (apparent antagonism), because cidal drugs act primarily on rapidly multiplying bacteria, while the static drug inhibits multiplication. This has been observed with penicillin + tetracycline/chloramphenicol on pneumococci which are highly sensitive to penicillin. Pneumococcal meningitis treated with

penicillin + tetracycline had higher mortality than those treated with penicillin alone. Penicillin + erythromycin for group A *Streptococci* and nalidixic acid + nitrofurantoin for *E. coli* have also shown antagonism.

(ii) If the organism has low sensitivity to the cidal drug—synergism may be seen, e.g.:

- Penicillin + sulfonamide for actinomycosis
- Streptomycin + tetracycline for brucellosis
- Streptomycin + chloramphenicol for *K. pneumoniae* infection
- Rifampin + dapsone in leprosy.

Thus, wherever possible, synergistic combinations may be used to treat infections that are normally difficult to cure. Full doses of individual drugs are given for optimum synergism.

2. To prevent emergence of resistance Mutation conferring resistance to one AMA is independent of that conferring resistance to another. If the incidence of resistant mutants of a bacillus infecting an individual for drug P is 10^{-5} and for drug Q is 10^{-7}, then only one out of 10^{12} bacilli will be resistant to both. The chances of its surviving host defence and causing a relapse would be meagre.

This principle of using two or more AMAs together is valid primarily for chronic infections needing prolonged therapy. It has been widely employed in tuberculosis, leprosy, HIV and now adopted for *H. pylori,* malaria as well. This principle is not applicable in most acute and short-lived infections, because resistance rarely develops during the course of treatment of an individual patient.

3. To broaden the spectrum of antimicrobial action This is needed in:

(a) *Treatment of mixed infection* Bronchiectasis, peritonitis, certain urinary tract infections, brain abscesses, diabetic foot infection, bedsores, gynaecological infections are mostly mixed infections. Often, aerobic and anaerobic organisms sensitive to different drugs are involved. Obviously two or more AMAs have to be used to cover the pathogens. Drugs should be chosen on the basis of bacteriological diagnosis and sensitivity pattern (known or presumed), and should be employed in full doses. Clindamycin or metronidazole are generally included to cover anaerobes. However, it may sometimes be possible to find a single agent effective against all the causative organisms.

(b) *Initial treatment of severe infections* For empirical therapy, since bacterial diagnosis is not known; drugs covering gram-positive and gram-negative (in certain situations anaerobes as well), e.g. penicillin + gentamicin; cephalosporin or erythromycin + an aminoglycoside ± metronidazole or clindamycin, may be given together. Rational combinations improve the certainty of curing the infection in the first attempt, but should be continued only till bacteriological data become available. When the organism and its sensitivity has been determined, severity of infection is in itself not an indication for combination therapy. Combinations should not be used as a substitute for accurate diagnosis.

(c) *Topically* Generally, AMAs which are not used systemically, are poorly absorbed from the local site and cover a broad range of gram-positive and gram-negative bacteria are combined for topical application, e.g. bacitracin, neomycin, polymyxin B.

Disadvantages of antimicrobial combinations

1. They foster a casual rather than rational outlook in the diagnosis of infections and choice of AMA.
2. Increased incidence and variety of adverse effects. Toxicity of one agent may be enhanced by another, e.g. vancomycin + tobramycin or gentamicin produce exaggerated kidney failure.
3. Increased risk of superinfections.
4. If inadequate doses of nonsynergistic drugs are used—emergence of resistance may be promoted.
5. Higher cost of therapy.

PROPHYLACTIC USE OF ANTIMICROBIALS

This refers to the use of AMAs for preventing the setting in of an infection or suppressing contacted

infection before it becomes clinically manifest. The latter is also called *'preemptive therapy'*, which capitalizes on the small population of pathogen in the body before the disease is manifest. AMAs are frequently given prophylactically, but in a number of circumstances this is at best wasteful if not harmful. The difference between treating an infection and preventing it is that treatment is directed against a specific organism infecting an individual patient (targeted therapy), while prophylaxis is often against all organisms that may cause infection. The valid as well as improper prophylactic uses may be categorized as:

1. Prophylaxis against specific organisms This in general is highly satisfactory and the choice of drug is clearcut, because it is targeted.

(a) Rheumatic fever: Benzathine penicillin is the drug of choice for preventing infection by group A *streptococci* which cause recurrences.

(b) Tuberculosis: Children, HIV positive and other susceptible contacts of open cases need to be protected. Isoniazid alone for 6 months is recommended.

(c) *Mycobacterium avium* complex (MAC): HIV/AIDS patients with low CD4 count may be protected against MAC infection by azithromycin/clarithromycin.

(d) HIV infection: Health care workers exposed to blood by needle stick injury are to be protected by tenofovir + emtricitabine ± lopinavir or atazanavir. The offspring of HIV positive pregnant woman can be protected by treating the woman with tenofovir + lamivudine + efavirenz. After delivery the neonate should be given syrup nevirapine for 6 weeks.

(e) Meningococcal meningitis: during an epidemic, especially in contacts; rifampin/ciprofloxacin/ceftriaxone may be used.

(f) Gonorrhoea/syphilis: before or immediately after contact: ampicillin/ceftriaxone.

(g) Recurrent genital herpes simplex: Acyclovir prophylaxis may be given when four or more recurrences occur in a year.

(h) Malaria: Travellers to endemic areas with high transmission rate many be covered by mefloquine or doxycycline.

(i) Influenza A_2 or H1N1 (swine flu): during an epidemic, especially in contacts: oseltamivir.

(j) Cholera: tetracycline prophylaxis may be given to close contacts of a case.

(k) Whooping cough: non-immunized child contact during the incubation period: erythromycin or azithromycin can abort clinical disease.

(l) Plague: Doxycycline prophylaxis is recommended for contacts during an epidemic.

(m) *Pneumocystis jiroveci* pneumonia: Transplant recipients on immunosuppressants/leukaemia or AIDS patients may be protected by cotrimoxazole.

2. Prevention of infection in high risk situations Such use of AMAs may be valid and satisfactory in certain situations, but is controversial in others.

(a) Dental extraction, tonsillectomy, endoscopies cause damage to mucosa harbouring bacteria and induce bacteremia. This is harmless in most subjects, but in those with valvular defects, this can cause endocarditis. Appropriate prophylaxis with amoxicillin or clindamycin may be given few hours before to few hours after the procedure.

(b) Catheterization or instrumentation of urinary tract: prophylaxis with cotrimoxazole or norfloxacin decreases the risk of urinary tract infection (UTI). Patients with cardiac valvular lesions may be protected with ampicillin, gentamicin or vancomycin during catheterization.

(c) To prevent recurrences of UTI in patients with abnormalities of the tract: cotrimoxazole or nitrofurantoin may be given on a long-term basis since the organism mostly is *E. coli.*

(d) Chronic obstructive lung disease, chronic bronchitis: ampicillin/doxycycline/ciprofloxacin have been used to prevent acute exacerbations; but are of doubtful value.

(e) Immunocompromized patients (receiving corticosteroids or antineoplastic chemotherapy or immunosuppressants after organ transplantation,

neutropenic patients): penicillin/cephalosporin ± an aminoglycoside or fluoroquinolone are often used to prevent respiratory tract infections and septicaemia, but incidence of superinfections is high.

3. Prevention of infection in general This is highly unsatisfactory in most cases and must be condemned. Examples are:

(a) Neonates, especially after prolonged or instrumental delivery.

(b) To prevent postpartum infections in the mother after normal delivery.

(c) Viral upper respiratory tract infections: to prevent secondary bacterial invasion.

(d) To prevent respiratory infections in unconscious patients or in those on respirators.

Antimicrobial prophylaxis in these situations may be hazardous. Infection by resistant organisms, fungal and other superinfections can occur, because it is not possible to prevent all infections, at all times, in all individuals.

Prophylaxis of surgical site infection

Surgical site infection (SSI) includes superficial incisional infections (e.g. stitch abscess), deep incisional infection (of soft tissue) and organ/space infection. The purpose of surgical prophylaxis is to reduce the incidence of SSI with minimal alteration of normal microbial flora of the host and minimal adverse effects.

For grading the need and intensity of antimicrobial prophylaxis, the operative wounds have been classified into 4 categories with increasing risk of SSI (*see* box).

Wound infection occurs due to microbial contamination of the surgical site. It is important for the surgeon to see that the wound left after surgery does not get infected. Use of sterile instruments, cross-infection control measures (antiseptic/disinfectant, etc.) and good surgical technique to minimise tissue damage, haematoma and devascularization are the primary, and often the only, measures needed. However, extensive, prolonged and often combined use of AMAs is made for prophylaxis of infection after practically all surgeries. Such misuse is particularly rampent in developing countries, probably because of unreliability of infection control measures. The SSI is directly related to the number of bacteria present in the surgical wound at the time of closure. Systemic antimicrobial prophylaxis should be employed only when there is clear risk of more than the critical number of bacteria remaining in the wound at the time of closure and occurrence of SSI. In general, it is not required for clean surgery, except in patient at special risk. Clean surgery in otherwise healthy subjects is associated with very low risk of SSI.

Classification of operative wounds* with increasing risk of infection

- *Clean:* Elective, nontraumatic surgery, no viscera or tract (respiratory, g.i., biliary, genitourinary) entered, no infection at site, no break in technique.
- *Clean-contaminated:* Otherwise clean but emergency surgery, or elective surgery with opening of any viscera/tract but minimal spillage, no contact with infected material or minor break in technique.
- *Contaminated:* Gross spillage from g.i. tract (gut resection), opening of infected biliary or genitourinary tract, penetrating injury < 4 hr old, grafting on chronic open wound, major break in technique.
- *Dirty:* Opening of abscess or purulent site, preoperative perforation of g.i./respiratory/genitourinary tract/penetrating injury > 4 hr old.

* based on National Research Council (NRC) criteria.

Incidence of postoperative infection is higher when surgery had lasted 2 hours or more. Prophylaxis should be given for surgeries in which a prosthesis is inserted into the bone or soft tissue. Even clean surgery needs to be covered by AMA in diabetics, corticosteroid recipients and other immunocompromised subjects, infants, elderly, malnourished and when there is extensive tissue handling/use of electrocautery, etc.

The selection of drug, dose, timing and duration of prophylactic medication is crucial. It is important that the antibiotic is not started prematurely and is not continued

beyond the time when bacteria have access to the surgical wound. Administration of the AMA has to be so timed that peak blood levels occur when clot is forming in the surgical wound, and it is present throughout the procedure. Thus, most of the oral drugs are given 1 hour before incision, while i.v. administration just before/after anaesthesia best ensures effective blood levels of the AMA during surgery. Most AMAs do not penetrate the clot once it is formed and is older than 3 hours. Thus, late and prolonged presence of the antibiotic in circulation serves no purpose, but can foster resistant organisms. In case of prolonged surgery, the AMA may be repeated i.v. during the procedure. Postoperative administration of the AMA, especially after 4 hours of wound closure is recommended only in case of contaminated and dirty surgery, in which case it may be given for upto 5 days.

To be maximally effective, a relatively high dose of the AMA is selected which yields peak blood level several times higher than MIC for the likely pathogens. The drug or combination of drugs is selected based on the knowledge of the organism most commonly causing SSI in a given procedure. Local patterns of wound infection (e.g. prevalence of MRSA) and sensitivities of the causative organisms should guide the selection. The commonly employed AMAs for prophylaxis in case of clean and clean-contaminated surgeries are listed in the box.

Dirty contaminated wounds (including road side accidents): The antimicrobial regimens generally administered for 5 days in case of contaminated dirty wounds are:

1. Cefazolin 1 g i.v. 8 hourly
   + vancomycin 1 g i.v. 12 hourly.
2. Cefoxitin 1 g i.v. 6 hourly/ceftizoxime 1 g i.v. 12 hourly.
3. Clindamycin 0.6 g i.v. 8 hourly
   + Gentamicin 80 mg i.v. 8 hourly.
4. Ampicillin 2 g i.v. 6 hourly/vancomycin 1 g i.v. 12 hourly
   + Gentamicin 80 mg i.v. 8 hourly
   + Metronidazole 0.5 g i.v. 8 hourly.
5. Amoxicillin 1 g + Clavulanate 0.2 g i.v. 12 hourly.

   All given for 5 days

Commonly used antimicrobials drugs for surgical prophylaxis

Oral (single dose given 1 hour before procedure)

1. Amoxicillin 2 g (50 mg/kg)
2. Cephalexin 2 g (50 mg/kg)
3. Cefadroxil 2 g (50 mg/kg)
4. Clindamycin 600 mg (20 mg/kg) } For patients
5. Azithromycin 500 mg (15 mg/kg) } allergic to
6. Clarithromycin 500 mg (15 mg/kg) } penicillin

Parenteral (single injection just before procedure)

1. Ampicillin 2 g (50 mg/kg) i.m./i.v.
2. Cefazolin 1 g (25 mg/kg) i.v.
3. Vancomycin 1 g (20 mg/kg) i.v. (in MRSA prevalent areas and/or penicillin allergic patients).
4. Clindamycin 600 mg (20 mg/kg) i.v. (for penicillin allergic patients).
5. Cefuroxime 1.5 g (30 mg/kg) i.v. + Metronidazole 0.5 g (10 mg/kg) i.v. } For gut and biliary surgery
6. Gentamicin 160 mg (3 mg/kg) i.v. + Metronidazole 0.5 g (10 mg/kg) i.v. } For gut and biliary surgery

FAILURE OF ANTIMICROBIAL THERAPY

The success of antimicrobial therapy can be measured either clinically in terms of improvement in symptoms/signs or microbiologically as eradication of the infecting organism.

Antimicrobials may fail to cure an infection/fever, or there may be relapses. This is infrequent when antimicrobial therapy was begun, in the first place, on sound clinical and/or bacteriological basis. When a real or apparent failure of the antimicrobial regimen occurs, the diagnosis and therapy should be reviewed. One of the following causes will usually be identified.

1. Improper selection of drug, dose, route or duration of treatment.
2. Treatment begun too late.
3. Noncompliance by the patient.

4. Failure to take necessary adjuvant measures, e.g. drainage of abscesses, empyema, etc.; removal of renal stones, other foreign bodies or infected gallbladder, adjustment of proper urinary pH in case of UTI; cavity closure; control of diabetes, etc.
5. Poor host defence—as in leukaemias, neutropenia and other causes, especially if a bacteriostatic AMA is used.
6. Infecting organism present behind barriers, such as vegetation on heart valves (SABE), inside the eyeball, blood brain-barrier.
7. Trying to treat untreatable (viral) infections or other causes of fever (malignancy, collagen diseases).
8. Presence of dormant or altered organisms (the persisters) which later give rise to a relapse.

☞ PROBLEM DIRECTED STUDY

50.1 A lady aged 40 years and weighing 60 kg is to undergo elective cholecystectomy for multiple gallstones. She is asymptomatic.

(a) Does she require antimicrobial prophylaxis?

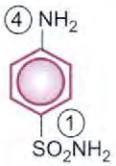
(b) If she does, which antimicrobial(s) should be selected? When, by what route and dose, and how long the antimicrobial(s) should be administered?

(see Appendix-1 for solution)

Chapter 51 Sulfonamides, Cotrimoxazole and Quinolones

SULFONAMIDES

Sulfonamides were the first antimicrobial agents (AMAs) effective against pyogenic bacterial infections. Sulfonamido-chrysoidine (Prontosil Red) was one of the dyes included by Domagk to treat experimental streptococcal infection in mice and found it to be highly effective. Subsequently an infant was cured of staphylococcal septicaemia (which was 100% fatal at that time) by prontosil. By 1937, it became clear that prontosil was broken down in the body to release sulfanilamide which was the active antibacterial agent. A large number of sulfonamides were produced and used extensively in the subsequent years, but because of rapid emergence of bacterial resistance and the availability of many safer and more effective antibiotics, they are currently used only in combination with trimethoprim (as cotrimoxazole) or with pyrimethamine (for malaria).



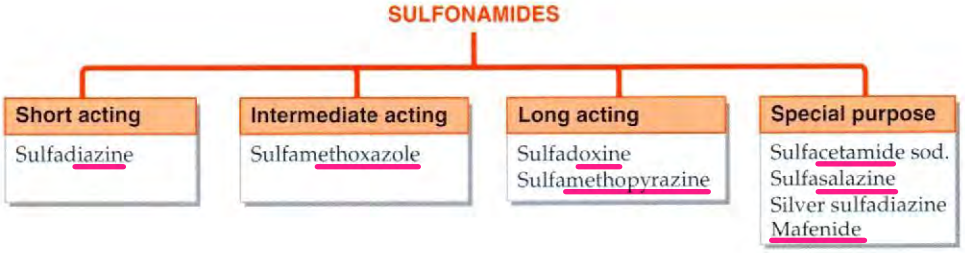
SULFANILAMIDE

Chemistry All sulfonamides may be considered to be derivatives of sulfanilamide (p-aminobenzene sulfonamide). Individual members differ in the nature of N^1 (Sulfonamido N) substitution, which governs solubility, potency and pharmacokinetic property. A free amino group in the para position (N^4) is required for antibacterial activity.

Sulfonamides that are still of clinical interest are listed in the chart.

Antibacterial Spectrum

Sulfonamides are primarily bacteriostatic against many gram-positive and gram-negative bacteria. However, bactericidal concentrations may be attained in urine. Sensitivity patterns among



microorganisms have changed from time-to-time and place-to-place. Those still sensitive are:

many *Strepto. pyogenes, Haemophilus influenzae, H. ducreyi, Calymmatobacterium granulomatis, Vibrio cholerae. Only a* few *Staph. aureus,* gonococci, meningococci, pneumococci, *Escherichia coli,* and *Shigella* respond, but majority are resistant.

Anaerobic bacteria are not susceptible.

Chlamydiae: trachoma, lymphogranuloma venereum, inclusion conjunctivitis, are sensitive, as are *Actinomyces, Nocardia* and *Toxoplasma.*

Mechanism of action Many bacteria synthesize their own folic acid (FA) of which p-aminobenzoic acid (PABA) is a constituent, and is taken up from the medium. Woods and Fildes (1940) proposed the hypothesis that sulfonamides, being structural analogues of PABA, inhibit bacterial folate synthase, so that FA is not formed and a number of essential metabolic reactions suffer. Sulfonamides competitively inhibit the union of PABA with pteridine residue to form dihydropteroic acid which conjugates with glutamic acid to produce dihydrofolic acid. Moreover, being chemically similar to PABA, the sulfonamide may itself get incorporated to form an altered folate which is metabolically injurious.

Host cells also require FA, but they utilize preformed FA supplied in diet and are unaffected by sulfonamides. Evidences in favour of this mechanism of action of sulfonamides are:

(a) PABA, in small quantities, antagonizes the antibacterial action of sulfonamides.
(b) Only those microbes which synthesize their own FA, and cannot take it from the medium are susceptible to sulfonamides.

Pus and tissue extracts contain purines and thymidine which decrease bacterial requirement for FA and antagonize sulfonamide action. Pus is also rich in PABA.

Resistance to sulfonamides Most bacteria are capable of developing resistance to sulfonamides. Prominent among these are gonococci, pneumococci, *Staph. aureus*, meningococci, *E. coli, Shigella, Strep. pyogenes, Strep. viridans* and anaerobes. The resistant mutants either:

(a) produce increased amounts of PABA, or
(b) their folate synthase enzyme has low affinity for sulfonamides, or
(c) adopt an alternative pathway in folate metabolism.

Sensitivity patterns have changed depending on the extent of use. When an organism is resistant to one sulfonamide, it is resistant to them all. No cross-resistance between sulfonamides and any other AMAs has been noted. Development of resistance has markedly limited the clinical usefulness of this class of compounds.

Pharmacokinetics

Sulfonamides are rapidly and nearly completely absorbed from g.i.t. Extent of plasma protein binding differs considerably (10–95%) among different members. The highly protein bound members are longer acting. Sulfonamides are widely distributed in the body—enter serous cavities easily. The free form of sulfadiazine attains the same concentration in CSF as in plasma. They cross placenta freely.

The primary pathway of metabolism of sulfonamides is acetylation at N^4 by nonmicrosomal acetyl transferase, primarily in liver. The extent of metabolism differs for different members. The acetylated derivative is inactive, but can contribute to the adverse effects. It is generally less soluble in acidic urine than the parent drug—may precipitate and cause crystalluria.

Sulfonamides are excreted mainly by the kidney through glomerular filtration. Both renal tubular secretion and reabsorption occur. The more lipid-soluble members are highly reabsorbed in the tubule, therefore are longer acting.

Sulfamethoxazole Due to slower oral absorption and urinary excretion, it has intermediate duration of action; t½ in adults averages 10 hours. It is the preferred compound for combining with trimethoprim because the t½ of both is similar (*see* under cotrimoxazole). However, a high fraction is acetylated, which is relatively insoluble—crystalluria can occur.

Sulfadoxine, Sulfamethopyrazine These are ultralong acting compounds, action lasting > 1 week because of high plasma protein binding and slow renal excretion (t½ 5–9 days). They attain low plasma concentration (of free form) and are not suitable for treatment of acute pyogenic infections, but are used in combination with pyrimethamine in the treatment of malaria (especially chloroquine resistant *P. falciparum*; *see* Ch. 61), *Pneumocystis jiroveci* pneumonia in AIDS patients and in toxoplasmosis. Because they have caused serious cutaneous reactions, large-scale use of the combination for prophylaxis of malaria is not recommended.

Sulfacetamide sod. It is a highly soluble compound yielding neutral solution which is only mildly irritating to the eye in concentrations up to 30%. It is used topically for ocular infections due to susceptible bacteria and chlamydia, including ophthalmia neonatorum caused by *Ch. oculogenitalis*. After topical instillation it attains high concentrations in anterior segment and aqueous humour. The incidence of sensitivity reactions with ocular use of sulfacetamide sod. has been low; but it must be promptly stopped when they occur.

LOCULA, ALBUCID 10%, 20%, 30% eye drops, 6% eye oint.

Mafenide It is not a typical sulfonamide, because a —CH_2—bridge separates the benzene ring and the amino group. Mafenide is used only topically—inhibits a variety of gram-positive and gram-negative bacteria. In contrast to typical sulfonamides, it is active in the presence of pus and against *Pseudomonas*, clostridia which are not inhibited by typical sulfonamides. It has been mainly employed for burn dressing to prevent infection, but not to treat already infected cases.

The biggest limitation is that mafenide produces burning sensation and severe pain when applied to raw surface. It is rapidly absorbed from the raw surface, metabolized and excreted in urine. Mafenide and its metabolite are carbonic anhydrase (CAse) inhibitors. Accordingly, they alkalinize urine, can cause acidosis and hyperventilation. Mafenide must not be applied over large areas. Allergic reactions, particularly rashes also occur. Because of the above problems, it is infrequently used now.

SULFAMYLON 1% cream for surface application.

Silver sulfadiazine Used topically as 1% cream, it is active against a large number of bacteria and fungi, even those resistant to other sulfonamides, e.g. *Pseudomonas*. It slowly releases silver ions which appear to be largely responsible for the antimicrobial action. It is considered to be one of the most effective drugs for preventing infection of burnt surfaces and chronic ulcers and is well tolerated. However, it is not good for treating established infection.

SILVIRIN 1% cream, ARGENEX 1% cream with chlorhexidine 0.2%.

Local side effects are—burning sensation on application and itch. Released sulfadiazine may be absorbed systemically and produce its own adverse effects.

Sulfasalazine (*see* p. 228, 734) It is used in ulcerative colitis and rheumatoid arthritis.

Adverse Effects

Adverse effects of sulfonamides are relatively common. These are:

- Nausea, vomiting and epigastric pain.
- Crystalluria is dose related, but infrequent now. Precipitation in urine can be minimized by taking plenty of fluids and by alkalinizing the urine.
- Hypersensitivity reactions occur in 2–5% patients. These are mostly in the form of rashes, urticaria and drug fever. Stevens-Johnson syndrome and exfoliative dermatitis are serious reactions reported with the long-acting agents.
- Hepatitis, unrelated to dose, occurs in 0.1% patients.
- Haemolysis can occur in G-6-PD deficient individuals with high doses of sulfonamides. Neutropenia and other blood dyscrasias are rare.
- Kernicterus may be precipitated in the newborn, especially premature, whose blood-brain barrier is more permeable, by displacement of bilirubin from plasma protein binding sites.

Fixed dose combinations of sulfonamides with penicillin are banned in India.

USES

Systemic use of sulfonamides alone (not combined with trimethoprim or pyrimethamine) is obsolete.

Combined with trimethoprim (as cotrimoxazole) sulfamethoxazole is used for many bacterial infections, *P. jiroveci* and nocardiosis (*see* below). Along with pyrimethamine, certain sulfonamides are used for malaria (*see Ch.* 61) and toxoplasmosis.

Ocular sulfacetamide sod. (10–30%) is a cheap alternative in trachoma/inclusion conjunctivitis, though additional systemic azithromycin or tetracycline therapy is required for eradication of the disease. Topical silver sulfadiazine or mafenide are used for preventing infection on burn surfaces.

COTRIMOXAZOLE

The fixed dose combination of trimethoprim and sulfamethoxazole is called *cotrimoxazole*. Trimethoprim is a diaminopyrimidine related to the antimalarial drug pyrimethamine which selectively inhibits *bacterial* dihydrofolate reductase (DHFRase). Cotrimoxazole introduced in 1969 causes sequential block of folate metabolism as depicted in Fig. 51.1. Trimethoprim is >50,000 times more active against bacterial DHFRase than against the mammalian enzyme. Thus, human folate metabolism is not interfered at antibacterial concentrations of trimethoprim. Individually, both sulfonamide and trimethoprim are bacteriostatic, but the combination becomes cidal against many organisms. Maximum synergism is seen when the organism is sensitive to both the components, but even when it is moderately resistant to one component, the action of the other may be enhanced.

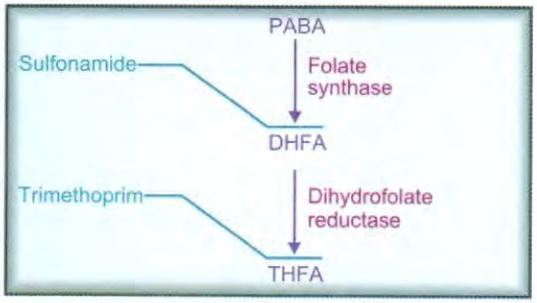


Fig. 51.1: Sequential block in bacterial folate metabolism
PABA—Para aminobenzoic acid; DHFA—Dihydrofolic acid; THFA—Tetrahydrofolic acid

Sulfamethoxazole was selected for combining with trimethoprim because both have nearly the same t½ (~ 10 hr). Optimal synergy in case of most organisms is exhibited at a concentration ratio of sulfamethoxazole 20 : trimethoprim 1, the MIC of each component may be reduced by 3–6 times. This ratio is obtained in the plasma when the two are given in a dose ratio of 5 : 1, because trimethoprim is more lipid soluble, enters many tissues, has a larger volume of distribution than sulfamethoxazole and attains lower plasma concentration. However, trimethoprim adequately crosses blood-brain barrier and placenta, while sulfamethoxazole has a poorer entry. Moreover, trimethoprim is more rapidly absorbed than sulfamethoxazole—concentration ratios may vary with time. Trimethoprim is 40% plasma protein bound, while sulfamethoxazole is 65% bound. Trimethoprim is partly metabolized in liver and excreted in urine.

Spectrum of action Antibacterial spectra of trimethoprim and sulfonamides overlap considerably. Additional organisms covered by the combination are—*Salmonella typhi, Serratia, Klebsiella, Enterobacter, Yersinia enterocolitica, Pneumocystis jiroveci* and many sulfonamide-resistant strains of *Staph. aureus, Strep. pyogenes, Shigella,* enteropathogenic *E. coli, H.influenzae,* gonococci and meningococci.

Resistance Bacteria are capable of acquiring resistance to trimethoprim mostly through plasmid mediated acquisition of a DHFRase having lower affinity for the inhibitor. Resistance to the combination has been slow to develop compared to either drug alone, but widespread use of the combination over a long period has resulted in reduced responsiveness of over 30% originally sensitive strains.

Adverse effects All adverse effects seen with sulfonamides can be produced by cotrimoxazole.

- Nausea, vomiting, stomatitis, headache and rashes are the usual manifestations.
- Folate deficiency (megaloblastic anaemia) is infrequent, occurs only in patients with marginal folate levels.
- Blood dyscrasias occur rarely.

Cotrimoxazole should not be given during ~~pregnancy.~~ Trimethoprim being an antifolate, there is theoretical teratogenic risk. Neonatal haemolysis and methaemoglobinaemia can occur if it is given near term.

- Patients with renal disease may develop uremia. Dose should be reduced in moderately severe renal impairment.
- A high incidence (upto 50%) of fever, rash and bone marrow hypoplasia has been reported among AIDS patients with *Pneumocystis jiroveci* infection when treated with high dose cotrimoxazole.
- The elderly are also at greater risk of bone marrow toxicity from cotrimoxazole.
- Diuretics given with cotrimoxazole have produced a higher incidence of thrombocytopenia.

Preparations SEPMAX, CIPLIN, ORIPRIM, SUPRISTOL, FORTRIM

Trimethoprim	*Sulfamethoxazole*
80 mg +	400 mg tab: 2 BD for 2 days then 1 BD.
160 mg +	800 mg tab: double strength (DS); 1 BD.
20 mg +	100 mg pediatric tab.
40 mg +	200 mg per 5 ml susp; infant 2.5 ml (not to be used in newborns), children 1–5 yr 5 ml, 6–12 year 10 ml (all BD).

Uses

Though cotrimoxazole is still used, its popularity in the treatment of systemic infections has declined. Common indications are:

1. *Urinary tract infections* Most acute uncomplicated infections respond rapidly. Single dose therapy with 4 tablets of cotrimoxazole has been used successfully for acute cystitis. Courses of 3–10 days have been advised for lower and upper urinary tract infections, according to associated features. Cotrimoxazole is specially valuable for chronic or recurrent cases or in prostatitis, because trimethoprim is concentrated in prostate due to relatively acidic pH of prostatic fluid.

2. *Respiratory tract infections* Both upper and lower respiratory tract infections, including chronic bronchitis and facio-maxillary infections, otitis media caused by gram positive cocci and *H. influenzae*, *Moraxella catarrhalis* respond well.

3. *Bacterial diarrhoeas and dysentery* Cotrimoxazole may be used for severe and invasive infections by *E. coli*, *Shigella*, nontyphoid *Salmonella*, and *Y. enterocolitica* (*see* p. 730, 731). Though response rate is lower than previously, and fluoroquinolones are more commonly used, it is still a valuable alternative for empirical therapy of infective diarrhoea.

4. *Pneumocystis jiroveci* causes severe pneumonia in neutropenic and AIDS patients. Cotrimoxazole has prophylactic as well as therapeutic value, but high doses are needed. One DS tablet 4–6 times/day for 2–3 weeks may be curative, but adverse effects necessitate discontinuation in upto 20% cases. One DS tab. daily has been used for prophylaxis and this is better tolerated.

5. *Chancroid* Cotrimoxazole (800 + 160 mg) BD for 14 days is a rarely used alternative to ceftriaxone/azithromycin.

6. *Typhoid* Initially cotrimoxazole was an effective alternative to chloramphenicol. However, it has become unreliable, and is seldom used now.

QUINOLONES

These are synthetic antimicrobials having a quinolone structure and are active primarily against gram-negative bacteria, though the newer fluorinated compounds also inhibit gram-positive ones. The first member *Nalidixic acid* introduced in mid-1960s had usefulness limited to urinary and g.i. tract infections because of low potency, modest blood and tissue levels, restricted spectrum and high frequency of bacterial resistance. A breakthrough was achieved in the early 1980s by fluorination of the quinolone structure at position 6 and introduction of a piperazine substitution at position 7 resulting in derivatives called *fluoroquinolones* (FQs) with high potency, expanded spectrum, slow development of resistance, better tissue penetration and good tolerability.

Nalidixic acid

It is active against gram-negative bacteria, especially coliforms: *E. coli, Proteus, Klebsiella, Enterobacter, Shigella* but not *Pseudomonas*. It acts by inhibiting bacterial DNA gyrase and is bactericidal. Resistance to nalidixic acid develops rather rapidly.

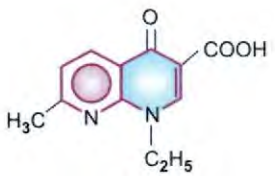
Nalidixic acid is absorbed orally, highly plasma protein bound and partly metabolized in liver: one of the metabolites is active. It is excreted in urine with a plasma $t_{1/2}$ ~8 hrs. Concentration of the free drug in plasma and most tissues attained with the usual doses is nontherapeutic for systemic infections. However, high concentration attained in urine (20–50 times that in plasma) and gut lumen is lethal to the common urinary pathogens and diarrhoea causing coliforms.

Adverse effects These are relatively infrequent, consist mostly of g.i. upset and rashes.

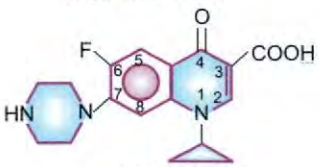
Most important toxicity is neurological—headache, drowsiness, vertigo, visual disturbances, occasionally seizures (especially in children).

Individuals with G-6-PD deficiency may develop haemolysis. Nalidixic acid is contraindicated in infants.

Dose: 0.5–1 g TDS or QID; GRAMONEG 0.5 g tab, 0.3 g/5 ml susp, DIARLOP 0.3 g/5 ml susp.



NALIDIXIC ACID



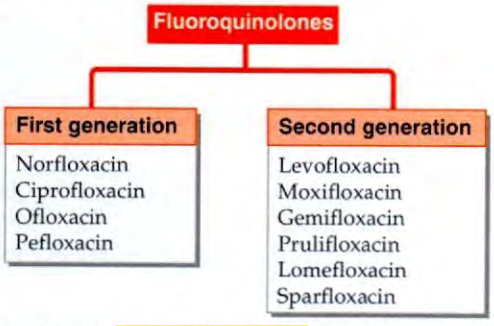
CIPROFLOXACIN

CHAPTER 51

Nalidixic acid has been largely superseded by FQs, but may occasionally be used for urinary tract infection and in diarrhoea.

FLUOROQUINOLONES

These are quinolone antimicrobials having one or more fluorine substitutions. The 'first generation' fluoroquinolones (FQs) introduced in 1980s have one fluoro substitution. In the 1990s, compounds with additional fluoro and other substitutions have been developed—further extending antimicrobial activity to gram-positive bacteria and anaerobes, and/or confering metabolic stability (longer t½). These are referred to as 'second generation' FQs. Some of the newe ones have high activity against gram positive cocci.



In addition, two other FQs *Pazufloxacin* and *Balofloxacin* are available in India.

Mechanism of action The FQs inhibit the enzyme *bacterial DNA gyrase* (primarily active in gram negative bacteria), which nicks double-stranded DNA, introduces negative supercoils and then reseals the nicked ends. This is necessary to prevent excessive positive supercoiling of the strands when they separate to permit replication or transcription. The DNA gyrase consists of two A and two B subunits: The A subunit carries out nicking of DNA, B subunit introduces negative supercoils and then A subunit reseals the strands. The FQs bind to A subunit with high affinity and interfere with its strand cutting and resealing function.

In gram-positive bacteria the major target of FQ action is a similar enzyme *topoisomerase IV* which nicks and separates daughter DNA strands after DNA replication. Greater affinity of a FQ for topoisomerase IV may confer higher potency against gram-positive bacteria. The bactericidal action probably results from digestion of the DNA by exonucleases whose production is signalled by the damaged DNA.

In place of DNA gyrase or topoisomerase IV, the mammalian cells possess an enzyme topoisomerase II (that also removes positive supercoils) which has very low affinity for FQs—hence the low toxicity to host cells.

Mechanism of resistance Because of the unique mechanism of action, ~~plasmid mediated transferable resistance~~ is less likely. Resistance noted so far is due to chromosomal mutation producing a DNA gyrase or topoisomerase IV with reduced affinity for FQs, or due to reduced permeability/increased efflux of these drugs across bacterial membranes. In contrast to nalidixic acid which selects single step resistant mutants at high frequency, FQ-resistant mutants are not easily selected. Therefore, resistance to FQs has been slow to develop. However, increasing resistance has been reported among *Salmonella, Pseudomonas,* staphylococci, gonococci and pneumococci.

Ciprofloxacin (prototype)

It is the most potent first generation FQ active against a broad range of bacteria, the most susceptible ones are the aerobic gram-negative bacilli, especially the Enterobacteriaceae and *Neisseria.* The MIC of ciprofloxacin against these bacteria is usually < 0.1 µg/ml, while gram-positive bacteria are inhibited at relatively higher concentrations. The original spectrum of action is summarized below:

Highly susceptible

E. coli
K. pneumoniae
Enterobacter
Neisseria gonorrhoeae
N. meningitidis
H. influenzae

Salmonella typhi	*H. ducreyi*
Nontyphoid *Salmonella*	*Campylobacter jejuni*
Shigella	*Yersinia enterocolitica*
Proteus	*Vibrio cholerae*

Moderately susceptible

Pseudomonas aeruginosa	*Legionella*
Brucella	*Mycoplasma*
Listeria	*Chlamydia pneumophila*
Staph. epidermidis	*Bacillus anthracis*
Branhamella catarrhalis	*Mycobact. tuberculosis*

Organisms which have shown low/variable susceptibility are: *Strep. pyogenes, Strep. faecalis, Strep. pneumoniae, MRSA, Mycobact. kansasii, Mycobact. avium.*

Notable resistant bacteria are: *Bacteroides fragilis, Clostridia*, anaerobic cocci.

The distinctive microbiological features of ciprofloxacin (also other FQs) are:

- Bactericidal activity and high potency: MBCs are close to MICs.
- Relatively long post-antibiotic effect on Enterobacteriaceae, *Pseudomonas* and *Staph.*
- Low frequency of mutational resistance.
- Low propensity to select plasmid type resistant mutants.
- Protective intestinal streptococci and anaerobes are spared.
- Less active in acidic pH.

Pharmacokinetics Ciprofloxacin is rapidly absorbed orally, but food delays absorption, and first pass metabolism occurs. The pharmacokinetic values are given in Table 51.1. Ciprofloxacin (and other FQs except norfloxacin) attain bactericidal levels in blood and have good tissue penetrability. Concentration in lung, sputum, muscle, prostate and phagocytes exceeds that in plasma, but CSF and aqueous levels are lower. It is excreted primarily in urine, both by glomerular filtration and tubular secretion. Urinary and biliary concentrations are 10–50 fold higher than plasma.

Adverse effects Ciprofloxacin has good safety record: side effects occur in ~10% patients, but are generally mild; withdrawal is needed only in 1.5%.

- Gastrointestinal: nausea, vomiting, bad taste, anorexia. Because gut anaerobes are not affected—diarrhoea is infrequent.
- CNS: dizziness, headache, restlessness, anxiety, insomnia, impairment of concentration and dexterity (caution while driving). Tremor and seizures are rare, occur only at high doses or when predisposing factors are present.
- Skin/hypersensitivity: rash, pruritus, photosensitivity, urticaria, swelling of lips, etc. Serious cutaneous reactions are rare.
- Tendonitis and tendon rupture: a few cases have occurred. Risk of tendon damage is higher in patients above 60 years of age and in those receiving corticosteroids. Due to reports of cartilage damage, FQs should be used cautiously in children.

Ciprofloxacin and other FQs are contraindicated during pregnancy.

Interactions

- Plasma concentration of theophylline, caffeine and warfarin is increased by ciprofloxacin due to inhibition of metabolism: CNS toxicity can occur by concurrent use of theophylline and a FQ.
- NSAIDs may enhance the CNS toxicity of FQs; seizures are reported.
- Antacids, sucralfate and iron salts given together reduce absorption of FQs.

CIFRAN, CIPLOX, CIPROBID, QUINTOR, CIPROLET 250, 500, 750 mg tab, 200 mg/100 ml i.v. infusion, 3 mg/ml eye drops.

Uses Ciprofloxacin is effective in a broad range of infections. Because of wide-spectrum bactericidal activity, oral efficacy and good tolerability, it is being extensively employed for empirical therapy of any infection, but should not be used for minor cases or where gram-positive organisms and/or anaerobes are primarily causative. In severe infections, therapy may be initiated by i.v. infusion and then switched over to oral route.

1. *Urinary tract infections (UTI):* High cure rates, even in complicated cases or those

Table 51.1: Pharmacokinetic characteristics and doses of fluoroquinolones

	CIPROFL	NORFL	PEFL	OFL	LEVOFL	GEMI	PRULI	MOXI
1 Oral bioavailability (%)	60–80	35–45	90–100	85–95	~100	70	90	85
2. Plasma protein binding (%)	20–35	15	20–30	25	25	55–73	45	40
3. Vol. of distribution (L/kg)	3–4	2	2	1.5	1.3	—	—	2
4. Percent metabolized	20	25	85	5–10	5	—	>90	70–80
5. Elimination t½ (hr)	3–5	4–6	8–14	5–8	8	7	10–12	10–15
6. Routes of administration	oral, i.v.	oral	oral, i.v.	oral, i.v.	oral, i.v.	oral	oral	oral, i.v.
7. Dose (mg) : oral	250–750 (BD)	400 (BD)	400 (BD)	200–400 (BD)	500 (OD)	320 (OD)	600 (OD)	400 (OD)
: iv	100–200	—	400	200	500	—	—	400

SECTION 12

with indwelling catheters/prostatitis, have been achieved. Comparative trials have reported higher success rates than with cotrimoxazole. Chronic *Pseudomonas* infections respond less completely, but among all FQs ciprofloxacin is the most active against *Pseudomonas*..

2. *Gonorrhoea:* Initially ciprofloxacin was nearly 100% curative in non-PPNG as well as PPNG infections, but has become nondependable now; therefore not used.

3. *Chancroid:* Ciprofloxacin 500 mg BD for 3 days is a second line alternative drug to ceftriaxone/azithromycin.

4. *Bacterial gastroenteritis:* Currently, ciprofloxacin is the most commonly used drug for empirical therapy of diarrhoea. However, it should be reserved for moderate-to-severe cases only. It can reduce stool volume in cholera.

5. *Typhoid:* Chloramphenicol, ampicillin and cotrimoxazole became unreliable for treating typhoid many years back due to development of resistance. In India and elsewhere up to 95% *S. typhi* isolates were sensitive to ciprofloxacin, and it has been used as a first line drug. However, increasing number of nonresponsive cases are being reported. Ceftriaxone (or cefoperazone) is more commonly used now. If the *S. typhi* strain is sensitive, ciprofloxacin given in a dose of 750 mg BD for 10 days is recommended. Patients unable to take the drug orally may be treated with 200 mg. i.v. 12 hourly in the beginning. Being bactericidal, the advantages of ciprofloxacin are quick defervescence, early relief from symptoms and prevention of carrier state. It can also be used to treat typhoid carriers (750 mg BD for 4–8 weeks). This has been found to achieve 92% eradication rate.

(For alternative drugs *see* box)

Drugs for typhoid fever

1. **Ceftriaxone** (*see* p. 778): Currently, it is the most reliable and fastest acting bactericidal drug for enteric fever. Practically all *S. typhi* isolates, including multidrug resistant ones, are susceptible. However, it has to be injected i.v. (2 g twice daily for 2 days followed by 2 g/day till 2 days after fever subsides; children 75 mg/kg/day) and is expensive. Generally 7–10 days treatment is required. Being bactericidal, it also prevents relapses and carrier state. Ceftriaxone is to be preferred over FQs in children, pregnant women and in areas with FQ resistance.
   Cefoperazone and *cefotaxime* are the other third generation cephalosporins used in typhoid.
2. **Fluoroquinolones:** Ciprofloxacin (750 mg BD) is mostly used. Ofloxacin (400 mg BD), levofloxacin (500 mg OD/BD) are nearly equally efficacious alternatives.
3. **Azithromycin** (500 mg OD for 7 days) is a second line alternative in multidrug resistant typhoid, and in patients to whom the 1st line drugs cannot be given.
4. **Chloramphenicol** (*see* p. 792): Since majority of *S. typhi* strains are now chloramphenicol resistant, it has become clinically unreliable.
5. **Cotrimoxazole** (*see* p. 759): It was effective in typhoid till plasmid mediated multidrug resistance spread among *S. typhi*. Now it is rarely used.

6. *Bone, soft tissue, gynaecological and wound infections:* caused by resistant *Staph.* and gram-negative bacteria mostly respond to ciprofloxacin. High cure rates have been obtained in osteomyelitis and joint infections but prolonged treatment (6–8 weeks) with high doses (750 mg BD) is required. Used along with clindamycin/metronidazole (to cover anaerobes) it is a good drug for diabetic foot.

7. *Respiratory infections:* Ciprofloxacin should not be used as the primary drug because pneumococci and streptococci have low and variable susceptibility. However, it can treat atypical pneumonia due to *Mycoplasma, Legionella, H. influenzae, Branh. catarrhalis*, and *Chlamydiae*. Several 2nd generation FQs (levofloxacin, gemifloxacin, moxifloxacin) have now become available for the treatment of pneumonias and chronic bronchitis.

Anthrax: Ciprofloxacin is considered to be the drug of choice. The US-FDA has approved its use for post exposure treatment of inhalational *anthrax* which may occur due to bioterrorism.

8. *Tuberculosis* Moxifloxacin and levofloxacin are second line drugs which can be used as a component of combination chemotherapy against multidrug resistant tuberculosis (*see Ch.* 56). Ciprofloxacin is less active against *M. tuberculosis*, but is the most active FQ against *Mycobact. avium complex* (MAC).

9. *Gram-negative septicaemias:* Parenteral ciprofloxacin may be combined with a third generation cephalosporin or an aminoglycoside.

10. *Meningitis:* Though penetration in CSF is not very good, ciprofloxacin has been successfully used in gram-negative bacterial meningitis, especially that occurring in immunocompromised patients or those with CSF shunts. It can cure meningococcal carrier state.

11. *Prophylaxis:* of infections in neutropenic/cancer and other susceptible patients.

12. *Conjunctivitis:* by gram-negative bacteria: topical therapy is effective.

Norfloxacin It is the least potent FQ: MIC values for most gram-negative bacteria are 2–8 times higher than that of ciprofloxacin. Many *Pseudomonas* and gram-positive organisms are not inhibited. Moreover, it attains lower concentration in tissues which are non-therapeutic.

Norfloxacin is primarily used for urinary tract infections. Given for 8–12 weeks, it can treat chronic UTI. It is also good for bacterial diarrhoeas, because high concentrations are present in the gut, and anaerobic flora of the gut is not disturbed.

NORBACTIN, NORFLOX 200, 400, 800 mg tab, 3 mg/ml eye drops; UROFLOX, NORILET 200, 400 mg tab. BACIGYL 400 mg tab, 100 mg/5 ml susp.

Pefloxacin It is the methyl derivative of norfloxacin which is more lipid soluble, completely absorbed orally, penetrates tissues better and attains higher plasma concentrations. Passage into CSF is greater than other FQs—can be used for meningeal infections. It is highly metabolized—partly to norfloxacin which contributes to its activity. Pefloxacin has longer t½: cumulates on repeated dosing achieving plasma concentrations twice as high as after a single dose. Because of this it is effective in some systemic infections as well. Dose of pefloxacin needs to be reduced in liver disease, but not in renal insufficiency.

PELOX, 200, 400 mg tab, to be taken with meals; 400 mg/5 ml inj (to be diluted in 100–250 ml of glucose solution but not saline, because it precipitates in presence of Cl^- ions).

Ofloxacin This FQ is somewhat less active than ciprofloxacin against gram-negative bacteria, but equally or more potent against *Strep. pyogenes* and other gram-positive cocci and certain anaerobes. Good activity against *Chlamydia* and *Mycoplasma* has been noted. It is an alternative drug for nonspecific urethritis, cervicitis and atypical pneumonia caused by *Chlamydia trachomatis*. It also inhibits *M. tuberculosis*; can be used in resistant cases of TB. High activity is exhibited against *M. leprae*, and it is being used in alternative multidrug therapy regimens.

Ofloxacin is relatively lipid soluble; oral bioavailability is high, and higher plasma concentrations are attained. Food does not interfere with its absorption. It is excreted

largely unchanged in urine; dose needs to be reduced in renal failure.

Ofloxacin is comparable to ciprofloxacin in the therapy of systemic and mixed infections. It is suitable for chronic bronchitis and other respiratory or ENT infections as well as for chlamydia urethritis as an alternative drug. Inhibition of theophylline metabolism is less marked.
ZANOCIN, TARIVID 100, 200, 400 mg tab; 200 mg/100 ml i.v. infusion, ZENFLOX also 50 mg/5 ml susp.
ZANOCIN, OFLOX, EXOCIN 0.3% eye drops.

Levofloxacin It is the active levo(S) isomer of ofloxacin having improved activity against *Strep. pneumoniae, M. tuberculosis* and some other gram-positive and gram-negative bacteria. Anaerobes are moderately susceptible. Oral bioavailability of levofloxacin is nearly 100%; oral and i.v. doses are similar. It is mainly excreted unchanged, and a single daily dose is sufficient because of slower elimination and higher potency.

Theophylline, warfarin, cyclosporine and zidovudine pharmacokinetics has been found to remain unchanged during levofloxacin treatment. The primary indication of levofloxacin is community acquired pneumonia and exacerbations of chronic bronchitis in which upto 90% cure rate has been obtained. High cure rates have been noted in sinusitis, pyelonephritis, prostatitis and other UTI, as well as skin/soft tissue infections. Levofloxacin is an alternative drug for chlamydial urethritis. It is the second most active FQ for TB, and in India it is a component of the standardized regimen for MDR-TB.
TAVANIC, GLEVO 500 mg tab, 500 mg/100 ml inj.
LOXOF, GLEVO, LEVOFLOX, LEVODAY 250, 500, 750 mg tabs, 500 mg/100 ml inj; GLEVO 0.5% eye drops.

Lomefloxacin It is a second generation difluorinated quinolone, more active against some gram-negative bacteria and chlamydia. However, due to higher incidence of phototoxicity and Q-T prolongation, it has been withdrawn in ~~USA~~ and some other countries, but is available in India, though infrequently used.
LOMEF-400, LOMEDON, LOMADAY 400 mg tab.
LOMIBACT, LOX 0.3% eye drops.

Sparfloxacin Another second generation difluorinated quinolone which has enhanced activity against gram-positive bacteria, *Bacteroides fragilis*, other anaerobes and mycobacteria. Its major indications include pneumonia, exacerbations of chronic bronchitis, sinusitis and other ENT infections. However, it has frequently caused phototoxic reactions: recipients should be cautioned not to go out in the sun. Prolongation of QTc interval has been noted in 3% recipients; fatal arrhythmias have occurred. It has been discontinued in many countries including ~~USA~~, but not yet in India.
Dose: 200–400 mg OD oral.
TOROSPAR 200, 400 mg tab; SPARTA, SPARQUIN, SPARDAC 100, 200 mg tab, ZOSPAR, SPARC, EYPAR 0.3% eye drops.

Moxifloxacin A long-acting 2nd generation FQ having high activity against *Str. pneumoniae*, other gram-positive bacteria including β-lactam/macrolide resistant ones and some anaerobes. It is the most potent FQ against *M. tuberculosis*, and is extensively used in MDR-TB. Bacterial topoisomerase IV is the major target of action. Moxifloxacin is primarily used for pneumonias, bronchitis, sinusitis, otitis media, in which efficacy is comparable to β-lactam antibiotics. Because urinary concentrations are low, it is not used for urinary tract infections. It is primarily metabolized in liver; should not be given to liver disease patients. No dose modification is needed in renal disease. Side effects are similar to other FQs. It should not be given to patients predisposed to seizures and to those receiving proarrhythmic drugs, because it can prolong Q-T interval, and the combination may precipitate serious arrhythmias. Phototoxicity occurs rarely.
Dose: 400 mg OD; MOXIF, MOXICIP, STAXOM 400 mg tab, 400 mg/250 ml i.v. infusion.
MOXICIP, MILFLOX, VIGAMOX 0.5% eye drops for conjunctivitis caused by gram-positive as well as negative bacteria.

Gemifloxacin Another broad spectrum FQ, active mainly against aerobic gram positive bacteria, especially *Strep. pneumoniae, H. influenzae, Moraxella, Mycoplasma pneumoniae, Chlamydia pneumophila, Klebsiella* including some multidrug resistant strains. Some anaerobes are also inhibited. Gemifloxacin is rapidly absorbed, undergoes limited metabolism, and is excreted in urine as well as faeces, both as unchanged drug and as metabolites. Dose needs to be halved if creatinine clearance is <40 ml/min.

Side effects are diarrhoea, nausea, headache, dizziness and rise in serum amino-transferases.

Skin rashes are more common. It can enhance warfarin effect, and carries the risk of additive Q-T prolongation with other drugs. Gemifloxacin is indicated in community acquired pneumonia and for acute exacerbations of chronic bronchitis.
Dose: 320 mg OD for 5–7 days.
TOPGEM, GEMBAX, GEMISTAR, GEMI 320 mg tab.

Prulifloxacin This newer 2nd generation FQ is a prodrug of *Ulifloxacin*, a broad spectrum antibacterial active against both gram positive as well as gram negative bacteria, including many resistant strains. Prulifloxacin is rapidly absorbed and converted to ulifloxacin during first pass metabolism. Ulifloxacin is then excreted primarily unchanged in urine. Prulifloxacin has shown good efficacy in acute exacerbations of chronic bronchitis, as well as in uncomplicated or complicated UTI. Its side effect profile is similar to that of ciprofloxacin. Gastrointestinal and CNS disturbances, urticaria and photosensitivity are reported. It is claimed not to prolong ~~Q-T interval~~.
Dose: 600 mg OD, single dose in uncomplicated lower UTI; upto 10 days treatment for complicated UTI and bronchitis.
ALPRULI, PRULIFOX, PRULIFACT 600 mg tab.

Pazufloxacin It is an atypical quinolone antimicrobial with a fused tricyclic ring, developed in Japan in the 1990s. Only an injectable formulation as 'mesylate' is marketed for i.v. infusion. Antimicrobial spectrum of Pazufloxacin is wide covering both gram +ive and –ive bacteria, including several resistant strains and some anaerobes. It inhibits both bacterial DNA gyrase and topoisomerase IV confering gram –ive and gram +ive activity as well as low potential to select resistant mutants. Most enterobacteriaceae are highly susceptible while good activity has been noted against resistant *Pseudomonas*, MRSA, ampicillin resistant *H.influenzae* and *K.pneumoniae*.

After i.v. infusion pazufloxacin penetrates most body fluids including CSF, and is mainly excreted unchanged in urine with a t½ of 1.5–2 hours. Clinical indications of pazufloxacin are pneumonia, lung abscesses, upper and lower UTI, peritonitis, intraabdominal abscesses, endometritis, secondary infections after burns, injuries and empirical therapy of nosocomial infections. Adverse effects are nausea, diarrhoea, rashes, rarely seizures. However, evidence of its efficacy and safety are limited. It is not approved in USA and in UK, etc. Risk of seizures may limit dosage.
Dose: 500 mg (elderly 300 mg) infused i.v. over 30–60 min) twice daily for max 14 days.
PAZACE, PAZFLO, PAZUBID 500 mg/100 ml and 300 mg/100 ml inj.

Balofloxacin This FQ produced in Korea in 1990s is marketed only in India and few other countries, but not in Europe and USA. Balofloxacin is shown to be batericidal against many gram +iv and gram –ive bacteria, including *Strep. pneumoniae* and MRSA, by inhibiting bacterial DNA gyrase. It is well absorbed orally, very little metabolized and excreted in urine with a t½ of 7–8 hrs. Adverse effects are nausea, dizziness, loss of appetite, skin rashes, photosensitivity reactions, peripheral neuropathy. Indications of balofloxacin include sinusitis, exacerbations of chronic bronchitis, community acquired pneumonia and UTI. However, only limited data on its efficacy and safety are available. Its potential to prolong QTc is not known.
Dose: 100–200 mg BD
BALOSTAR, BALOWIN, B-CIN, 100 mg tab.

☞ PROBLEM DIRECTED STUDY

51.1 A 62-year-old lady presented with acute onset frontal headache which is worse in the morning, thick, yellowish discharge from the nose, nasal blockage and fever for the past 2 days. She has been suffering from cold and cough for the last one week. The forehead is tender on pressing, particularly in the middle. A plain X-ray of the face and head showed both sided frontal sinusitis. Her husband informed that 3 months back she sufferred an episode of depression, for which she is receiving Tab amitryptyline 75 mg once daily at bed time and her mental condition is stable now. The doctor decides to start empirical therapy with moxifloxacin 400 mg once daily for 10 days. He also prescribes paracetamol 500 mg 8 hourly for fever and oxymetazoline nasal drops twice daily for blocked nose.
(a) Is the choice of antibiotic appropriate for her? If yes, what could be the considerations for selecting moxifloxacin. If no, then give reasons, and suggest the alternative antibiotic(s) that would be appropriate.
(see Appendix-1 for solution)

Chapter 52 Beta-Lactam Antibiotics

These are antibiotics having a β-lactam ring. The two major groups are penicillins and cephalosporins. Monobactams and carbapenems are relatively later additions.

PENICILLINS

Penicillin was the first antibiotic to be used clinically in 1941. It is a miracle that the least toxic drug of its kind was the first to be discovered. Penicillin was originally obtained from the fungus *Penicillium notatum*, but the present source is a high yielding mutant of *P. chrysogenum*.

Chemistry and properties The penicillin nucleus consists of fused thiazolidine and β-lactam rings to which side chains are attached through an amide linkage (Fig. 52.1). Penicillin G (PnG), having a benzyl side chain at R (benzyl penicillin), is the original penicillin used clinically.

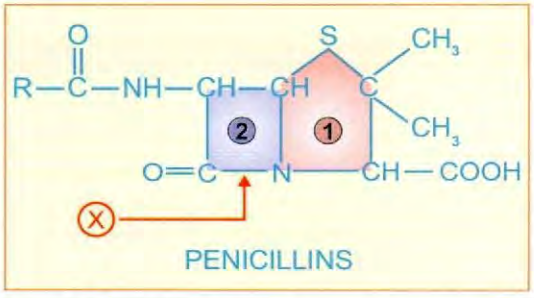


Fig. 52.1: Chemical structure of penicillins. (1) Thiazolidine ring; (2) β-lactam ring; (X) Bond which is broken by penicillinase (a β-lactamase)

The side chain of natural penicillin can be split off by an amidase to produce 6-amino-penicillanic acid. Other side chains can then be attached to it resulting in different semisynthetic penicillins with unique antibacterial activities and different pharmacokinetic profiles.

At the carboxyl group attached to the thiazolidine ring, salt formation occurs with Na^+ and K^+. These salts are more stable than the parent acid. Sod. PnG is highly water soluble. It is stable in the dry state, but solution deteriorates rapidly at room temperature, though it remains stable at 4°C for 3 days. Therefore, PnG solutions are always prepared freshly. PnG is also thermolabile and acid labile.

Unitage 1 U of crystalline sod. benzyl penicillin = 0.6 μg of the standard preparation. Accordingly, 1 g = 1.6 million units or 1 MU = 0.6 g.

Mechanism of action

All β-lactam antibiotics interfere with the synthesis of bacterial cell wall. The bacteria synthesize UDP-N-acetylmuramic acid pentapeptide, called 'Park nucleotide' (because Park in 1957 found it to accumulate when susceptible *Staphylococcus* was grown in the presence of penicillin) and UDP-N-acetyl glucosamine. The peptidoglycan residues are linked together forming long strands and UDP is split off. The final step is cleavage of the terminal D-alanine of the peptide chains by transpeptidases; the energy so released is utilized for establishment of cross linkages between peptide chains of the

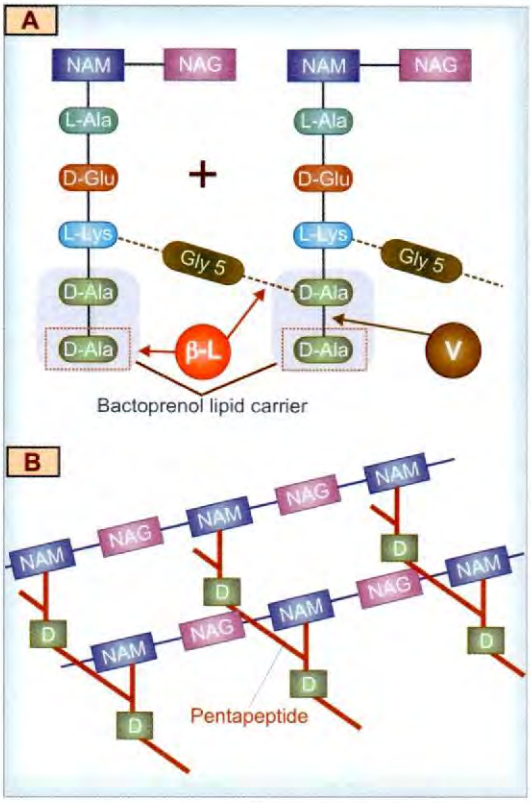


Fig. 52.2: Key features of bacterial cell wall synthesis and cell wall structure, depicting the site of action of β-lactam antibiotics and vancomycin.

A. Cross linking of peptidoglycan residues of neighbouring strands by cleavage of terminal D-alanine (D-Ala) and transpeptidation with the chain of 5 glycine (Gly5) residues. The β-lactam antibiotics (β-L) block cleavage of terminal D-Ala and transpeptidation. The peptidoglycan units are synthesized within the bacterial cell and are transported across the cell membrane by attachment to a bactoprenol lipid carrier for assembly into strands. Vancomycin (V) binds tightly to the terminal D-Ala-D-Ala sequence and prevents its release from the carrier, so that further transpeptidation cannot take place.

B. The highly cross linked peptidoglycan strands in bacterial cell wall

NAM—N-acetyl muramic acid
NAG—N-acetylglucosamine
L-Ala—L-alanine
D-Glu—D-glutamic acid
L-Lys—L-Lysine

neighbouring strands (Fig. 52.2). This cross linking provides stability and rigidity to the cell wall.

The β-lactam antibiotics inhibit the transpeptidases so that cross-linking (which maintains the close knit structure of the cell wall) does not take place. These enzymes and related proteins constitute the *penicillin binding proteins (PBPs)* which have been located in the bacterial cell membrane. Each organism has several PBPs, and PBPs obtained from different species differ in their affinity towards different β-lactam antibiotics. This fact probably explains their differing sensitivity to the various β-lactam antibiotics.

When susceptible bacteria divide in the presence of a β-lactam antibiotic—cell wall deficient (CWD) forms are produced. Because the interior of the bacterium is hyperosmotic, the CWD forms swell and burst → bacterial lysis occurs. This is how β-lactam antibiotics exert bactericidal action. Under certain conditions and in case of certain organisms, bizarre shaped or filamentous forms, which are incapable of multiplying, result. Grown in hyperosmotic medium, globular 'giant' forms or *protoplasts* are produced. Lytic effect of these antibiotics may also be due to derepression of some bacterial autolysins which normally function during cell division.

Rapid cell wall synthesis occurs when the organisms are actively multiplying; β-lactam antibiotics are more lethal in this phase.

The peptidoglycan cell wall is unique to bacteria. No such substance is synthesized (particularly, D-alanine is not utilized) by higher animals. This is why penicillin is practically nontoxic to man.

In gram-positive bacteria, the cell wall is almost entirely made of peptidoglycan, which is >50 layers thick and extensively cross linked, so that it may be regarded as a single giant mucopeptide molecule. In gram-negative bacteria, the cell wall consists of alternating layers of lipoprotein and peptidoglycan (each layer 1–2

molecule thick with little cross linking). This may be the reason for higher susceptibility of the gram-positive bacteria to PnG.

Blood, pus, and tissue fluids do not interfere with the antibacterial action of β-lactam antibiotics.

PENICILLIN-G (BENZYL PENICILLIN)

Antibacterial spectrum PnG is a narrow spectrum antibiotic; activity is limited primarily to gram-positive bacteria, few gram negative ones and anaerobes.

Cocci: *Streptococci* (except *viridans*, group D or enterococci) are highly sensitive, so are many pneumococci. *Staph. aureus*, though originally very sensitive, has acquired resistance to such an extent that it must be counted out of PnG spectrum. Gram negative cocci—*Neisseria gonorrhoeae* and *N. meningitidis* are susceptible to PnG, though increasing number of gonococci have developed partial and others high degree resistance.

Bacilli: Gram-positive bacilli—majority of *B. anthracis, Corynebacterium diphtheriae,* and practically all *Clostridia (tetani* and others), *Listeria* are highly sensitive, so are spirochetes (*Treponema pallidum, Leptospira,* and others), but *Bacteroides fragilis* is largely resistant.

Actinomyces israelii is only moderately sensitive.

Majority of aerobic gram-negative bacilli, *Mycobacterium tuberculosis*, rickettsiae, chlamydiae, protozoa, fungi and viruses are totally insensitive to PnG.

Bacterial resistance Many bacteria are inherently insensitive to PnG because in them the target enzymes and PBPs are located deeper under lipoprotein barrier where PnG is unable to penetrate or have low affinity for PnG. The primary mechanism of acquired resistance is production of penicillinase.

Penicillinase It is a narrow spectrum β-lactamase which opens the β-lactam ring and inactivates PnG and some closely related congeners. Majority of *Staphylococci* and some strains of gonococci, *B. subtilis, E. coli, H. influenzae* and few other bacteria produce penicillinase. The gram-positive penicillinase producers elaborate large quantities of the enzyme which diffuses into the surroundings and can protect other inherently sensitive bacteria. In gram-negative bacteria, penicillinase is found in small quantity, but is strategically located inbetween the lipoprotein and peptidoglycan layers of the cell wall. Staphylococcal penicillinase is inducible, and methicillin is an important inducer; while in gram-negative organisms, it is mostly a constitutive enzyme.

Penicillinase has been successfully used to destroy PnG in patient's blood sample so that it does not interfere with bacterial growth when such blood is cultured.

Some resistant bacteria become *penicillin tolerant* and not penicillin destroying. Their target enzymes are altered to have low affinity for penicillin, e.g. highly resistant pneumococci isolated in some areas have altered PBPs. The methicillin-resistant *Staph. aureus* (MRSA) have acquired a PBP which has very low affinity for β-lactam antibiotics. Some penicillin resistant pneumococci and enterococci have altered PBPs. The low level penicillin-resistant gonococci become less permeable to the drug, while high degree resistant ones produce penicillinase, as do highly resistant *H. influenzae*. Both these bacteria appear to have acquired the penicillinase plasmid by conjugation or transduction and then propagated it by selection.

The gram-negative bacteria have 'porin' channels formed by specific proteins located in their outer membrane. Permeability of various β-lactam antibiotics through these channels differs: ampicillin and other members which are active against gram-negative bacteria cross the porin channels much better than PnG. Some gram-negative bacteria become resistant by loss or alteration of porin channels. Resistance due to impaired permeability of the β-lactam occurs only in gram –ive bacteria.

Pharmacokinetics

Penicillin G is acid labile, therefore destroyed by gastric acid. As such, less than 1/3rd of an oral dose is absorbed in the active form. Absorption of sod. PnG from i.m. site is rapid and complete; peak plasma level is attained in 30 min. It is distributed mainly extracellularly; reaches most body fluids, but penetration in serous cavities and CSF is poor. However, in the presence of inflammation (sinovitis, meningitis, etc.) adequate amounts may reach these sites. About 60% is plasma protein bound. It is little metabolized because of rapid excretion.

The pharmacokinetics of PnG is dominated by very rapid renal excretion; about 10% by glomerular filtration

and the rest by tubular secretion. The plasma t½ of PnG in healthy adult is 30 min. Neonates have slower tubular secretion—t½ of PnG is longer; but approaches adult value at 3 months and then is even shorter during childhood. Aged and those with renal failure excrete penicillin slowly. Tubular secretion of PnG can be blocked by probenecid—higher and longer lasting plasma concentrations are achieved. Probenecid also decreases the volume of distribution of penicillins.

Preparations and dose

1. *Sod. penicillin G (crystalline penicillin) injection* 0.5–5 MU i.m./i.v. 6–12 hourly. It is available as dry powder in vials to be dissolved in sterile water at the time of injection.

BENZYL PENICILLIN 0.5, 1 MU inj.

Repository penicillin G injections These are insoluble salts of PnG which must be given by deep i.m. (never i.v.) injection. They release PnG slowly at the site of injection, which then meets the same fate as soluble PnG.

1. *Procaine penicillin G inj.* 0.5–1 MU i.m. 12–24 hourly as aqueous suspension. Plasma concentrations attained are lower, but are sustained for 12–24 hours; PROCAINE PENICILLIN-G 0.5, 1 MU dry powder in vial.

Fortified procaine penicillin G inj: contains 3 lac U procaine penicillin and 1 lac U sod. penicillin G to provide rapid as well as sustained blood levels. FORTIFIED P.P. INJ 3+1 lac U vial; BISTREPEN 6+4 lac U/vial.

2. *Benzathine penicillin G* 0.6–2.4 MU i.m. every 2–4 weeks as aqueous suspension. It releases penicillin extremely slowly—plasma concentrations are very low but remain effective for prophylactic purposes for up to 4 weeks:

PENIDURE-LA (long acting), LONGACILLIN, 0.6, 1.2, 2.4 MU as dry powder in vial.

Adverse effects

Penicillin G is one of the most nontoxic antibiotics; up to 20 MU has been injected in a day without any organ toxicity.

Local irritancy and direct toxicity Pain at i.m. injection site, nausea on oral ingestion and thrombophlebitis of injected vein are dose-related expressions of irritancy.

Toxicity to the brain may be manifested as mental confusion, muscular twitchings, convulsions and coma, when very large doses (> 20 MU) are injected i.v.; especially in patients with renal insufficiency. Bleeding has also occurred with such high doses due to interference with platelet function. Intrathecal injection of PnG is not recommended.

Accidental i.v. injection of procaine penicillin produces CNS stimulation, hallucinations and convulsions due to procaine. Being insoluble, it may also cause microembolism.

Hypersensitivity These reactions are the major problem in the use of penicillins. An incidence of 1–10% is reported. Individuals with an allergic diathesis are more prone to develop penicillin reactions. PnG is the most common drug implicated in drug allergy, because of which it has practically vanished from use in general practice.

Frequent manifestations of penicillin allergy are—rash, itching, urticaria and fever. Wheezing, angioneurotic edema, serum sickness and exfoliative dermatitis are less common. Anaphylaxis is rare (1 to 4 per 10,000 patients), but may be fatal.

All forms of natural and semisynthetic penicillins can cause allergy, but it is more commonly seen after parenteral than oral administration. Incidence is highest with procaine penicillin: procaine is itself allergenic. The course of penicillin hypersensitivity is unpredictable, i.e. an individual who tolerated penicillin earlier may show allergy on subsequent administration and *vice versa*.

There is partial cross sensitivity between different types of penicillins; an individual who has exhibited immediate type of hypersensitivity—urticaria, angioedema, bronchospasm, anaphylaxis or serum sickness with one penicillin should not be given any other type of penicillin. However, if the earlier reaction had been only a rash, penicillin may be given cautiously—often no untoward effect is seen. History of penicillin allergy must be elicited before injecting it. A scratch test or intradermal test (with 2–10 U) may be performed first. On occasions, this itself has caused fatal anaphylaxis. Testing with benzylpenicilloyl-polylysine is safer. However, a negative intradermal test does not rule out delayed hypersensitivity. It should also be realised that presence of antibodies to penicillin does not mean allergy to it, because practically everyone who receives penicillin develops antibodies to it.

For the development of antibodies, penicillin or a product of it (mostly penicilloyl moiety, which is the major determinant) acts as a hapten. There are many minor determinants as well.

Topical application of penicillin is highly sensitizing (contact dermatitis and other reactions). Therefore, all topical preparations of penicillin have been banned.

If a patient is allergic to penicillin, it is best to use an alternative antibiotic. Hyposensitization by the injection of increasing amounts of penicillin intradermally at hourly intervals may be tried, only if there is no other choice.

Superinfections These are rare with PnG because of its narrow spectrum; though bowel, respiratory and cutaneous microflora does undergo changes.

Jarisch-Herxheimer reaction Penicillin injected in a syphilitic patient (particularly secondary syphilis) may produce shivering, fever, myalgia, exacerbation of lesions, even vascular collapse. This is due to sudden release of spirochetal lytic products. It does not recur and does not need interruption of therapy. Aspirin and sedation afford relief of symptoms.

Uses

Penicillin G is the drug of choice for infections caused by organisms susceptible to it, unless the patient is allergic to this antibiotic. However, use has declined very much due to fear of causing anaphylaxis.

1. *Streptococcal infections* Like pharyngitis, otitis media, scarlet fever, rheumatic fever respond to ordinary doses of PnG because *Strep. pyogenes* has not developed significant resistance. For subacute bacterial endocarditis (SABE) caused by *Strep. viridans* or *faecalis* high doses (10–20 MU i.v. daily) along with gentamicin given for 2–6 weeks is needed.

2. *Pneumococcal infections* PnG is infrequently used now for pneumococcal (lobar) pneumonia and meningitis, only if the strain is sensitive.

3. *Meningococcal infections* are still mostly responsive; meningitis and other infections may be treated with intravenous injection of high doses of PnG.

4. *Gonorrhoea* PnG has become unreliable for the treatment of gonorrhoea.

5. *Syphilis* *T. pallidum* has not shown any resistance and PnG is the drug of choice. Early and latent syphilis is treated either with daily i.m. injection of 1.2 MU of procaine penicillin for 10 days or with 1–3 weekly doses of 2.4 MU benzathine penicillin. For late syphilis, benzathine penicillin 2.4 MU weekly for 4 weeks is recommended. Cardiovascular and neurosyphilis requires sod. PnG 5 MU i.m. 6 hourly for 10–14 days followed by the above regimen.

Leptospirosis: PnG 1.5 MU injected i.v. 6 hourly for 7 days is curative.

6. *Diphtheria* Antitoxin therapy is of prime importance. Procaine penicillin 1–2 MU daily for 10 days may be used to prevent carrier state.

7. *Tetanus and gas gangrene* Antitoxin and other measures are more important; PnG 6–12 MU/day is used to kill the causative organism and has adjuvant value.

8. Penicillin G may be used for rare infections like anthrax, actinomycosis, rat bite fever and those caused by *Listeria monocytogenes, Pasteurella multocida.*

For trench mouth or acute necrotizing ulcerative gingivitis (ANUG) which is a mixed infection caused by spirochetes and fusobacteria, PnG (i.m.)/penicillin V (oral) or amoxicillin are generally combined with metronidazole.

9 *Prophylactic uses*

(a) Rheumatic fever: Low concentrations of penicillin prevent colonization by streptococci that are indirectly responsible for rheumatic fever. Benzathine penicillin 1.2 MU every 4 weeks till 18 years of age or 5 years after an attack, whichever is more.

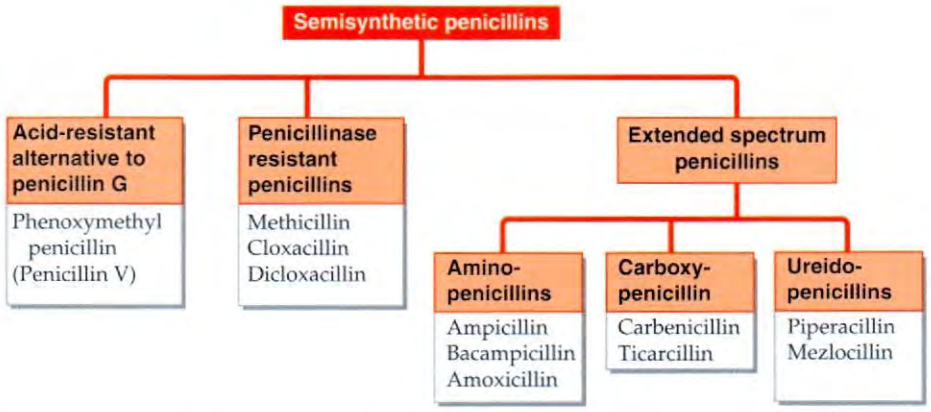
(b) Bacterial endocarditis: Dental extractions, endoscopies, catheterization, etc. cause bacteremia which in patients with valvular defects can cause endocarditis. PnG can afford protection, but amoxicillin is preferred now.

SEMISYNTHETIC PENICILLINS

Semisynthetic penicillins are produced by chemically combining specific side chains (in place of benzyl side chain of PnG) or by incorporating specific precursors in the mould cultures. Thus, procaine penicillin and benzathine penicillin are salts of PnG and *not* semisynthetic penicillins. The aim of producing semisynthetic penicillins has been to overcome the shortcomings of PnG, which are:

1. Poor oral efficacy.
2. Susceptibility to penicillinase.
3. Narrow spectrum of activity.
4. Hypersensitivity reactions (this has not been overcome in any preparation).

In addition, some β-lactamase inhibitors have been developed which themselves are not



antibacterial, but augment the activity of penicillins against β-lactamase producing organisms.

ACID-RESISTANT ALTERNATIVE TO PENICILLIN-G

Phenoxymethyl penicillin (Penicillin V)

It differs from PnG only in that it is acid stable. Oral absorption is better; peak blood level is reached in 1 hour and plasma t½ is 30–60 min.

The antibacterial spectrum of penicillin V is identical to PnG, but it is about 1/5 as active against *Neisseria*, other gram negative bacteria and anaerobes. It cannot be depended upon for more serious infections and is occasionally used for streptococcal pharyngitis, sinusitis, otitis media, prophylaxis of rheumatic fever (when an oral drug has to be selected), less serious pneumococcal infections and trench mouth.

Dose: 250–500 mg, infants 60 mg, children 125–250 mg; given 6 hourly, (250 mg = 4 lac U). CRYSTAPEN-V, 125, 250 mg tab, 125 mg/5 ml dry syr—for reconstitution, PENIVORAL 65, 130 mg tab.

PENICILLINASE-RESISTANT PENICILLINS

These congeners have side chains that protect the β-lactam ring from attack by staphylococcal penicillinase. However, this also partially protects the bacteria from the β-lactam ring: nonpenicillinase producing organisms are less sensitive to these drugs than to PnG. Their only indication is infections caused by penicillinase producing *Staphylococci*, which are not ~~methicillin resistant~~ as well. Utility of these penicillins has markedly declined, because 'methicillin resistant *Staph. aureus*' (MRSA) have become universally prevalent. These drugs are not resistant to β-lactamases produced by gram negative bacteria.

Methicillin It is staphylococcal penicillinase resistant but not acid resistant. Because MRSA have emerged in many areas, and because methicillin caused haematuria, albuminuria and interstitial nephritis, it is no longer used.

Cloxacillin/Dicloxacillin It has an isoxazolyl side chain and is highly penicillinase as well as acid resistant. Activity against PnG sensitive organisms is weaker, and it should not be used as a substitute of PnG for any other infection. Activity against penicillinase producing *Staph*, is greater than that of methicillin, but not against ~~MRS~~A.

Cloxacillin is incompletely but dependably absorbed from oral route, especially if taken in empty stomach. It is > 90% plasma protein bound. Elimination occurs primarily by kidney, also partly by liver. Plasma t½ is about 1 hour.

Dose: 0.25–0.5 g orally every 6 hours; for severe infections 0.25–1 g may be injected i.m. or i.v.—higher blood levels are produced.

KLOX, BIOCLOX, 0.25, 0.5 g cap; 0.25, 0.5 g/vial inj., CLOPEN 0.25, 0.5 g cap.

Oxacillin, Flucloxacillin (Floxacillin) are other isoxazolyl penicillins, similar to cloxacillin, but not marketed in India. Nafcillin is another parenteral penicillinase resistant penicillin.

EXTENDED SPECTRUM PENICILLINS

These semisynthetic penicillins are in addition active against a variety of gram-negative bacilli because of improved ability to penetrate through their cell membrane. However, they are susceptible to several β-lactamases. Semisynthetic penicillins are grouped according to their spectrum of activity.

1. Aminopenicillins

This group includes ampicillin, its prodrug bacampicillin, and amoxicillin.

Ampicillin It is active against all organisms sensitive to PnG. In addition, non-β-lactamase producing strains of many gram-negative bacilli, e.g. *H. influenzae, E. coli, Proteus, Salmonella, Shigella* and *Helicobacter pylori* are inhibited. However, due to widespread use, many of these have developed resistance; usefulness of this antibiotic has decreased considerably.

Ampicillin is more active than PnG for *Strep. viridans,* enterococci and *Listeria;* equally active for pneumococci, gonococci and meningococci, but penicillin-resistant strains are resistant to ampicillin as well. Ampicillin is less active against other gram-positive cocci. Penicillinase producing *Staph.* are not affected, as are other gram-negative bacilli, such as *Pseudomonas, Klebsiella*, indole positive *Proteus* and anaerobes like *Bacteroides fragilis.*

Pharmacokinetics Ampicillin is not degraded by gastric acid; oral absorption is incomplete but adequate. Food interferes with absorption. It is partly excreted in bile and reabsorbed—enterohepatic circulation occurs. However, primary channel of excretion is kidney, but tubular secretion is slower than for PnG; plasma t½ is 1 hr.

Dose: 0.5–2 g oral/i.m./i.v. depending on severity of infection, every 6 hours; children 50–100 mg/kg/day.
AMPILIN, ROSCILLIN, BIOCILIN 250, 500 mg cap; 125, 250 mg/5 ml dry syr; 100 mg/ml pediatric drops; 250, 500 mg and 1.0 g per vial inj.

Uses

1. Urinary tract infections (UTI): Ampicillin has become unreliable for empirical therapy of UTI, due to development of resistance by many urinary pathogens, but may be used if the strain is sensitive. Fluoroquinolones are now more commonly employed for empirical therapy.

2. Respiratory tract infections: including bronchitis, sinusitis, otitis media, etc. are usually treated with ampicillin, but higher doses (50–80 mg/kg/day) are generally required now.

3. Meningitis: Ampicillin has been a first line drug, but several meningococci, pneumococci and *H. influenzae* are now resistant. For empirical therapy, it may be combined with a third generation cephalosporin.

4. Gonorrhoea: It is one of the first line drugs for oral treatment of nonpenicillinase producing gonococcal infections. A single dose of 3.5 g ampicillin + 1 g probenecid (ROSCIND, DYNACIL-PRB cap) is adequate and convenient for urethritis.

5. Typhoid fever: Due to emergence of resistance, it is now rarely used.

6. Bacillary dysentery: Due to *Shigella* may respond to ampicillin, but many strains are now resistant; quinolones are preferred.

7. Cholecystitis: Ampicillin is a preferred drug because high concentrations are attained in bile.

8. Subacute bacterial endocarditis: Ampicillin 2 g i.v. 6 hourly is used in place of PnG. Concurrent gentamicin is advocated.

9. *H. pylori:* Though amoxicillin is mostly used for eradication of *H. pylori* from stomach and duodenum, ampicillin is also active.

10. Septicaemias and mixed infections: Injected ampicillin may be combined with gentamicin or one of the third generation cephalosporins.

11. *Acute necrotizing ulcerative gingivitis (ANUG):* Ampicillin/amoxicillin are generally preferred over penicillin V for combining with metronidazole to treat this condition.

Adverse effects Diarrhoea is frequent after oral administration. Ampicillin is incompletely absorbed—the unabsorbed drug irritates the lower intestines as well as causes marked alteration of bacterial flora.

It produces a high incidence (up to 10%) of rashes, especially in patients with AIDS, EB virus infections or lymphatic leukaemia. Concurrent administration of allopurinol also increases the incidence of rashes. Sometimes the rashes may not be allergic, but toxic in nature.

Patients with a history of immediate type of hypersensitivity to PnG should not be given ampicillin as well.

Interactions Hydrocortisone inactivates ampicillin if mixed in the i.v. solution.

By inhibiting colonic flora, it may interfere with deconjugation and enterohepatic cycling of oral contraceptives resulting in failure of oral contraception.

Probenecid retards renal excretion of ampicillin.

Bacampicillin It is an ester prodrug of ampicillin which is nearly completely absorbed from the g.i.t.; and is largely hydrolysed during absorption. Thus, higher plasma levels are attained. Incidence of diarrhoea is claimed to be lower, but it is seldom used now.

Dose: 400–800 mg BD; PENGLOBE 200, 400 mg tab.

Note: A fixed dose combination of ampicillin + cloxacillin (AMPILOX and others) or amoxicillin + cloxacillin (NOVACLOX and others) containing 250 mg or 500 mg of each per cap or per vial for injection is vigorously promoted for postoperative, skin and soft tissue, respiratory, urinary and other infections. This combination is not synergistic since cloxacillin is not active against gram-negative bacteria, while ampicillin is not active against staphylococci. Since mixed staphylococcal and gram-negative bacillary infections are uncommon, for any given infection, one of the components is useless but adds to the cost and adverse effects. Since the amount of the drug which is actually going to act in any individual patient is halved (when the combination is used), efficacy is reduced and chances of selecting resistant strains are increased. Due to prevalence of MRSA, cloxacillin, in any case, has limited utility now. Recently, this combination has been banned in India.

Amoxicillin It is a close congener of ampicillin (but not a prodrug); similar to it in all respects except:

- Oral absorption is better; food does not interfere with absorption; higher and more sustained blood levels are produced.
- Amoxicillin given 3 times a day is equivalent to ampicillin given 4 times a day.
- Incidence of diarrhoea is lower.
- It is less active against *Shigella* and *H. influenzae*.
- It is more active against relatively penicillin-resistant *Strep. pneumoniae*.

Many physicians now prefer amoxicillin over ampicillin for bronchitis, urinary infections, SABE and gonorrhoea. It is a component of most triple drug *H. pylori* eradication regimens (*see* p. 705-06).

Dose: 0.25–1 g TDS oral/i.m.; or slow i.v. injection, child 25–75 mg/kg/day. AMOXYLIN, NOVAMOX, SYNAMOX 250, 500 mg cap, 125 mg/5 ml dry syr. AMOXIL, MOX 250, 500 mg caps; 125 mg/5 ml dry syr; 250, 500 mg/vial inj. MOXYLONG: Amoxicillin 250 mg + probenecid 500 mg tab (also 500 mg + 500 mg DS tab).

2. Carboxypenicillins

Carbenicillin The special feature of this penicillin congener is its activity against *Pseudomonas aeruginosa* and indole positive *Proteus* which are not inhibited by PnG or aminopenicillins. It is less active against *Salmonella, E. coli* and *Enterobacter*, while *Klebsiella* and gram-positive cocci are unaffected by it. In many areas *Pseudomonas* strains less sensitive to carbenicillin have become prevalent, and utility of this pencillin has declined.

Carbenicillin is not penicillinase-resistant. It is inactive orally and is excreted rapidly in urine ($t_{½}$ 1 hr). It is used as sodium salt in a dose of 1–2 g i.m. or 1–5 g i.v. every 4–6 hours. At the higher doses, enough Na may be administered to cause fluid retention and CHF in patients with borderline renal or cardiac function.

High doses have also caused bleeding by interfering with platelet function. This appears to result from perturbation of agonist receptors on platelet surface.

CARBELIN 1 g, 5 g, per vial inj.

The indications for carbenicillin are—serious infections caused by *Pseudomonas* or *Proteus*, e.g. burns, urinary tract infection, septicaemia, but more active and better tolerated ticarcillin or piperacillin are now mostly used.

Ticarcillin It is the second carboxypenicillin, similar in properties to carbenicillin, but is more active and produces fewer adverse effects. Ticarcillin has therefore mostly displaced carbenicillin for treating *Pseudomonas* and *Proteus* infections. Its combination with clavulanic acid extends efficacy to cover β-lactamase producing strains. For the treatment of serious *Pseudomonas* infections it is often used along with gentamicin.

Dose: 3 g i.m./i.v. 6 hourly.
TIMENTIN inj: Ticarcillin disod. + clavulanate pot. 3.1 g/vial inj; dry powder for reconstitution before injection.

3. Ureidopenicillins

Piperacillin This antipseudomonal penicillin is about 8 times more active than carbenicillin. In addition, it has good activity against *Klebsiella*, many Enterobacteriaceae and some *Bacteroides*. Piperacillin is frequently employed for treating serious gram-negative infections in neutropenic/immunocompromised or burn patients. Elimination t½ is 1 hr. It is combined with tazobactam to cover β-lactamase producing strains (*see* p. 775). Concurrent use of gentamicin or tobramycin is advised.
Dose: 100–150 mg/kg/day in 3 divided doses (max 16 g/day) i.m. or i.v. The i.v. route is preferred when > 2 g is to be injected.
PIPRAPEN 1 g, 2 g vials; PIPRACIL 2 g, 4 g vials for inj; contains 2 mEq Na^+ per g.

Mezlocillin Another antipseudomonas penicillin, not marketed in USA and in India.

BETA-LACTAMASE INHIBITORS

β-lactamases are a family of enzymes produced by many gram-positive and gram-negative bacteria that inactivate β-lactam antibiotics by opening the β-lactam ring. Different β-lactamases differ in their substrate affinities. Three inhibitors of this enzyme *clavulanic acid*, *sulbactam* and *tazobactam* are available for clinical use only in combination with specific penicillins or cephalosporins.

Clavulanic acid Obtained from *Streptomyces clavuligerus*, it has a β-lactam ring but no/weak antibacterial activity of its own. It inhibits a wide variety (class II to class V) of β-lactamases (but not class I cephalosporinase) produced by both gram-positive and gram-negative bacteria.

Clavulanic acid is a 'progressive' inhibitor, because binding with β-lactamase is reversible initially, but becomes covalent later—inhibition increases with time. Called a 'suicide' inhibitor, it gets inactivated after binding to the enzyme. Clavulanate permeates the outer layers of the cell wall of gram-negative bacteria and inhibits the periplasmically located β-lactamase.

Pharmacokinetics Clavulanic acid has rapid oral absorption and a bioavailability of 60%. It can also be injected. The elimination t½ of 1 hr and tissue distribution matches amoxicillin, with which it is combined (called coamoxiclav). However, clavulanate is eliminated mainly by glomerular filtration and its excretion is not affected by probenecid. Moreover, it is largely hydrolysed and decarboxylated before excretion, while amoxicillin is primarily excreted unchanged by tubular secretion.

Uses Addition of clavulanic acid re-establishes the activity of amoxicillin against β-lactamase producing resistant *Staph. aureus* (but not MRSA that have altered PBPs), *H. influenzae*, *N. gonorrhoeae*, *E. coli*, *Proteus*, *Klebsiella*, *Salmonella* and *Shigella*. Though *Bact. fragilis* and *Branhamella catarrhalis* are not responsive to amoxicillin alone, they are inhibited by the combination. Clavulanic acid does not potentiate the action of amoxicillin against strains that are already sensitive to it. Coamoxiclav is indicated for empirical therapy of:

- Skin and soft tissue infections, intra-abdominal and gynaecological sepsis, urinary, biliary and respiratory tract infections: especially for hospital acquired infections.
- Gonorrhoea (including PPNG) single dose amoxicillin 3 g + clavulanic acid 0.5 g + probenecid 1 g is curative.

AUGMENTIN, ENHANCIN, AMONATE: Amoxicillin 250 mg + clavulanic acid 125 mg tab; also 500 mg + 125 mg tab; 125 mg + 31.5 mg per 5 ml dry syr; CLAVAM 250 + 125 mg tab, 500 + 125 mg tab, 875 + 125 mg tab, 125 mg + 32 mg per 5 ml dry syr, 1–2 tab TDS.
Also AUGMENTIN, CLAVAM inj.: Amoxicillin 1 g + clavulanic acid 0.2 g vial and 0.5 g + 0.1 g vial; inject 1 vial deep i.m. or i.v. 6–8 hourly for severe infections.
It is more expensive than amoxicillin alone.

Adverse effects are the same as for amoxicillin alone; but g.i. tolerance is poorer—especially in children. Other adverse effects are *Candida* stomatitis/vaginitis and rashes. Some cases of hepatic injury have been reported with the combination.

ADV. of FDC:
- can widen spectrum
- dose of indiv. drug ↓
- Resistance ↓

Sulbactam It is a semisynthetic β-lactamase inhibitor, related chemically as well as in activity to clavulanic acid. It is also a progressive inhibitor, highly active against class II to V but poorly active against class I β-lactamase. On weight basis, it is 2–3 times less potent than clavulanic acid for most types of the enzyme, but the same level of inhibition can be obtained at the higher concentrations achieved clinically. Sulbactam does not induce chromosomal β-lactamases, while clavulanic acid can induce some of them.

Oral absorption of sulbactam is inconsistent. Therefore, it is preferably given parenterally. It has been combined with ampicillin for use against β-lactamase producing resistant strains. Absorption of its complex salt with ampicillin—*sultamicillin tosylate* is better, which is given orally. Indications are:

- PPNG gonorrhoea; sulbactam *per se* also inhibits *N. gonorrhoeae.*
- Mixed aerobic-anaerobic infections, intra-abdominal, gynaecological, surgical and skin/ soft tissue infections, especially those acquired in the hospital.

SULBACIN, AMPITUM: Ampicillin 1 g + sulbactam 0.5 g per vial inj; 1–2 vial deep i.m. or i.v. injection 6–8 hourly.
Sultamicillin tosylate: BETAMPORAL, SULBACIN 375 mg tab.
Sulbactam has been combined with cefoperazone and ceftriaxone also (*see* p. 778).

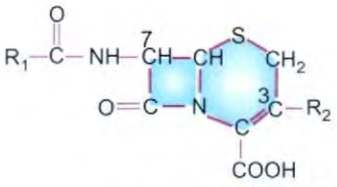
Pain at site of injection, thrombophlebitis of injected vein, rash and diarrhoea are the main adverse effects.

Tazobactam Another β-lactamase inhibitor similar to sulbactam, whose pharmacokinetics matches with piperacillin. Tazobactam is combined with piperacillin for use in severe infections like peritonitis, pelvic/urinary/ respiratory infections caused by β-lactamase producing bacilli. However, the combination is not active against piperacillin-resistant *Pseudomonas,* because tazobactam (like clavulanic acid and sulbactam) does not inhibit inducible chromosomal β-lactamase produced by *Pseudomonas* and other Enterobacteriaceae. It is also of no help against *Pseudomonas* that develop resistance by losing permeability to piperacillin.

Dose: 0.5 g combined with piperacillin 4 g injected i.v. over 30 min 8 hourly.
PYBACTUM, TAZACT, TAZOBID, TAZAR 4 g + 0.5 g vial for inj., also 2.0 g + 250 mg and 1 g + 125 mg vials.
Tazobactam has been combined with ceftriaxone as well (*see* p. 778).

CEPHALOSPORINS

These are a group of semisynthetic antibiotics derived from 'cephalosporin-C' obtained from a fungus *Cephalosporium.* They are chemically related to penicillins; the nucleus consists of a β-lactam ring fused to a dihydrothiazine ring, (7-aminocephalosporanic acid). By addition of different side chains at position 7 of β-lactam ring (altering spectrum of activity) and at position 3 of dihydrothiazine ring (affecting pharmacokinetics), a large number of semisynthetic compounds have been produced. Cephalosporins have been conventionally



CEPHALOSPORIN

divided into 4 generations, and now some lately added members have been designated '5th generation'. This division has a chronological sequence of development, but more importantly, takes into consideration the overall antibacterial spectrum as well as potency.

All cephalosporins are bactericidal and have the same mechanism of action as penicillin, i.e. inhibition of bacterial cell wall synthesis. However, they bind to different PBPs than those which bind penicillins. This may explain differences in spectrum, potency and lack of cross resistance.

Acquired resistance to cephalosporins could have the same basis as for penicillins, i.e.:

First generation cephalosporins	
Parenteral	*Oral*
Cefazolin	Cephalexin
	Cefadroxil
Second generation cephalosporins	
Parenteral	*Oral*
Cefuroxime	Cefaclor
Cefoxitin*	Cefuroxime axetil
	Cefprozil
Third generation cephalosporins	
Parenteral	*Oral*
Cefotaxime	Cefixime
Ceftizoxime	Cefpodoxime proxetil
Ceftriaxone	Cefdinir
Ceftazidime	Ceftibuten
Cefoperazone	Ceftamet pivoxil
Fourth generation cephalosporins	
Parenteral	
Cefepime	
Cefpirome	
Fifth generation cephalosporins	
Parenteral	
Ceftaroline fosamil	
Ceftobiprole medocaril	

uses bile for excretion

*Not available in India

(a) alteration in target proteins (PBPs) reducing affinity for the antibiotic.
(b) impermeability to the antibiotic or its efflux so that it does not reach its site of action.
(c) elaboration of β-lactamases which destroy specific cephalosporins (cephalosporinases); the most common mechanism.

Though the incidence is low, resistance has been developed by some organisms, even against the third generation compounds. Individual cephalosporins differ in their:

- Antibacterial spectrum and relative potency against specific organisms.
- Susceptibility to β-lactamases elaborated by different organisms.
- Pharmacokinetic properties—many have to be injected, some are oral; majority are not metabolized, and are excreted rapidly by the kidney; have short t½s, probenecid inhibits their tubular secretion.

FIRST GENERATION CEPHALOSPORINS

G +ve cocci

These were developed in the 1960s, have high activity against gram-positive but weaker against gram-negative bacteria.

Cefazolin It is the prototype first generation cephalosporin that is active against most PnG sensitive organisms, i.e. *Streptococci (pyogenes* as well as *viridans)*, gonococci, meningococci, *C. diphtheriae, H. influenzae,* clostridia and *Actinomyces.* Activity against *Klebsiella, Moraxella catarrhalis* and *E. coli* is relatively high, but it is quite susceptible to staphylococcal β-lactamase. It can be given i.m. (mildly painful) as well as i.v. and has a longer t½ (2 hours) due to slower tubular secretion. Cefazolin attains higher concentration in plasma and in bile. It is the preferred parenteral first generation cephalosporin, especially for surgical prophylaxis.

Dose: 0.5 g 8 hourly (mild cases), 1 g 6 hourly (severe cases), children 25–50 mg/kg/day i.m. or i.v.; surgical prophylaxis 1.0 g 1/2 hour before surgery.

REFLIN, ALCIZON, ORIZOLIN 0.25 g, 0.5 g, 1 g per vial inj.

Cephalexin It is the most commonly used orally effective first generation cephalosporin, similar in spectrum to cefazolin, but less active against penicillinase producing staphylococci and *H. influenzae*. Plasma protein binding is low; it attains high concentration in bile and is excreted unchanged in urine; t½ ~60 min.

Dose: 0.25–1 g 6–8 hourly (children 25–100 mg/kg/day).

CEPHACILLIN 250, 500 mg cap; SPORIDEX, ALCEPHIN, CEPHAXIN 250, 500 mg cap, 125 mg/5 ml dry syr., 100 mg/ml pediatric drops.

ALCEPHIN-LA: Cephalexin + probenecid (250 + 250 mg and 500 + 500 mg) tabs.

Cefadroxil A close congener of cephalexin; has good tissue penetration—exerts more sustained action at the site of infection, because of which it can be given 12 hourly despite a t½ of 1 hr. It is excreted unchanged in urine; the dose needs to be reduced only if creatinine clearance is < 50 ml/min. The antibacterial activity of cefadroxil and indications are similar to those of cephalexin.

Dose: 0.5–1 g BD. DROXYL 0.5, 1 g tab, 250 mg/5 ml syr; CEFADROX 0.5 g cap, 125 mg/5 ml syr and 250 mg kid tab; KEFLOXIN 0.5 g cap, 0.25 g Distab, 125 mg/5 ml susp.

SECOND GENERATION CEPHALOSPORINS

These were developed subsequent to the first generation compounds and are more active against gram-negative organisms with wider coverage, including some strains resistant to first generation compounds. Few members, *i.e.* cefoxitin are active against anaerobes as well, but none inhibits *P. aeruginosa*. They are weaker than the first generation compounds against gram positive bacteria. Their utility has declined in favour of the 3rd generation agents.

Cefuroxime It is resistant to gram-negative β-lactamases, and has high activity against organisms producing these enzymes including PPNG and ampicillin-resistant *H. influenzae*, while retaining significant activity on gram-positive cocci and certain anaerobes, but not *B. fragilis*. Cefuroxime can be injected i.m., and attains relatively higher CSF levels, but has been superseded by 3rd generation cephalosporins in the treatment of meningitis. It can be employed for single dose i.m. therapy of gonorrhoea due to PPNG.

CEFOGEN, SUPACEF, FUROXIL 250 mg and 750 mg/vial inj; 0.75–1.5 g i.m. or i.v. 8 hourly, children 30–100 mg/kg/day. For gonorrhoea 1.5 g divided at 2 sites i.m. inj + probenecid 1.0 g oral single dose.

Cefuroxime axetil This ester of cefuroxime is effective orally, despite incomplete oral absorption. The activity depends on *in vivo* hydrolysis and release of cefuroxime.

Dose: 250–500 mg BD, children half dose; CEFTUM, SPIZEF 125, 250, 500 mg captab and 125 mg/5 ml susp.

Cefaclor It retains significant activity by the oral route and is more active than the first generation compounds against *H. influenzae*, *E. coli*, *Pr. mirabilis* and some anaerobes, but highly susceptible to β-lactamases which may limit utility.

Dose: 0.25–1.0 g 8 hourly

KEFLOR, VERCEF, DISTACLOR 250 mg cap, 125 and 250 mg distab, 125 mg/5 ml dry syr, 50 mg/ml ped. drops.

Cefprozil This 2nd generation cephalosporin has good oral absorption (>90%) with augmented activity against *Strep. pyogenes*, *Strep. pneumoniae*, *Staph. aureus* (but not MRSA), *H. influenzae*, *Moraxella* and *Klebsiella*. It is excreted by the kidney, with a t½ of 1.3 hours. The primary indications of cefprozil are bronchitis, ENT and skin infections.

Dose: 250–500 mg BD, (child 20 mg/kg/day).

ORPROZIL, ZEMETRIL 250, 500 mg tab; REFZIL 250, 500 mg tab., 125 mg/5 ml and 250 mg/5 ml syr.

THIRD GENERATION CEPHALOSPORINS

These compounds introduced in the 1980s have highly augmented activity against gram-negative Enterobacteriaceae; and few members inhibit *Pseudomonas* as well. All are highly resistant to β-lactamases from gram-negative bacteria. However, they are less active on gram-positive cocci and anaerobes. Some members have good blood-brain barrier penetrability and are useful in meningitis.

Cefotaxime It is the prototype of the third generation cephalosporins; exerts potent action on aerobic gram-negative as well as some gram-positive bacteria, but is not active on anaerobes (particularly *Bact. fragilis*), *Staph. aureus* and *Ps. aeruginosa*. Prominent indications are meningitis caused by gram-negative bacilli (attains relatively high CSF levels), life-threatening resistant/hospital-acquired infections, septicaemias and infections in immunocompromised patients. It is an alternative to ceftriaxone for typhoid fever, and can be utilized for single dose therapy (1 g i.m. + 1 g probenecid oral) of PPNG urethritis, but is not dependable for *Pseudomonas* infections.

Cefotaxime is deacetylated in the body; the metabolite exerts weaker but synergistic action with the parent drug. The plasma t½ of cefotaxime is 1 hr, but is longer for the deacetylated metabolite—permitting 12 hourly doses in many situations.

Dose: 1–2 g i.m./i.v. 6–12 hourly, children 50–100 mg/kg/day.

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OMNATAX, ORITAXIM, CLAFORAN 0.25, 0.5, 1.0 g per vial inj.

Ceftizoxime It is similar in antibacterial activity and indications to cefotaxime, but inhibits *B. fragilis* also. It is not metabolized—excreted by the kidney at a slower rate; t½ 1.5–2 hr.

Dose: 0.5–2.0 g i.m./i.v. 8 or 12 hourly.

CEFIZOX, EPOCELIN 0.5 and 1 g per vial inj.

Ceftriaxone The distinguishing feature of this cephalosporin is its longer duration of action (t½ 8 hr), permitting once, or at the most twice daily dosing. Penetration into CSF is good and elimination occurs equally in urine and bile.

Ceftriaxone has shown high efficacy in a wide range of serious infections including bacterial meningitis (especially in children), multiresistant typhoid fever, complicated urinary tract infections, abdominal sepsis and septicaemias. A single 1.0 g i.m. dose is curative in gonorrhoea (including PPNG) and in chancroid. For syphilis, it is an alternative drug, but 1.0 g i.m. needs to be given for 7 days (in early) and for 15 days (in late syphilis).

Hypoprothrombinaemia and bleeding are the specific adverse effects. Haemolysis is reported.

OFRAMAX, MONOCEF, MONOTAX 0.25, 0.5, 1.0 g per vial inj.

For skin/soft tissue/urinary infections: 1–2 g i.v. or i.m./day.

Meningitis: 4 g followed by 2 g i.v. (children 75–100 mg/kg) once daily for 7–10 days.

Typhoid: 4 g i.v. daily × 2 days followed by 2 g/day (children 75 mg/kg) till 2 days after fever subsides.

To overcome resistance, it has been combined with sulbactam or tazobactam.

CEFTICHEK, SUPRAXONE ceftriaxone + sulbactam 250 mg + 125 mg and 1.0 g + 0.5 g vial.

MONTAZ, EXTACEF-TAZO, FINECEF-T ceftriaxone 1 g + tazobactam 125 mg vial.

Ceftazidime The most prominent feature of this third generation cephalosporin is its high activity against *Pseudomonas aeruginosa*, and the specific indications are—febrile neutropenic patients with haematological malignancies, burn, etc. Its activity against Enterobacteriaceae is similar to that of cefotaxime, but it is less active on *Staph. aureus*, other gram positive cocci and anaerobes like *Bact. fragilis*. The plasma t½ of ceftazidime is 1.5–1.8 hr.

Neutropenia, thrombocytopenia, rise in plasma transaminases and blood urea have been reported.

Dose: 0.5–2 g i.m. or i.v. every 8 hr, children 30 mg/kg/day. Resistant typhoid 30 mg/kg/day.

FORTUM, CEFAZID, ORZID 0.25, 0.5 and 1 g per vial inj.

COMBITAZ: Ceftazidime 1 g + tazobactam 125 mg/vial inj.

Cefoperazone Like ceftazidime, it differs from other third generation compounds in having stronger activity on *Pseudomonas* and weaker activity on other organisms. Cefoperazone is good for *S. typhi* and *B. fragilis* also, but more susceptible to β-lactamases. The indications are—severe urinary, biliary, respiratory, skin-soft tissue infections, typhoid and septicaemias. It is primarily excreted in bile; t½ is 2 hr. It has hypoprothrombinaemic action but does not affect platelet function. A disulfiram-like reaction with alcohol has been reported.

Dose: 1–3 g i.m./i.v. 8–12 hourly.

MAGNAMYCIN 0.25 g, 1, 2 g inj; CEFOMYCIN, NEGAPLUS 1 g inj.

It has been combined with sulbactam.

CEFOBETA, KEFBACTUM Cefoperazone 500 mg + sulbactam 500 mg vial, CEFACTUM 1 g + 1 g vial.

Cefixime It is an orally active third generation cephalosporin highly active against Enterobacteriaceae, *H. influenzae, Strep. pyogenes,* and is resistant to many β-lactamases. However, it is not active on *Staph. aureus*, most pneumococci and *Pseudomonas*. Cefixime is longer acting (t½ 3 hr) and has been used in a dose of 200–400 mg BD for respiratory, urinary and biliary infections. Stool changes and diarrhoea are the most prominent side effects.

TOPCEF, ORFIX 100, 200 mg tab/cap, CEFSPAN 100 mg cap, 100 mg/5 ml syr, TAXIM-O 100, 200 mg tab, 50 mg/5 ml dry syr.

Fixed dose combination of cefixime with azithromycin is banned in India.

Cefpodoxime proxetil It is the orally active ester prodrug of 3rd generation cephalosporin cefpodoxime. In addition to being highly active against Enterobacteriaceae and streptococci, it inhibits *Staph. aureus*. It is used mainly for respiratory, urinary, skin and soft tissue infections.

Dose: 200 mg BD (max 800 mg/day)

CEFOPROX, CEPODEM, DOXCEF 100, 200 mg tab, 50 mg/5 ml and 100 mg/5 ml dry syr.

Cefdinir This orally active 3rd generation cephalosporin has good activity against many β-lactamase producing organisms. Most respiratory pathogens including gram-positive cocci are susceptible. Indications of cefdinir are pneumonia, acute exacerbations of chronic bronchitis, ENT and skin infections.
Dose: 300 mg BD
SEFDIN, ADCEF 300 mg cap, 125 mg/5 ml susp.

Ceftibuten Another oral 3rd generation cephalosporin, active against gram-positive and few gram-negative bacteria, but not *Staph. aureus*. It is stable to β-lactamases, and is indicated in respiratory and ENT infections; t½ 2–3 hours.
Dose: 200 mg BD or 400 mg OD.
PROCADAX 400 mg cap, 90 mg/5 ml powder for oral suspension.

Ceftamet pivoxil This ester prodrug of ceftamet, a 3rd generation cephalosporin has high activity against gram-negative bacteria, especially Enterobacteriaceae and *N. gonorrhoea*. Ceftamet pivoxil is indicated in respiratory, skin and soft tissue infections, etc.
Dose: 500 mg BD–TDS.
ALTAMET 250 mg tab; CEPIME-O 500 mg tab.

FOURTH GENERATION CEPHALOSPORINS

The distinctive feature of this newer subgroup of cephalosporins is non-susceptibility to inducible chromosomal β lactamases produced by some resistant bacteria alongwith high potency against Enterobacteriaceae and spectrum of activity resembling the 3rd generation compounds.

Cefepime Developed in 1990s, this 4th generation cephalosporin has antibacterial spectrum similar to that of 3rd generation compounds, but is highly resistant to β-lactamases, hence active against many bacteria resistant to the earlier drugs. *Ps. aeruginosa, Strep. pneumoniae, H. influenzae* and *Staph. aureus* are also inhibited but not ~~MRSA~~. Due to high potency and extended spectrum, it is effective in many serious infections like hospital-acquired pneumonia, febrile neutropenia, bacteraemia, septicaemia. Higher concentrations are attained in the CSF, and it is excreted by the kidney with a t½ of 2 hours.
Dose: 1–2 g i.v. 8–12 hourly. Child with febrile neutropenia 50 mg/kg i.v. 8 hourly.
KEFAGE, CEFICAD, CEPIME 0.5, 1.0 g inj.

Cefpirome This 4th generation cephalosporin is indicated for the treatment of serious and resistant hospital-acquired infections including septicaemias, lower respiratory tract infections, etc. Its zwitterion character permits better penetration through porin channels of gram-negative bacteria. Cefpirome is resistant to many β-lactamases; inhibits type 1 β-lactamase producing Enterobacteriaceae and it is more potent against gram-positive and some gram-negative bacteria than the 3rd generation compounds.
Dose: 1–2 g i.m./i.v. 12 hourly;
CEFROM, CEFORTH 1 g inj; BACIROM, CEFOR 0.25, 0.5, 1.0 g inj.

FIFTH GENERATION CEPHALOSPORINS

The recently developed members of this new group are distinguished by their ability to kill MRSA and some other bacteria which developed penicillin resistance by producing altered PBPs. Thus, these antibiotics are effective in many resistant and hospital acquired infections. They are also designated 'cephalosporins with anti-MRSA activity'.

Ceftaroline fosamil It is a prodrug which after i.v. infusion is rapidly converted by phosphatases to the active *ceftaroline* that is cidal to many gram +ive and gram –ive bacteria including MRSA, penicillin resistant *Strep. pneumoniae* and *Enterococcus faecalis*, etc. Ceftaroline owes its activity to its ability to bind altered PBPs expressed in these bacteria. It has high affinity for PBP2a (in MRSA), for PBP2b and PBP2x (in penicillin resistant *Strep. pneumoniae*). It thus interferes with transpeptidation step of bacterial cell wall synthesis and exerts lethal effect. However, it is susceptible to extended-spectrum and some other β-lactamases so that organisms expressing these enzymes are nonresponsive.

Ceftaroline fosamil was approved by CDSCO India in 2016, and is being used for

the treatment of complicated skin and soft tissue infections as well as for community acquired pneumonia (CAP), particularly those caused by MRSA, resistant *Strep. pneumoniae*, etc. Ceftaroline is eliminated mainly by the kidney with a t½ of 2.6 hours. Adverse effects noted are headache, dizziness, itching, rashes, fever, diarrhoea, and irritation of the injected vein.

Dose: 600 mg infused i.v. over 60 min every 12 hours for 5–14 days; dose to be adjusted if CLcr is < 50 ml/min.

ZINFORO, TEFLARO 600 mg/vial inj.

Ceftobiprole medocaril This is another 5th generation cephalosporin active against MRSA and several gram +ive and gram –ive bacteria associated with hospital acquired pneumonia (HAP) as well as with CAP. Ceftobiprole medocaril is also a prodrug, which is rapidly converted to the active ceftobiprole by type A esterases in humans. It unergoes minimal metabolism and is excreted unchanged by glomerular filtration into urine with a terminal t½ of 3 hours. No accumulatoin occurs on 8 hourly infusion.

Ceftobiprole binds to PBP2a in MRSA, to PBP2b and PBP2x in penicillin resistant *Strep. pneumoniae*, and to PBP5 in resistant *Enterococcus faecalis* to exert bactericidal activity. It is approved in EU and in Canada as monotherapy of HAP, excluding ventilator associated pneumonia (VAP), and severe CAP. It is also being tried for complicated skin and soft tissue infections. Adverse effects are nausea, diarrhoea, infusion site reactions, rise in hepatic transaminases and hyponatraemia. Withdrawal was needed in 10% cases.

Dose: 500 mg infused i.v. over 2 hours, every 8 hours.

Adverse effects

Cephalosporins are generally well tolerated, but are more toxic than penicillin.

1. *Pain* after i.m. injection occurs with many cephalosporins, but some can be injected i.m., while others are injected only i.v. (*see* individual compounds). Thrombophlebitis of injected vein can occur.
2. *Diarrhoea* due to alteration of gut ecology or irritative effect is more common with orally administered compounds like cephalexin, cefixime and parenteral cefoperazone, which is largely excreted in bile.
3. *Hypersensitivity reactions* are the most important adverse effects of cephalosporins. Manifestations are similar to those with penicillin, but incidence is lower. Rashes are the most frequent but anaphylaxis, angioedema, asthma and urticaria have also occurred. About 10% patients allergic to penicillin show cross reactivity with cephalosporins. Those with a history of immediate type of reactions to penicillin should better not be given a cephalosporin. Skin tests for sensitivity to cephalosporins are unreliable.

A positive Coombs' test occurs in many patients, but haemolysis is rare.

4. *Nephrotoxicity* Some cephalosporins have low-grade nephrotoxicity which may be accentuated by preexisting renal disease, concurrent administration of an aminoglycoside or loop diuretic.
5. *Bleeding* occurs with cephalosporins having a methylthiotetrazole or similar substitution at position 3 (cefoperazone, ceftriaxone). This is due to hypoprothrombinaemia caused by the same mechanism as warfarin and is more common in patients with cancer, intra-abdominal infection or renal failure.
6. Neutropenia and thrombocytopenia are rare adverse effects reported with ceftazidime and some others.
7. A disulfiram-like interaction with alcohol has been reported with cefoperazone.

Uses

Currently cephalosporins are one of the most commonly used antibiotics. Among them they cover a wide range of gram-positive and gram-negative bacteria including some anaerobes, but not ~~*B. fragilis*~~, ~~mycobacteria~~ and ~~chlamydia~~. Recently, some anti-MRSA cephalosporins have been added to further extend their coverage. Their indications are:

1. As alternatives to penicillins for ENT, upper respiratory and cutaneous infections, one of the first generation compounds may be used.
2. Respiratory, urinary and soft tissue infections caused by gram-negative organisms, especially *Klebsiella, Proteus, Enterobacter, Serratia*. Cephalosporins preferred for these infections are cefuroxime, cefotaxime, ceftriaxone. CAP due to penicillin-resistant *Strep. pneumoniae* can now be treated by ceftaroline fosamil and HAP by ceftobiprole medocaril.
3. Penicillinase producing staphylococcal infections. Complicated skin and soft tissue

G - GIT - Nausea vomit diarrhoea
I - Inj & Infusion related
A - Anaphylaxis
N - Nephrotoxicity
T - Thrombocytopenia
A E

infections due to MRSA can now be treated by ceftaroline fosamil.

4. Septicaemias caused by gram-negative organisms: an aminoglycoside may be combined with a cephalosporin.

5. Surgical prophylaxis: the first generation cephalosporins are popular drugs. Cefazolin (i.m. or i.v.) is employed for most types of surgeries including those with surgical prosthesis such as artificial heart valves, artificial joints, etc.

6. Meningitis: Optimal therapy of pyogenic meningitis requires bactericidal activity in the CSF, preferably with antibiotic concentrations several times higher than the MBC for the infecting organism. For empirical therapy before bacterial diagnosis, i.v. cefotaxime/ceftriaxone is generally combined with ampicillin or vancomycin or both. Ceftazidime + gentamicin is the most effective therapy for *Pseudomonas* meningitis. All oral 3rd generation cephalosporins achieve low CSF levels, and are not useful in meningitis.

7. Gonorrhoea caused by penicillinase producing organisms: ceftriaxone is a first choice drug for single dose therapy of gonorrhoea if the penicillinase producing status of the organism is not known, but higher dose is now recommended due to resistance. Combination with azithromycin is also advised. Cefuroxime and cefotaxime have also been used for this purpose. For chancroid also, a single dose is as effective as erythromycin given for 7 days. Ceftriaxone is an alternative drug for syphilis.

8. Typhoid: Currently, ceftriaxone and cefoperazone injected i.v. are the fastest acting and most reliable drugs for enteric fever. They are preferred over fluoroquinolones (especially in children) for empirical therapy, since many *S. typhi* strains are resistant to chloramphenicol, ampicillin, cotrimoxazole, and lately FQs.

Advantages of ceftriaxone/cefoperazone in treating typhoid fever are:

- Quick defervescence, usually in 2-3 days.
- Early abetment of symptoms.
- Low risk of relapse and complications.
- Prevention of carrier state due to cidal action on the bacilli.
- Can be used to treat typhoid carriers.

9. Mixed aerobic-anaerobic infections in cancer patients, those undergoing colorectal surgery, obstetric complications: cefuroxime, cefaclor or one of the third generation compounds is used.

10. Hospital acquired infections, especially respiratory and other infections in intensive care units, resistant to commonly used antibiotics. Cefotaxime, ceftizoxime or a fourth generation cephalosporin may be combined with vancomycin. *Ceftobiprole medocaril* is an alternative.

11. Prophylaxis and treatment of infections in neutropenic patients: ceftazidime or another third generation compound, alone or in combination with an aminoglycoside is effective.

MONOBACTAMS

Aztreonam It is an atypical β-lactam antibiotic in which the other ring is missing (hence monobactam), but acts by binding to specific PBPs. The spectrum of action is narrow, it inhibits gram-negative enteric bacilli and *H. influenzae* at very low concentrations and *Pseudomonas* at moderate concentrations, but does not inhibit gram-positive cocci or faecal anaerobes. Thus, it is a β-lactam antibiotic with a spectrum resembling aminoglycosides, and is resistant to gram-negative β-lactamases. The main indications of aztreonam are hospital-acquired infections originating from urinary, biliary, gastrointestinal and female genital tracts.

Lack of cross sensitivity with other β-lactam antibiotics except ceftazidime (which has chemical similarity to aztreonam) is the most prominent feature of aztreonam: permiting its use in patients allergic to penicillins or cephalosporins. Rashes and rise in serum aminotransferases are the notable adverse effects. It is eliminated unchanged in urine with a t½ of 1.8 hr.

Dose: 0.5–2 g i.m. or i.v. 6–12 hourly.

AZENAM, TREZAM 0.5, 1.0, 2.0 g/vial inj.

CARBAPENEMS

Imipenem A derivative of thienamycin, imipenem is the first member of this class, and is an extremely potent and broad-spectrum β-lactam antibiotic whose range of activity includes gram-positive cocci, Enterobacteriaceae, *Ps. aeruginosa, Listeria* as well as anaerobes like *Bact. fragilis* and *Cl. difficile*. It is resistant to most β-lactamases; inhibits penicillinase producing staphylococci, but is not reliable for MRSA infections.

A limiting feature of imipenem is its rapid hydrolysis by the enzyme dehydropeptidase I located on the brush border of renal tubular cells. An innovative solution to this problem is its combination with cilastatin, a reversible inhibitor of dehydropeptidase I, which has matched pharmacokinetics with imipenem (t½ of both is 1 hr) and protects it. All carbapenems are eliminated by the kidney; dose reduction is needed in renal failure.

Imipenem-cilastatin 0.5 g i.v. 6 hourly (max 4 g/day) has proved effective in a wide range of serious hospital-acquired respiratory, urinary, abdominal, pelvic, skin and soft tissue infections including those in neutropenic, cancer and AIDS patients. For *Ps. aeruginosa* infections, it should be combined with gentamicin.

Imipenem has propensity to induce seizures at higher doses and in predisposed patients. Diarrhoea, vomiting, skin rashes and other hypersensitivity reactions are the side effects.

IMINEM: Imipenem + cilastatin 250 mg + 250 mg and 500 mg + 500 mg/vial inj.

LASTINEM: Imipenem + cilastatin 125 + 125 mg, 250 + 250 mg, 500 + 500 mg and 1000 mg + 1000 mg/vial inj.

Meropenem This newer carbapenem is not hydrolysed by renal peptidase; does not need to be protected by cilastatin. Like imipenem, it is active against both gram-positive and gram-negative bacteria, aerobes as well as anaerobes; somewhat more potent on gram-negative aerobes, especially *Ps. aeruginosa* but less potent on gram-positive cocci.

Meropenem is a reserve drug for the treatment of serious nosocomial infections like septicaemia, febrile neutropenia, intraabdominal and pelvic infections, etc. caused by cephalosporin-resistant bacteria and diabetic foot. For *Ps. aeruginosa* infections, it should be combined with an aminoglycoside. The adverse effects of meropenem are similar to imipenem, but it is less likely to cause seizures, therefore preferred over imipenem-cilastatin.

Dose: 0.5–2.0 g (10–40 mg/kg) by slow i.v. injection 8 hourly.

MERONEM, MENEM, UBPENEM 0.5, 1.0 g/vial inj.

Faropenem Another carbapenem β-lactam antibiotic that is orally active against many gram-positive as well as gram-negative bacteria, including some anaerobes. *Strep. pneumoniae, H. influenzae, Moraxella catarrhalis* are highly susceptible. It has been mainly used in respiratory, ENT and genitourinary infections. Usual side effects are diarrhoea, abdominal pain, nausea and rashes.

Dose: 150–300 mg oral TDS; FARONEM, FAROZET 150 mg, 200 mg tab.

Doripenem This later introduced carbapenem has antimicrobial activity similar to meropenem, but is more active against some resistant *Pseudomonas*. Other properties, including nonsusceptibility to renal peptidase, as well as clinical indications are also similar to meropenem. Adverse effects are nausea, diarrhoea, superinfections and phlebitis of the injected vein. Seizures are less likely.

Dose: 500 mg by slow i.v. infusion over 1 hr, every 8 hours.

DORIGLEN, DORICRIT 500 mg/vial inj., SUDOPEN 250, 500 mg/vial inj.

Ertapenem It is a new carbapenem with antibacterial activity similar to other members, but less broad spectrum. While ertapenem is highly active against *E.coli, H.influenzae, K.pneumoniae, Moraxella catarrhalis, Proteus* and many anaerobes, it has poor action on *Pseudomonas, Acinetobacter*, MRSA, penicillin-resistant *Strep. pneumoniae* and atypical respiratory pathogens. The major mechanism of acquired-resistance to ertapenem is by upregulation of antibiotic efflux mechanisms and by selection of mutants with deficient

porin channels. Indications of ertapenem include resistant skin and skin structure infections, diabetic foot infection (without osteomyelitis), CAP, complicated UTI, intraabdominal, pelvic and gynaecological infections and prophylaxis after colorectal surgery. It is effective in infections caused by extended-spectrum β-lactamase (ESBL) producing gram –ive bacteria and anaerobes. Another important feature of ertapenem is its longer t½ of 4 hours, permiting single daily i.v. infusion. It is excreted mainly in urine. Adverse effects are headache, confusion, diarrhoea, thromboflebitis of injected vein, but it is less likely to precipitate seizures than imipenem.

Dose: 1.0 g infused i.v. over 60 min daily for 7–14 days.
ERTACRIT, ZIVATOR 1.0 g per vial inj (for reconstitution before injection).

☞ PROBLEM DIRECTED STUDY

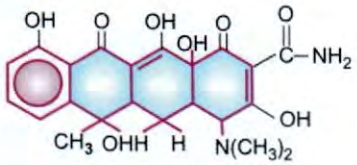
52.1 A 10-year-old boy weighing 25 kg is brought with continuous fever for the past 7 days. Initially the fever was mild, but has gradually increased and the body temp. now is 103°F. The boy also complains of abdominal pain, bloating, loose motions, loss of appetite, occasional vomiting, weakness, malaise and cough. A local doctor had given some tablets for the past 3 days, but the condition has worsened. He looks ill, mildly dehydrated with coated tongue; pulse is 70/min, abdomen is distended and tender on pressing. Liver and spleen are palpable. The total leucocyte count is 5000/cumm. Blood for culture is sent. A provisional diagnosis of *typhoid (enteric)* fever is made.

(a) Should antibiotic therapy be started right away, or the report of blood culture awaited?
(b) If treatment is to be started, which antibiotic would be the most appropriate, and why? What should be the dose and duration of antibiotic therapy?
(c) Should a single antibiotic or a combination be used?
(*see* Appendix-1 for solution)

Chapter 53 Tetracyclines and Chloramphenicol (Broad-Spectrum Antibiotics)

TETRACYCLINES

These are a class of antibiotics having a nucleus of four cyclic rings.



TETRACYCLINE

All tetracyclines are obtained from soil actinomycetes. The first to be introduced was chlortetracycline in 1948 under the name *aureomycin* (because of the golden yellow colour of *S. aureofaciens* colonies producing it). It contrasted markedly from penicillin and streptomycin (the other two antibiotics available at that time) in being active orally and in affecting a wide range of microorganisms—hence called 'broad-spectrum antibiotic'. Oxytetracycline soon followed; others were produced later, either from mutant strains or semisynthetically. A new synthetic subclass 'glycylcyclines' represented by *Tigecycline* has been added recently.

All tetracyclines are mildly bitter solids which are slightly water soluble, but their hydrochlorides are more soluble. Aqueous solutions are unstable. All have practically the same antimicrobial activity (with minor differences). The subsequently developed members have high lipid solubility, greater potency and some other differences. Several tetracyclines introduced inbetween have gone out of use. Those still clinically relevant are:

Tetracycline	Doxycycline
Oxytetracycline	Minocycline
Demeclocycline	

Synthetic subclass of drugs

Glycylcycline: Tigecycline

Chlortetracycline, Methacycline, Rolitetracycline, Lymecycline have been discontinued.

Mechanism of action The tetracyclines are primarily bacteriostatic. They inhibit protein synthesis by binding to 30S ribosomes in susceptible organisms. Subsequent to such binding, attachment of aminoacyl-t-RNA to the acceptor (A) site of mRNA-ribosome complex is blocked (Fig. 53.1). As a result, the peptide chain fails to grow.

The sensitive organisms have an energy dependent active transport process which concentrates tetracyclines intracellularly. In gram-negative bacteria tetracyclines diffuse through porin channels as well. The more lipid-soluble members (doxycycline, minocycline) enter by passive diffusion also (this is partly responsible for their higher potency). The carrier involved in active transport of tetracyclines is absent in the host cells. Moreover, protein synthesizing apparatus of host cells is less susceptible to tetracyclines. These two factors are responsible for the selective toxicity of tetracyclines for the microbes.

Antimicrobial spectrum When originally introduced, tetracyclines inhibited practically all types of pathogenic microorganisms except fungi and viruses; hence the name 'broad-spectrum antibiotic'. However, promiscous and often indiscriminate use has gradually narrowed the field of their usefulness.

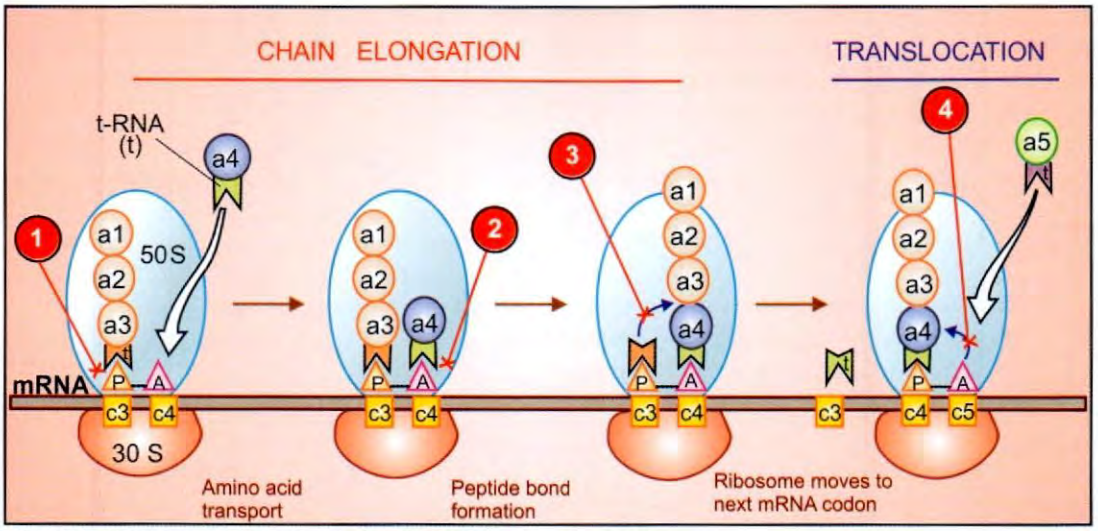


Fig. 53.1: Bacterial protein synthesis and the site of action of antibiotics

The messenger RNA (mRNA) attaches to the 30S ribosome. The initiation complex of mRNA starts protein synthesis and polysome formation. The nascent peptide chain is attached to the peptidyl (P) site of the 50S ribosome. The next amino acid (a) is transported to the acceptor (A) site of the ribosome by its specific tRNA which is complementary to the base sequence of the next mRNA codon (C). The nascent peptide chain is transferred to the newly attached amino acid by peptide bond formation. The elongated peptide chain is shifted back from the 'A' to the 'P' site and the ribosome moves along the mRNA to expose the next codon for amino acid attachment. Finally the process is terminated by the termination complex and the protein is released.

(1) Aminoglycosides bind to several sites at 30S and 50S subunits as well as to their interface—freeze initiation, interfere with polysome formation and cause misreading of mRNA code.

(2) Tetracyclines bind to 30S ribosome and inhibit aminoacyl tRNA attachment to the 'A' site.

(3) Chloramphenicol binds to 50S subunit—interferes with peptide bond formation and transfer of peptide chain from 'P' site.

(4) Erythromycin and clindamycin also bind to 50S ribosome and hinder translocation of the elongated peptide chain back from 'A' site to 'P' site and the ribosome does not move along the mRNA to expose the next codon. Peptide synthesis may be prematurely terminated.

1. Cocci: All gram-positive and gram-negative cocci were originally sensitive, but now only few *Strep. pyogenes*, *Staph. aureus* (including MRSA) and enterococci respond. Responsiveness of *Strep. pneumoniae* has decreased. Tetracyclines are now active against relatively few *N. gonorrhoeae* and *N. meningitidis*. However, minocycline may still have significant activity against these cocci.

2. Most gram-positive bacilli, e.g. *Clostridia* and other anaerobes, *Listeria, Corynebacteria, Propionibacterium acnes, B. anthracis* are inhibited but not *Mycobacteria*, except *M. leprae* (to minocycline) and some atypical ones.

3. Sensitive gram-negative bacilli are—*H. ducreyi, Calymmatobacterium granulomatis, V. cholerae, Yersinia pestis, Y. enterocolitica, Campylobacter, Brucella, Pasteurella multocida, F. tularensis* and many anaerobes. Some *H. influenzae* have become insensitive.

Enterobacteriaceae are now largely resistant. Notable bacilli that are not inhibited are *Pseudomonas aeruginosa, Proteus, Klebsiella, Salmonella typhi* and many *Bact. fragilis*. MIC against anaerobes is relatively higher.

4. Spirochetes, including *T. pallidum* and *Borrelia* are quite sensitive.

5. All rickettsiae (typhus, etc.) and chlamydiae are highly sensitive.

6. *Mycoplasma* and *Actinomyces* are moderately sensitive.

7. Protozoa like *Entamoeba histolytica* and *Plasmodia* are inhibited at high concentrations.

Resistance Resistance to tetracyclines develops slowly in a graded manner. In such bacteria, usually the tetracycline concentrating mechanism becomes less efficient or the bacteria acquire capacity to pump it out. However, doxycycline and minocycline are not effectively effluxed. Therefore, some tetracycline-resistant strains may respond to these members. Another mechanism is plasmid mediated synthesis of a 'protection' protein which protects the ribosomal binding site from tetracycline. Elaboration of tetracycline inactivating enzymes is an unimportant mechanism of the tetracycline resistance. Due to widespread use since 1950s, tetracycline resistance has become common among gram-positive cocci, *E. coli, Enterobacter* and many others.

Incomplete cross resistance is seen among different members of the tetracycline group. Some organisms not responding to other tetracyclines may be inhibited by therapeutically attained concentrations of doxycycline and minocycline (the most potent agent).

Partial cross resistance between tetracyclines and chloramphenicol has been noted.

Pharmacokinetics

The pharmacokinetic differences between individual tetracyclines are included in Table 53.1. The older tetracyclines are incompletely absorbed from g.i.t.; absorption is better if taken in empty stomach. Doxycycline and minocycline are completely absorbed irrespective of food. Tetracyclines have chelating property—form insoluble and unabsorbable complexes with calcium and other metals. Milk, iron preparations, nonsystemic antacids and sucralfate reduce their absorption. Administration of these substances and tetracyclines should be staggered, if they cannot be avoided altogether.

Tetracyclines are widely distributed in the body (volume of distribution > 1 L/kg). Variable degree of plasma protein binding is exhibited by different members. They are concentrated in liver, spleen and bind to the connective tissue in bone and teeth. Minocycline being highly lipid soluble accumulates in body fat. The CSF concentration of most tetracyclines is about 1/4 of plasma concentration, whether meninges are inflamed or not.

Most tetracyclines are primarily excreted in urine by glomerular filtration; dose has to be reduced in renal failure; doxycycline is an exception to this. They are partly metabolized and significant amounts enter bile—some degree of enterohepatic circulation occurs. They are secreted in milk in amounts sufficient to affect the suckling infant.

Enzyme inducers like phenobarbitone, carbamazepine and phenytoin hasten metabolism and shorten the t½ of doxycycline.

Administration Oral capsule is the dosage form in which tetracyclines are most commonly administered. The capsule should be taken ½ hr before or 2 hr after food. Liquid oral preparations for pediatric use are banned in India.

Tetracyclines are not to be injected i.m. because it is painful. Slow i.v. injection may be given in severe cases, but is rarely required now. Doxycycline 100 mg once or twice daily is the most commonly used tetracycline.

A variety of topical preparations (ointment, cream, etc.) are available, but should not be used, because there is high risk of sensitization. However, ocular application is not contraindicated.

Preparations

1. Oxytetracycline: TERRAMYCIN 250, 500 mg cap, 50 mg/ml in 10 ml vials inj; 3% skin oint, 1% eye/ear oint.
2. Tetracycline: ACHROMYCIN, HOSTACYCLINE, RESTECLIN 250, 500 mg cap. 3% skin oint, 1% eye/ear drops and oint.
3. Demeclocycline (Demethylchlortetracycline): LEDERMYCIN 150, 300 mg cap/tab.
4. Doxycycline: TETRADOX, DOXICIP, DOXT, NOVADOX 100 mg cap.
5. Minocycline: CYANOMYCIN, DIVAINE, MINOSTAR 50, 100 mg caps.

Adverse effects

Irritative effects Tetracyclines have irritant property; can cause epigastric pain, nausea, vomiting and diarrhoea. The irritative diarrhoea is to be distinguished from that due to

Table 53.1: Comparative features of tetracyclines

	Tetracycline (T) Oxytetracycline (OxyT)	*Demeclocycline*	*Doxycycline (Doxy) Minocycline (Mino)*
1. Source	Oxy T: *S. rimosus* T: semisynthetic	*S. aureofaciens* (mutant)	Doxy: semisynthetic Mino: semisynthetic
2. Potency	Low	Intermediate	High (Doxy < Mino)
3. Intestinal absorption	60–80%	60–80%	95–100% no interference by food
4. Plasma protein binding	Oxy T: Low T: Moderate	High	High
5. Elimination	T: Rapid renal Oxy T: excretion	Partial metabolism, slower renal excretion	Doxy: Primarily excreted in faeces as conjugate Mino: Primarily metabolized, excreted in urine and bile
6. Plasma t½	6–10 hr.	12–18 hr.	18–24 hr.
7. Dosage	250–500 mg QID or TDS	300 mg BD	200 mg initially, then 100–200 mg OD
8. Alteration of intestinal flora	Marked	Moderate	Least
9. Incidence of diarrhoea	High	Intermediate	Low
10. Phototoxicity	Low	Highest	Doxy: High
11. Specific toxicity	Oxy T: less tooth discolouration	More phototoxic, diabetes insipidus	Doxy: Low renal toxicity. Mino: Vestibular toxicity, less superinfections

superinfection. Odynophagia and esophageal ulceration has occurred by release of the material from capsules in the esophagus during swallowing, especially with doxycycline. Thrombophlebitis of the injected vein can occur.

Organ toxicity This is dose related.

1. *Liver damage* Fatty infiltration of liver and jaundice occurs occasionally. Oxytetracycline and tetracycline are safer in this regard. Tetracyclines are risky in pregnant women; can precipitate fatal acute hepatic necrosis.

2. *Kidney damage* Patients with kidney disease run the risk of tetracycline-induced kidney damage. Tetracyclines, except doxycycline, accumulate and worsen renal failure. A reversible *Fanconi syndrome* like condition is produced by outdated and degraded tetracyclines. Degradation products—epitetracycline, anhydrotetracycline and epianhydrotetracycline damage proximal tubules. Exposure to acidic pH, moisture and heat favours such degradation.

3. *Phototoxicity* A sunburn-like or other severe skin reaction on exposed parts is seen in some individuals. A higher incidence has been noted with demeclocycline and doxycycline. Distortion of nails occurs occasionally.

4. *Teeth and bones* Tetracyclines have chelating property. Calcium-tetracycline chelate gets deposited in developing teeth and bone. Given from midpregnancy to 5 months of extrauterine life, tetracyclines affect the deciduous teeth. Brown discolouration, ill-formed teeth which are more susceptible to caries are produced. Tetracyclines given between 3 months and 6 years of age affect the crown of permanent anterior dentition. Repeated courses are more damaging.

Given during late pregnancy or childhood, tetracyclines can cause temporary suppression of bone growth.

5. *Antianabolic effect* Tetracyclines reduce protein synthesis, induce negative nitrogen balance and tend to increase blood urea.

6. *Increased intracranial pressure* is noted in some infants.

7. *Diabetes insipidus* Demeclocycline antagonizes ADH action and reduces urine concentrating ability of the kidney.

8. *Vestibular toxicity* Minocycline can cause ataxia, vertigo and nystagmus, which subside when the drug is discontinued.

Hypersensitivity This is infrequent with tetracyclines. Skin rashes, urticaria, glossitis, pruritus ani and vulvae, even exfoliative dermatitis have been reported. Complete cross sensitization is exhibited by different tetracyclines.

Superinfection Tetracyclines are frequently responsible for superinfections, because they cause more marked suppression of the resident flora.

Though mouth, skin or vagina may be involved, intestinal superinfection by *Candida albicans* is most prominent (for details *see* p. 744–45); pseudomembranous enterocolitis is rare but serious. *Pseudomonas* and *Proteus* may also overgrow in the bowel. Higher doses suppress the flora more completely—greater chance of superinfection.

Doxycycline and minocycline are less liable to cause diarrhoea, because only small amounts reach the lower bowel in the active form.

Precautions

1. Tetracyclines should not be used during pregnancy, lactation and in children.
2. They should be avoided in patients on diuretics: blood urea may rise in such patients.
3. They should be used cautiously in renal or hepatic insufficiency.
4. Preparations should never be used beyond their expiry date.
5. Do not mix injectable tetracyclines with penicillin—inactivation occurs.
6. Do not inject tetracyclines i.m. or intrathecally.

Uses

Although tetracyclines are broad-spectrum antibiotics, they should be employed only for those infections for which a more selective and less toxic AMA is not available. Clinical use of tetracyclines has very much declined due to pervalence of tetracycline resistance. Availability of fluoroquinolones and other efficacious AMAs has also reduced their need.

1. *Empirical therapy* Tetracyclines are often employed when the nature and sensitivity of the infecting organism cannot be reasonably guessed. However, they are not dependable for empirical treatment of serious/life-threatening infections. They may also be used for initial treatment of *mixed infections*, although a combination of β-lactam with an aminoglycoside antibiotic or a third generation cephalosporin or a fluoroquinolone are now preferred.

2. *Tetracyclines are the first choice drugs:* Despite development of resistance by many organisms, tetracyclines are still the preferred drugs for:

(a) *Venereal diseases:*

- *Chlamydial nonspecific urethritis/endocervicitis:* 7 days doxycycline treatment is as effective as azithromycin single dose.
- *Lymphogranuloma venereum:* resolves in 2–3 weeks (*see* Table 55.1).
- *Granuloma inguinale*: due to *Calymm. granulomatis*: a tetracycline administered for 3 weeks is the most effective treatment.

(b) *Atypical pneumonia:* due to *Mycoplasma pneumoniae:* duration of illness is reduced by tetracycline therapy. Psittacosis is treated in 2 weeks by tetracyclines.

(c) *Cholera:* Tetracyclines have adjuvant value by reducing stool volume and limiting the duration of diarrhoea.

(d) *Brucellosis:* Tetracyclines are highly efficacious and cause rapid symptomatic relief. The therapy of choice is doxycycline 200 mg/day + rifampin 600 mg/day for 6 weeks. Gentamicin may be combined with doxycycline in acute cases.

(e) *Plague:* Tetracyclines are highly effective in both bubonic and pneumonic plague. They are preferred for blind/mass treatment of suspected cases during an epidemic, though streptomycin often acts faster.

(f) *Relapsing fever:* due to *Borrelia recurrentis* responds adequately.

(g) *Rickettsial infections:* Typhus, rocky mountain spotted fever, Q fever, etc. respond dramatically.

3. *Tetracyclines are second choice drugs:*

(a) To penicillin/ampicillin for tetanus, anthrax, actinomycosis and *Listeria* infections.

(b) To ceftriaxone, amoxicillin or azithromycin for gonorrhoea, in patients allergic to penicillin.

(c) To ceftriaxone for syphilis in patients allergic to penicillin; early syphilis can be treated in 2 weeks but late syphilis requires 1 month.

(d) To penicillin for leptospirosis; doxycycline 100 mg BD for 7 days is curative. Weekly doxycycline (200 mg) has been used as prophylactic in subjects at risk during an epidemic.

(e) To azithromycin for pneumonia due to *Chlamydia pneumoniae.* Oral as well as topical tetracycline has been used in trachoma.

(f) To ceftriaxone/azithromycin for chancroid.

(g) To streptomycin for tularemia.

4. *Other situations in which tetracyclines may be used are:*

(a) Urinary tract infections: Odd cases in which the organism has been found sensitive.

(b) Community-acquired pneumonia (CAP), when a more selective antibiotic cannot be used.

(c) Amoebiasis: along with other amoebicides for chronic intestinal amoebiasis.

(d) As adjuvant to quinine or artesunate for chloroquine-resistant *P. falciparum* malaria (*see* p. 877).

(e) Acne vulgaris: prolonged therapy with low doses may be used in severe cases (since *Propionibacterium acnes* is sensitive to tetracyclines), but simpler treatments are preferred in most cases (*see* p. 954).

Tigecycline

It is the first member of a new class of synthetic tetracycline analogues (glycylcyclines) which are active against most bacteria that have developed resistance to the classical tetracyclines. Thus, they have the braodest spectrum of activity. Tigecycline is a derivative of minocycline, and was introduced in 2005.

Tigecycline is active against most gram-positive and gram-negative cocci and anaerobes, including tetracycline resistant strains of *Strep. pyogenes*, *Strep. pneumoniae*, *Staph. aureus*, MRSA, VRSA, *Enterococcus faecalis* and VRE, most Enterobacteriaceae, *Acinetobacter*, as well as tetracycline sensitive organisms like *Rickettsia, Chlamydia, Mycoplasma, Legionella*, etc. However, *Pseudomonas* and *Proteus* are inherently nonresponsive to tigecycline.

Tigecycline acts in the same manner as tetracyclines. The lack of cross resistance between the two groups is mainly because the tetracycline efflux pumps acquired by many resistant bacteria have low affinity for tigecycline and are unable to pump it out. In other resistant bacteria, the ribosomal protection protein against tetracycline is less active in protecting the ribosomal binding site from tigecycline. Thus, the two most important mechanisms of tetracycline resistance do not operate against tigecycline.

Tigecycline is poorly absorbed from g.i.t; the only route of administration is by slow i.v. infusion. It is widely distributed in tissues, volume of distribution is large (>7 L/kg). Consequently, plasma concentrations are low. It is eliminated mainly in the bile; dose adjustment is not needed in renal insufficiency. The duration of action is long; elimination t½ is 36–60 hours.

Though, tigecycline can be used in many infections, it is approved only for treatment of serious and hospitalized patients of community acquired pneumonia (CAP), complicated skin and skin structure infections (but not diabetic foot), complicated intraabdominal infections caused by enterococci, anaerobes and Enterobacteriaceae. It is not recommended for hospital acquired/ventilator-associated chest infections, because in a comparative trial, the all cause mortality was higher in tigecycline group than in the comparator group receiving other antibiotics. It is also not suitable for urinary tract infection, because only low concentrations are attained in urine.

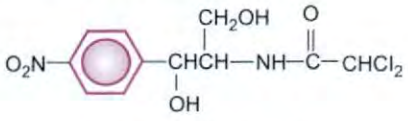
Dose: 100 mg loading dose, followed by 50 mg 12 hourly by i.v. infusion over 30–60 min, for 5–14 days.

TYGACIL, TEVRAN, TIGIMAX 50 mg lyophilized powder/vial inj.

The most common side effects are nausea and occasionally vomiting. Others are epigastric distress, diarrhoea, skin reactions, photosensitiviy and injection site complications. Superinfections and other adverse effects of tetracyclines can occur with tigecycline as well. It is not recommended for children and during pregnancy.

CHLORAMPHENICOL

Chloramphenicol was initially obtained from *Streptomyces venezuelae* in 1947. It was soon synthesized chemically and the commercial product now is all synthetic.



CHLORAMPHENICOL

It is a yellowish white crystalline solid, aqueous solution is quite stable, stands boiling, but needs protection from light. The nitrobenzene moiety of chloramphenicol is probably responsible for the antibacterial activity as well as for its intensely bitter taste.

Mechanism of action Chloramphenicol inhibits bacterial protein synthesis by interfering with 'transfer' of the elongating peptide chain to the newly attached aminoacyl-tRNA at the ribosome-mRNA complex. It specifically attaches to the 50S ribosome near the acceptor (A) site and prevents peptide bond formation between the newly attached aminoacid and the nascent peptide chain (*see* Fig. 53.1) without interfering with the aminoacyl-tRNA attachment to the 30S ribosome (the step blocked by tetracycline).

At high doses, it can inhibit mammalian mitochondrial protein synthesis as well. Bone marrow cells are especially susceptible.

Antimicrobial spectrum Chloramphenicol is primarily bacteriostatic, though high concentrations have been shown to exert cidal effect on some bacteria, e.g. *H. influenzae* and *N. meningitidis*. It is a broad-spectrum antibiotic, active against nearly the same range of organisms (gram-positive and negative cocci and bacilli, rickettsiae, mycoplasma) as tetracyclines. Notable differences between these two are:

- Chloramphenicol was highly active against *Salmonella* including *S. typhi*, but resistant strains are now rampant.
- It is more active than tetracyclines against *H. influenzae*, *B. pertussis*, *Klebsiella*, *N. meningitidis* and anaerobes including *Bact. fragilis*.
- It is less active against gram-positive cocci and spirochetes, while *Chlamydia*, *Entamoeba* and *Plasmodia* are not inhibited.

Like tetracyclines, it is ineffective against *Mycobacteria*, *Pseudomonas*, many *Proteus*, viruses and fungi.

Resistance Most bacteria are capable of developing resistance to chloramphenicol, which like tetracycline resistance generally emerges in a graded manner due to selection of less responsive mutants. Being orally active, broad-spectrum and relatively cheap, chloramphenicol was extensively and often indiscriminately used, resulting in high incidence of resistance among many bacteria.

Highly chloramphenicol resistant *S. typhi* have emerged due to transfer of R factor by conjugation. Resistance among gram-negative bacteria is generally due to acquisition of R plasmid encoded for an acetyl transferase which inactivates chloramphenicol. In many cases, this plasmid has also carried resistance to ampicillin and tetracycline. Multidrug-resistant *S. typhi* have arisen.

Decreased permeability into the resistant bacterial cells (chloramphenicol appears to enter bacterial cell both by passive diffusion as well as by facilitated transport) and lowered affinity of bacterial ribosome for chloramphenicol are the other mechanisms of resistance. Partial cross resistance between chloramphenicol and erythromycin/clindamycin has been noted. Some cross resistance with tetracyclines also occurs.

Pharmacokinetics

Chloramphenicol is rapidly and completely absorbed after oral ingestion; 50–60% bound to plasma proteins and very widely distributed: volume of distribution 1 L/kg. It freely penetrates serous cavities and blood-brain barrier: CSF concentration is nearly equal to that of unbound drug in plasma. It crosses placenta and is secreted in bile and milk.

Chloramphenicol is primarily conjugated with glucuronic acid in the liver and little is excreted unchanged in urine. Cirrhotics and neonates, who have low conjugating ability, require lower doses. The metabolite is excreted mainly in urine. Plasma t½ of chloramphenicol is 3–5 hours in adults. It is increased only marginally in renal failure: dose need not be modified.

Preparations and administration

The commonest route of administration of chloramphenicol is oral—as capsules; 250–500 mg 6 hourly (max. 100 mg/kg/day), children 25–50 mg/kg/day. It is also available for application to eye/ear, but topical use at other sites is not recommended.

CHLOROMYCETIN, ENTEROMYCETIN, PARAXIN, 250 mg, 500 mg cap, 1% eye oint, 0.5% eye drops, 5% ear drops, 1% applicaps.

Chloramphenicol palmitate (CHLOROMYCETIN PALMITATE, ENTEROMYCETIN, PARAXIN 125 mg/5 ml oral susp) is an insoluble tasteless ester of chloramphenicol, which is inactive as such. It is nearly completely hydrolysed in the intestine and absorbed as free chloramphenicol.

Chloramphenicol succinate (ENTEROMYCETIN, CHLOROMYCETIN SUCCINATE, PARAXIN 1 g/vial inj. is the soluble but inactive ester which is used in the parenteral preparations. Intramuscular injection is painful and not recommended. The ester is hydrolysed in tissues to the free active form. However, bioavailability even on i.v. injection is only 70% due to renal excretion of the ester before hydrolysis.

VANMYCETIN 0.4% eye drops, 250 mg opticaps.

Adverse effects

1. ***Bone marrow depression*** Of all antibiotics, chloramphenicol is the most prominent cause of aplastic anaemia, agranulocytosis, thrombocytopenia or pancytopenia. Two forms are recognized:

(a) *Non-dose related idiosyncratic reaction*: This is rare (1 in 40,000), unpredictable, but serious, often fatal, probably has a genetic basis and is more common after repeated courses. Many victims, even if they survive, develop leukaemias later.

(b) *Dose and duration of therapy related myelosuppression:* This is a direct toxic effect, predictable and probably due to inhibition of mitochondrial enzyme synthesis in the erythropoietic cells. This toxicity is often reversible without long-term sequelae.

2. ***Hypersensitivity reactions*** Rashes, fever, atrophic glossitis, angioedema are infrequent.

3. ***Irritative effects*** Nausea, vomiting, diarrhoea, pain on injection.

4. ***Superinfections*** These are similar to tetracyclines, but less common.

5. ***Gray baby syndrome*** It occurred when high doses (~100 mg/kg) were given prophylactically to neonates, especially premature. The baby stopped feeding, vomited, became hypotonic and hypothermic, abdomen distended, respiration became irregular; an ashen gray cyanosis developed in many, followed by cardiovascular collapse and death. Blood lactic acid was raised.

It occurs because of inability of the newborn to adequately metabolize and excrete chloramphenicol. Chloramphenicol should be avoided in neonates.

Interactions Chloramphenicol inhibits metabolism of warfarin, cyclophosphamide and phenytoin. Phenobarbitone, phenytoin, rifampin enhance chloramphenicol metabolism so that failure of therapy may occur.

Uses

Clinical use of chloramphenicol for systemic infections is now highly restricted due to fear of fatal toxicity. Because of risk of serious (though rare) bone marrow aplasia:

(a) Never use chloramphenicol for ~~minor infec~~tions or those of ~~undefined etiology~~.

(b) Do not use chloramphenicol for ~~infections treatable by other safer~~ antimicrobials.

(c) Avoid ~~repeated~~ courses.

(d) Daily dose not to exceed ~~2–3 g~~; duration of therapy to be < 2 weeks.

(e) Regular blood counts may detect dose-related bone marrow toxicity.

(f) Combined formulation of chloramphenicol with any drug meant for internal use is banned in India.

Indications of chloramphenicol are:

1. *Pyogenic meningitis:* Third generation cephalosporins (± vancomycin) are presently the first line drugs for empirical therapy of bacterial meningitis (*see* Ch. 52). Chloramphenicol in a dose of 50–75 mg/kg/day may be used as a second line drug for *H. influenzae* and meningococcal meningitis, because it has excellent penetration into CSF and clinical efficacy has been demonstrated.

2. *Anaerobic infections* caused by *Bact. fragilis* and others (wound infections, intraabdominal infections, pelvic abscess, and brain abscess, etc.) respond well to chloramphenicol. However, clindamycin or metronidazole are mostly used for these. A penicillin/cephalosporin is generally combined since most of these are mixed infections.

3. *Intraocular infections* Chloramphenicol given systemically attains high concentration in ocular fluid. It is the preferred drug for endophthalmitis caused by sensitive bacteria.

4. *Enteric fever:* Chloramphenicol was the first antibiotic and the drug of choice for typhoid fever till the 1980s when resistant *S. typhi* emerged and spread globally, including most parts of India. As a result, chloramphenicol became clinically unreliable; 50–80% isolates showed *in vitro* resistance. Many of these are multidrug resistant—not responsive to ampicillin and cotrimoxazole as well.

Being bacteriostatic, relapses occur in ~ 10% chloramphenicol treated patients. Also, it does not prevent or cure the carrier state.

5. *As second choice drug*

- to tetracyclines for brucellosis and rickettsial infections, especially in young children and pregnant women in whom tetracyclines are contraindicated.
- to erythromycin for whooping cough.

6. *Topically* In conjunctivitis, external ear infections—chloramphenicol 0.5–5.0% is highly effective. Topical use on skin or other areas is not recommended because of risk of sensitization.

SECTION 12

☞ PROBLEM DIRECTED STUDY

53.1 A 30-year-old mother of 2 children attends the gynaecology OPD of the District Hospital with the complaint of whitish watery foul smelling vaginal discharge for the past 2 months. She also suffers lower backache and feels deep pelvic pain during intercourse, which she has irregularly, because her husband works in the city and visits her off and on. She feels weak, but there is no fever. Her periods are regular, but somewhat painful. Last menstruation was 10 days back. Vaginal examination reveals mucopurulent discharge from the cervical canal and pelvic tenderness, but there is no pelvic mass or abscess. She expresses inability to get any investigations done, as she is poor and has to return to her village. A provisional diagnosis of chlamydial nonspecific endocervicitis is made, with possibility of gonococcal infection, concurrently or alone.

(a) What is the most appropriate drug treatment for her?

(b) Should her husband be also examined and treated?

(see Appendix-1 for solution)

Chapter 54 | Aminoglycoside Antibiotics

These are a group of natural and semisynthetic antibiotics having polybasic amino groups linked glycosidically to two or more aminosugar (streptidine, 2-deoxy streptamine, garosamine) residues.

Unlike penicillin, which was a chance discovery, aminoglycosides are products of deliberate search for drugs effective against gram-negative bacteria. *Streptomycin* was the first member discovered in 1944 by Waksman and his colleagues. It assumed great importance because it was active against tubercle bacilli. Others were produced later, and now aminoglycosides are a sizable family. All aminoglycosides are produced by soil actinomycetes and have many common properties (*see* box).

Systemic aminoglycosides

Streptomycin	Amikacin
Gentamicin	Sisomicin
Kanamycin	Netilmicin
Tobramycin	Paromomycin

Topical aminoglycosides

Neomycin	Framycetin

MECHANISM OF ACTION

The aminoglycosides are bactericidal antibiotics, all having the same general pattern of action which may be described in two main steps:
(a) Transport of the aminoglycoside through the bacterial cell wall and cytoplasmic membrane.
(b) Binding to ribosomes resulting in inhibition of protein synthesis.

Common properties of aminoglycoside antibiotics

1. All are used as sulfate salts, which are highly water soluble; solutions are stable for months.
2. They ionize in solution; are not absorbed orally; distribute only extracellularly; do not penetrate brain or CSF.
3. All are excreted unchanged in urine by glomerular filtration.
4. All are bactericidal and more active at alkaline pH.
5. They act by interfering with bacterial protein synthesis.
6. All are active primarily against aerobic gram-negative bacilli and do not inhibit anaerobes.
7. There is only partial cross resistance among them.
8. They have relatively narrow margin of safety.
9. All exhibit ototoxicity and nephrotoxicity.

Transport of aminoglycoside into the bacterial cell is a multistep process. They diffuse across the outer coat of gram-negative bacteria through porin channels. Entry from the periplasmic space across the cytoplasmic membrane is carrier mediated which is linked to the electron transport chain. Thus, penetration is dependent upon maintenance of a polarized membrane and on oxygen dependent active processes (energy dependent phase I or EDP_I entry). These processes are inactivated under anaerobic conditions. Therefore, anaerobes are not sensitive and facultative anaerobes are more resistant when O_2 supply is deficient, e.g. inside big abscesses. Penetration is favoured by high pH; aminoglycosides are ~20 times more active in alkaline than in acidic medium. Antibiotics affecting bacterial cell wall (β-lactams, vancomycin) enhance entry of aminoglycosides and

exhibit synergism in case of certain pathogens, i.e. bacterial killing is supraadditive, e.g. in enterococcal endocarditis.

Once inside the bacterial cell, streptomycin binds to 30S ribosomes, but other aminoglycosides bind to additional sites on 50S subunit, as well as to 30S-50S interface. They freeze initiation of protein synthesis (*see* Fig. 53.1), prevent polysome formation and promote their disaggregation to nonfunctional monosomes so that only one ribosome is attached to each strand of mRNA. Binding of aminoglycoside to 30S-50S juncture causes distortion of mRNA codon recognition resulting in misreading of the code: one or more wrong amino acids are entered in the peptide chain and/or peptides of abnormal lengths are produced. Different aminoglycosides cause misreading at different levels depending upon their selective affinity for specific ribosomal proteins.

The cidal action of these drugs appears to be based on secondary changes in the integrity of bacterial cell membrane, because other antibiotics which inhibit protein synthesis (tetracyclines, chloramphenicol, erythromycin) are only static. After exposure to aminoglycosides, sensitive bacteria become more permeable; ions, amino acids and even proteins leak out followed by cell death. This probably results from incorporation of the defective proteins into the cell membrane. One of the consequences of aminoglycoside induced alteration of cell membrane is augmentation of the carrier-mediated energy-dependent phase II (EDP_2) entry of the antibiotic. This reinforces their lethal action.

MECHANISM OF RESISTANCE

Resistance to aminoglycosides is acquired by one of the following mechanisms:

- Acquisition of cell membrane bound modifying enzymes which phosphorylate/adenylate or acetylate the antibiotic. The conjugated aminoglycosides do not bind to the target ribosomes and are incapable of enhancing active transport like the unaltered drug. These enzymes are acquired mainly by conjugation and transfer of plasmids. Nosocomial microbes have become rich in such plasmids, some of which encode for multidrug resistance. This is the most important mechanism of development of resistance to aminoglycosides. Susceptibility of different aminoglycosides to these enzymes differs. Thus, cross resistance among aminoglycosides is variable.
- Mutation decreasing the affinity of ribosomal proteins that normally bind the aminoglycoside: this mechanism can confer high degree resistance, but operates to a limited extent.
- Decreased efficiency of the aminoglycoside transporting mechanism: either the pores in the outer coat become less permeable or the active transport is interfered. This again is not frequently encountered in the clinical setting.

SHARED TOXICITIES

The aminoglycosides produce toxic effects which are common to all members, but the relative propensity differs (*see* Table 54.1).

The toxic effects are dependent on the dose as well as duration of exposure.

1. Ototoxicity This is the most important adverse effect. The vestibular or the cochlear part may be primarily affected by a particular aminoglycoside. These drugs are concentrated in the labyrinthine fluid and are slowly removed from it when the plasma concentration falls. Ototoxicity is greater when plasma concentration of the drug is persistently high and above a threshold value. For gentamicin this is estimated to be ~ 2 μg/ml; if the trough level is above this value, vestibular damage becomes concentration dependent. It is recommended that dosing of gentamicin should be such that the measured trough plasma concentration is < 1 μg/ml to avoid toxicity. The vestibular or cochlear sensory cells and hairs undergo concentration dependent destructive changes. Aminoglycoside ear drops can cause ototoxicity when instilled in patients with perforated eardrum. Such drops are contraindicated in them.

Table 54.1: Comparative toxicity of aminoglycoside antibiotics (tentative)

Systemically used aminoglycoside	*Ototoxicity*		*Nephrotoxicity*
	vestibular	*cochlear*	
1. Streptomycin	++	±	+
2. Gentamicin	++	+	++
3. Kanamycin	+	++	++
4. Tobramycin	+±	+	+±
5. Amikacin	+	+±	+±
6. Sisomicin	+±	+	+±
7. Netilmicin	+±	+	+±

Cochlear damage It starts from the base and spreads to the apex; hearing loss affects the high frequency sound first, then progressively encompasses the lower frequencies. No regeneration of the sensory cells occurs; auditory nerve fibres degenerate in a retrograde manner—deafness is permanent. Older patients and those with preexisting hearing defect are more susceptible. Initially, the cochlear toxicity is asymptomatic and can be detected only by audiometry. Tinnitus then appears, followed by progressive hearing loss. On stopping the drug, tinnitus disappears in 4–10 days, but frequency loss persists. Kanamycin and amikacin produce greater cochlear damage than other aminoglycosides.

Vestibular damage Headache is usually first to appear, followed by nausea, vomiting, dizziness, nystagmus, vertigo and ataxia. When the drug is stopped at this stage, it passes into a chronic phase lasting 6 to 10 weeks in which the patient is asymptomatic while in bed and has difficulty only during walking. Compensation by visual and proprioceptive positioning tends to allay symptoms, and recovery (often incomplete) occurs over 1–2 years. Permanency of changes depends on the extent of initial damage and the age of the patient; elderly have poor recovery. Steptomycin and gentamicin produce more vestibular than cochlear toxicity.

2. Nephrotoxicity It manifests as tubular damage resulting in loss of urinary concentrating power, low g.f.r., nitrogen retention, albuminuria and casts. Aminoglycosides attain high concentration in the renal cortex (proximal tubules). Toxicity is related to the total amount of the drug received by the patient. However, in patients with normal renal function, single daily dosing regimen appears to cause lesser nephrotoxicity than the conventional thrice daily dosing. Renal toxicity is more in the elderly and in those with preexisting kidney disease. Provided the drug is promptly discontinued, renal damage is totally reversible. An important implication of aminoglycoside-induced nephrotoxicity is reduced clearance of the antibiotic resulting in higher and more persistent blood levels causing enhanced ototoxicity. Streptomycin is the least nephrotoxic aminoglycoside.

3. Neuromuscular blockade All aminoglycosides reduce ACh release from the motor nerve endings. They interfere with mobilization of centrally located synaptic vesicles to fuse with the terminal membrane (probably by antagonizing Ca^{2+}) as well as decrease the sensitivity of the muscle end-plates to ACh. The effect of this action is not manifested ordinarily in the clinical use of these drugs. However, apnoea and fatalities have occurred when streptomycin/neomycin was put into peritoneal or pleural cavity after an operation, especially if a curare-like muscle relaxant was administered during surgery. Rapid absorption form the peritoneum/pleura produces high blood levels and adds to the residual action of the neuromuscular blocker.

The neuromuscular block produced by aminoglycosides can be partially antagonized by i.v. injection of a calcium salt. Neostigmine has inconsistent reversing action. Myasthenic weakness is accentuated by these drugs.

PRECAUTIONS AND INTERACTIONS

1. Avoid aminoglycosides during pregnancy due to risk of foetal ototoxicity.
2. Avoid concurrent use of other nephrotoxic drugs, e.g. NSAIDs, amphotericin B, vancomycin, cyclosporine and cisplatin.
3. Cautious use of other potentially ototoxic drugs like vancomycin, minocycline and furosemide, though clinical evidence of potentiated ototoxicity is meagre.
4. Cautious use in patients >60 years age and in those with kidney damage.

5. Do not mix aminoglycoside with any drug in the same syringe/infusion bottle.

PHARMACOKINETICS

All systemically administered aminoglycosides have similar pharmacokinetic features. They are highly ionized and are neither absorbed nor destroyed in the g.i.t. However, absorption from injection site in muscles is rapid: peak plasma levels are attained in 30–60 minutes. They are distributed only extracellularly, so that volume of distribution (~0.3 L/kg) is nearly equal to the extracellular fluid volume. Low concentrations are attained in serous fluids like synovial, pleural and peritoneal, but these levels may be significant after repeated dosing. Relatively higher concentrations are present in endolymph and renal cortex, which are responsible for ototoxicity and nephrotoxicity. Concentrations in CSF and aqueous humour are nontherapeutic even in the presence of inflammation. Aminoglycosides cross placenta and can be found in foetal blood/amniotic fluid. Their use during pregnancy can cause hearing loss in the offspring; should be avoided.

Aminoglycosides are not metabolized in the body, and are excreted unchanged in urine. Glomerular filtration is the main channel, because tubular secretion as well as reabsorption are negligible. The plasma t½ ranges between 2–4 hours, but small amount of drug persists longer in tissues. Renal clearance of aminoglycosides parallels creatinine clearance (CLcr), and is approximately 2/3 of it. The t½ is prolonged upto 24 hours, and accumulation occurs in patients with renal insufficiency; also in the elderly and in neonates who have low g.f.r. Reduction in dose or increase in dose-interval is essential in these situations. This should be done according to the measured CLcr. Generally, there is no need to reduce the daily dose till CLcr is above 70 ml/min. A simple guide to dose calculation for lower CLcr is given in the box.

Guideline for dose adjustment of gentamicin in renal insufficiency

CLcr (ml/min)	*% of daily dose*
70	70% daily
50	50% daily
30	30% daily
20–30	80% alternate day
10–20	60% alternate day
<10	40% alternate day

DOSING REGIMENS

Because of low safety margin, the daily dose of systemically administered aminoglycosides must be precisely calculated accordingly to body weight and level of renal function. For an average adult with normal renal function (CLcr >70 ml/min), the usual doses are:

Gentamicin/tobramycin/sisomicin/netilmicin	3–5 mg/kg/day
Streptomycin/kanamycin/amikacin	7.5–15 mg/kg/day

Considering the short t½ (2–4 hr) of aminoglycosides the daily doses are conventionally divided into 3 equal parts and injected i.m. (or i.v. slowly over 60 min) every 8 hours. However, most authorities now recommend a single total daily dose regimen for patients with normal renal function. This is based on the considerations that:

- Aminoglycosides exert concentration dependent bactericidal action and a long as well as concentration dependent post-antibiotic effect (*see* p. 748). Therefore higher plasma concentrations attained after the single daily dose will be equally or more effective than the divided doses.
- With the single daily dose, the plasma concentration will remain subthreshold for ototoxicity and nephrotoxicity for a longer period each day allowing washout of the drug from the endolymph and the renal cortex.

Several comparative studies with gentamicin and few other aminoglycosides and meta-analyses of these studies have validated this concept. The

single daily dose regimen has been found to be less nephrotoxic, but no dosing regimen appears to be less ototoxic than another. Both regimens are equally effective. Single daily doses are also more convenient and cheaper (require less man power). However, the safety of the high dose extended interval regimen in patients with renal insufficiency and in children is not established, and is therefore avoided. It is also not recommended when gentamicin is combined with a β-lactam antibiotic for obtaining cidal effect in bacterial endocarditis, etc.

Gentamicin

It was the 3rd systemically administered aminoglycoside antibiotic to be introduced for clinical use, and was obtained from *Micromonospora purpurea* in 1964. Gentamicin quickly surpassed streptomycin because of higher potency and broader spectrum of activity. Currently, it is the most commonly used aminoglycoside for acute infections and may be considered prototype of the class. It is active mainly against aerobic gram-negative bacilli, including *E. coli*, *Klebsiella pneumoniae*, *Enterobacter*, *H. influenzae*, *Proteus*, *Serratia* and *Pseudomonas aeruginosa*. Many strains of *Brucella*, *Campylobacter*, *Citrobacter*, *Fransisella* and *Yersinia* are also sensitive. Limited number of gram-positive bacteria are susceptible, especially *Staph. aureus*, *Strep. faecalis* and some *Listeria*, but *Strep. pyogenes*, *Strep. pneumoniae* and enterococci are usually insensitive.

Gentamicin is ineffective against *Mycobacterium tuberculosis* and other mycobacteria. It is more potent (its MIC values are lower) than streptomycin, kanamycin and amikacin, but equally potent as tobramycin, sisomicin and netilmicin. Bacteria that acquire resistance against gentamicin generally exhibit cross resistance to tobramycin and sisomicin. Gentamicin synergises with β-lactam antibiotics, especially against *Enterococcus* (endocarditis) and *Pseudomonas* (meningitis).

Dose: 3–5 mg/kg/day (single dose or divided in 3 doses) i.m. or in an i.v. line over 30–60 min.

GARAMYCIN, GENTASPORIN, GENTICYN 20, 60, 80, 240 mg per vial inj; also 0.3% eye/ear drops, 0.1% skin cream.

Uses Gentamicin is the cheapest (other than streptomycin) and the first line aminoglycoside antibiotic. It is often added when a combination antibiotic regimen is used empirically to treat serious infections by extending the spectrum of coverage to include aerobic gram –ive bacteria. Mostly, it is added to a penicillin/cephalosporin or vancomycin to obtain synergistic bacterial killing. Because of low therapeutic index, its use should be restricted to serious gram-negative bacillary infections.

1. Gentamicin is very valuable for preventing and treating respiratory infections in critically ill patients; in those with impaired host defence (receiving anticancer drugs or high-dose corticosteroids; AIDS; neutropenic), patients in resuscitation wards, with tracheostomy or on ventilators; postoperative pneumonias; patients with implants and in intensive care units. It is mostly combined with a penicillin/cephalosporin or another antibiotic in these situations. However, resistant strains have emerged in many hospitals and nosocomial infections are less amenable to gentamicin now. Another aminoglycoside (tobramycin, amikacin) is then selected on the basis of the local sensitivity pattern. Aminoglycosides should not be used to treat community acquired pneumonias (CAPs) which are mostly caused by gram-positive cocci and anaerobes.

   Gentamicin is often added to the peritoneal dialysate to prevent or treat peritonitis.

2. *Pseudomonas, Proteus* or *Klebsiella* infections: burns, urinary tract infection, pneumonia, lung abscesses, osteomyelitis, middle ear infection, septicaemia, etc., caused mostly by the above bacteria are an important area of use of gentamicin. It may be combined with piperacillin or a third generation cephalosporin for serious infections. Topical use on infected burns and in conjunctivitis is permissible.

3. Meningitis caused by gram negative bacilli: Because this is a serious condition, drug combinations including an aminoglycoside are often used. Third generation cephalosporins alone or with an aminoglycoside are favoured for this purpose.

4. Subacute bacterial endocarditis (SABE): Gentamicin (1 mg/kg 8 hourly i.m.) is generally combined with penicillin/ampicillin/vancomycin.

Streptomycin

It is the first aminoglycoside antibiotic obtained from *Streptomyces griseus* which was used extensively in the past, but is now practically restricted to treatment of tuberculosis. It is less potent (MICs are higher) than many other aminoglycosides. The antimicrobial spectrum of streptomycin is relatively narrow: primarily covers aerobic gram-negative bacilli. Sensitive organisms are—*H. ducreyi, Brucella, Yersinia pestis, Francisella tularensis, Nocardia, Calym. granulomatis, M. tuberculosis*. Only few strains of *E. coli, H. influenzae, V. cholerae, Shigella, Klebsiella*, enterococci and some gram-positive cocci are now inhibited, that too at higher concentrations. All other organisms including *Pseudomonas* are unaffected.

Resistance Many organisms rapidly develop resistance to streptomycin, either by one-step mutation or by acquisition of plasmid which codes for modifying enzymes. *E. coli, H. influenzae, Str. pneumoniae, Str. pyogenes, Staph. aureus* have become largely resistant. If streptomycin is used alone, *M. tuberculosis* also become resistant.

Streptomycin dependence Certain mutants grown in the presence of streptomycin become dependent on it. Their growth is promoted rather than inhibited by the antibiotic. This occurs when the antibiotic induced misreading of the genetic code becomes a normal feature for the organism. This phenomenon is probably significant only in the use of streptomycin for tuberculosis.

Cross resistance Only partial and often unidirectional cross resistance occurs between streptomycin and other aminoglycosides.

Adverse effects About 1/5 patients given streptomycin 1 g BD i.m. experience vestibular disturbances. Auditory disturbances are less common.

Streptomycin has the lowest nephrotoxicity among aminoglycosides; probably because it is not concentrated in the renal cortex. Hypersensitivity reactions are rare; rashes, eosinophilia, fever and exfoliative dermatitis have been reported. Anaphylaxis is very rare. Topical use is contraindicated for fear of contact sensitization.

Superinfections are not significant. Pain at injection site is common. Paraesthesias and scotoma are occasional. It is contraindicated during pregnancy due to risk of foetal ototoxicity.

AMBISTRYN-S 0.75, 1 g dry powder per vial for inj.

Acute infections: 1 g (0.75 g in those above 50 yr age) i.m. OD or BD for 7–10 days.

Tuberculosis: 1 g or 0.75 g i.m. OD or thrice weekly for 30–60 days.

Uses

1. Tuberculosis: *see* Ch. 56.
2. Subacute bacterial endocarditis (SABE): Streptomycin (now mostly gentamicin) is given in conjunction with penicillin/ampicillin/vancomycin for 4–6 weeks.
3. Plague: Streptomycin is rapidly curative (in 7–12 days). Alone or combined with a tetracycline, it is employed only in confirmed cases. Tetracyclines alone have been more commonly used for mass treatment of suspected cases during an epidemic.
4. Tularemia: Streptomycin is the drug of choice for this rare disease; effects cure in 7–10 days. Tetracyclines are the alternative drugs, especially in milder cases.

In most other situations, e.g. urinary tract infection, peritonitis, septicaemias, etc. where streptomycin was used earlier, gentamicin or one of the newer aminoglycosides is now employed due to widespread resistance to streptomycin and its low potency.

Oral use of streptomycin for diarrhoea is banned in India.

Kanamycin

Obtained from *S. kanamyceticus* (in 1957), it was the second systemically used aminoglycoside to be developed after streptomycin. Kanamycin is similar to streptomycin in all respects including efficacy against *M. tuberculosis* and lack of activity on *Pseudomonas* and *Streptococci*. However, it is more toxic, both to the cochlea and to kidney. Hearing loss, which is irreversible, is more common than vestibular disturbance. Because of toxicity and narrow spectrum of activity, it has been largely replaced by other aminoglycosides. Kanamycin is occasionally used as a second line drug in resistant tuberculosis.

Dose: 0.5 g i.m. BD (15 mg/kg/day);

KANCIN, KANAMAC 0.5 g, 1.0 g inj.

Tobramycin

It was obtained from *S. tenebrarius* in the 1970s. The antibacterial spectrum and pharmacokinetic properties, as well as dosage are almost identical to gentamicin, but it is 2–4 times more active against

Pseudomonas and *Proteus*. Some strains resistant to gentamicin are sensitive, but majority are cross resistant. However, tobramycin is not useful for combining with penicillin in the treatment of enterococcal endocarditis. It should be used only as an alternative to gentamicin. Serious infections caused by *Pseudomonas* and *Proteus* are its major indications. Ototoxicity and nephrotoxicity is probably less than gentamicin.

Dose: 3–5 mg/kg day in 1–3 doses. i.m. or i.v. infusion over 30–60 min.

TOBACIN 20, 60, 80 mg in 2 ml inj. 0.3% eye drops.
TOBRANEG 20, 40, 80 mg per 2 ml inj, TOBRABACT 0.3% eye drops.

Amikacin

It is a semisynthetic derivative of kanamycin to which it resembles in pharmacokinetics, dose and toxicity. The outstanding feature of amikacin is its resistance to bacterial aminoglycoside modifying enzymes. Thus, it has the widest spectrum of activity, including many organisms resistant to other aminoglycosides. However, relatively higher doses are needed for *Pseudomonas*, *Proteus* and *Staph.* infections.

The range of conditions in which amikacin can be used is the same as for gentamicin. It is recommended as a reserve drug for empirical treatment of hospital acquired gram-negative bacillary infections where gentamicin/tobramycin resistance is high. Amikacin is effective in tuberculosis, but used only for multidrug resistant infection. More hearing loss than vestibular disturbance occurs in toxicity.

Dose: 15 mg/kg/day in 1–3 doses i.m.; urinary tract infection 7.5 mg/kg/day.

AMICIN, MIKACIN, MIKAJECT 100 mg, 250 mg, 500 mg in 2 ml inj.

Sisomicin

Introduced in 1980s, it is a natural aminoglycoside from *Micromonospora inyoensis*. Sisomicin is chemically and pharmacokinetically similar to gentamicin, but somewhat more potent on *Pseudomonas*, and β haemolytic *Streptococci*. However, it is susceptible to aminoglycoside inactivating enzymes and offers no advantage in terms of ototoxicity and nephrotoxicity. Clinical use is very much restricted, and it has been discontinued in USA and UK.

Netilmicin

This semisynthetic derivative of gentamicin has a broader spectrum of activity than gentamicin. It is relatively resistant to some aminoglycoside modifying enzymes and thus effective against few gentamicin-resistant strains. It is more active against *Klebsiella, Enterobacter* and *Staphylococci*, but less active against *Ps. aeruginosa*.

Pharmacokinetic characteristics and dosage of netilmicin are similar to gentamicin but toxicity may be lower.

Netilmicin is an alternative to gentamicin, but has failed to gain clinical popularity, and has been discontinued in USA.

Dose: 4–6 mg/kg/day i.m. in 1–3 doses; NETROMYCIN 10, 25, 50 mg in 1 ml, 200 mg in 2 ml and 300 mg in 3 ml inj., NETICIN 200 mg (2 ml), 300 mg (3 ml) inj.

Neomycin

Obtained from *S. fradiae*, it is a wide-spectrum aminoglycoside active against most gram-negative bacilli and some gram-positive cocci. However, *Pseudomonas* and *Strep. pyogenes* are not sensitive. Neomycin is highly toxic to the internal ear (mainly auditory) and to kidney, therefore, not used systemically. Absorption from the g.i.t. is minimal. Oral and topical administration does not ordinarily cause systemic toxicity.

Dose: 0.25–1 g QID oral, 0.3–0.5% topical.

NEOMYCIN SULPHATE 350, 500 mg tab, 0.3% skin oint, 0.5% skin cream, eye oint.
NEBASULF: Neomycin sulph. 5 mg, bacitracin 250 U, sulfacetamide 60 mg/g oint. and powder for surface application.
POLYBIOTIC CREAM: Neomycin sulph. 5 mg, polymyxin 5,000 IU, gramicidin 0.25 mg/g cream.
NEOSPORIN: Neomycin 3400 iu, polymyxin B 5000 iu, bacitracin 400 iu/g oint and powder for surface application.
NEOSPORIN-H: Neomycin 3400 iu, polymyxin B 5000 iu, hydrocortisone 10 mg per g oint and per ml ear drops.

Uses

1. Topically (often in combination with polymyxin, bacitracin, etc.) for infected wound, ulcers, burn, external ear infections, conjunctivitis, but like other topical antiinfective preparations, benefits are limited.
2. Orally for:

(a) Preparation of bowel before surgery: Oral neomycin in a dose of 1 g 8 hourly for 1–2 days reduces aerobic gut flora, but has little effect on colonic anaerobes. Combined with metronidazole 0.5 g 8 hourly on day before surgery) may reduce postoperative infections.

(b) Hepatic coma: Neomycin, by suppressing intestinal flora, diminishes NH_3 production in the colon and lowers its blood level; clinical improvement in hepatic encephalopathy may occur within 2–3 days. However, because of toxic potential neomycin is infrequently used for this purpose; Lactulose (*see* p. 725) is preferred.

Adverse effects Applied topically neomycin has low sensitizing potential. However, rashes do occur.

Oral neomycin has a damaging effect on intestinal villi. Prolonged treatment can induce malabsorption syndrome with diarrhoea and steatorrhoea.

Due to marked suppression of gut flora, superinfection by *Candida* can occur.

Small amounts that are absorbed from the gut or topical sites are excreted unchanged by kidney. This may accumulate in patients with renal insufficiency—cause further kidney damage and ototoxicity. Neomycin is contraindicated if renal function is impaired.

Neomycin containing antidiarrhoeal formulations are banned in India.

Framycetin

Obtained from *S. lavendulae*, it is very similar to neomycin. Framycetin is too toxic for systemic administration and is used topically on skin, eye, ear in the same manner as neomycin.

SOFRAMYCIN, FRAMYGEN 1% skin cream, 0.5% eye drops or oint.

Paromomycin

Chemically related to neomycin, this aminoglycoside antibiotic has pronounced activity against many protozoan parasites, including *E. histolytica*, *Giardia lamblia*, *Trichomonas vaginalis*, *Cryptosporidium* and *Leishmania*, in addition to many bacteria sensitive to neomycin. Like other aminoglycosides, it is not absorbed from the gut. An oral formulation was marketed in many countries, including India, in the 1960s for treatment of intestinal amoebiasis and giardiasis, but was soon discontinued when metronidazole gained popularity. Recently, it has been reintroduced and is described in Ch. 62. For its antibacterial activity in the gut, it can be used as an alternative to neomycin for hepatic encephalopathy. Parenterally, it is being used for visceral leishmaniasis (*see* Ch. 62).

Dose: Oral 500 mg TDS (25–30 mg/kg/day)

PAROMYCIN, HUMATIN 250 mg cap.

Arbekacin It is a semisynthetic aminoglycoside of the kanamycin family which has been used in Japan since 1990 for the treatment of sepsis and pneumonia caused by MRSA. Arbekacin has been recently (May 2017) approved in India as 200 mg/4 ml injection, but is not approved in USA or UK. It has a broad spectrum activity covering many gram +ive and gram –ive bacteria including MRSA, *E. coli, P. aeruginosa, K. pneumoniae*, etc. and is stable to many commonly occurring aminoglycoside modifying enzymes, confering activity against many bacteria resistant to gentamicin and tobramycin. Like other aminoglycosides, it synergises with β-lactam antibiotics, and the combination may be useful in treating multidrug resistant *Pseudomonas* and *Acinetobacter* infections. Arbekacin (like other aminoglycosides) is ototoxic and nephrotoxic, but the incidence of toxicity is low in patients with normal renal function if the recommended doses are not exceeded. The mean plasma t½ is 3.5 hours in patients with CLcr >80 ml/min; and is prolonged in renal failure.

Dose: 1–3 mg/kg/day i.m. or slow i.v. injection.

SECTION 12

☞ PROBLEM DIRECTED STUDY

54.1 A 75-year-old unconscious male patient of cerebral stroke is maintained on ventilator in the intensive care unit of the hospital. On the 4th day he developed fever, and the total leucocyte count rose to 14000/μL, along with signs of chest infection. A sample of bronchial aspirate is sent for bacteriological tests, and it is decided to institute empirical treatment with cefotaxime and gentamicin. His body weight is 60 kg and creatinine clearance is estimated to be 50 ml/min.

(a) What should be the appropriate dose and dosing regimen for gentamicin and cefotaxime for this patient?

(see Appendix-1 for solution)

Chapter 55 Macrolide, Lincosamide, Glycopeptide and Other Antibacterial Antibiotics; Urinary Antiseptics

MACROLIDE ANTIBIOTICS

These are antibiotics having a macrocyclic lactone ring with attached sugars. *Erythromycin* is the first member discovered in the 1950s, *Roxithromycin, Clarithromycin, Telithromycin* and *Azithromycin* are the later additions.

ERYTHROMYCIN

It was isolated from *Streptomyces erythreus* in 1952. Since then it has been widely employed, mainly as alternative to penicillin. Water solubility of erythromycin is limited, and the solution remains stable only when kept in cold.

Mechanism of action Erythromycin is bacteriostatic at low but cidal (for certain bacteria only) at high concentrations. Cidal action depends on the organism concerned and its rate of multiplication. Sensitive gram-positive bacteria accumulate erythromycin intracellularly by active transport which is responsible for their high susceptibility to this antibiotic. Activity is enhanced several fold in alkaline medium, because the nonionized (penetrable) form of the drug is favoured at higher pH.

Erythromycin acts by inhibiting bacterial protein synthesis. It combines with 50S ribosome subunits and interferes with 'translocation' (*see* Fig. 53.1). After peptide bond formation between the newly attached amino acid and the nacent peptide chain at the acceptor (A) site, the elongated peptide is translocated back to the peptidyl (P) site, making the A site available for next aminoacyl tRNA attachment. This is prevented by erythromycin and the ribosome fails to move along the mRNA to expose the next codon. As an indirect consequence, peptide chain may be prematurely terminated: synthesis of larger proteins is especifically suppressed.

Antimicrobial spectrum It is narrow, includes mostly gram-positive and a few gram-negative bacteria, and overlaps considerably with that of penicillin G. Erythromycin is highly active against *Str. pyogenes* and *Str. pneumoniae, N. gonorrhoeae, Clostridia, C. diphtheriae* and *Listeria,* but penicillin-resistant *Staphylococci* and *Streptococci* are now resistant to erythromycin also.

In addition, *Campylobacter, Legionella, Branhamella catarrhalis, Gardnerella vaginalis* and *Mycoplasma,* that are not affected by penicillin, are highly sensitive to erythromycin. Few others, including *H. ducreyi, H. influenzae, B. pertussis, Chlamydia trachomatis, Str. viridans, N. meningitidis* and *Rickettsiae* are moderately sensitive. Enterobacteriaceae, other gram-negative bacilli and *B. fragilis* are not inhibited.

Resistance All cocci readily develop resistance to erythromycin, mostly by acquiring the capacity to pump it out. Resistant Enterobacteriaceae have been found to produce an erythromycin-esterase enzyme. Alteration in

the ribosomal binding site for erythromycin by a plasmid encoded methylase enzyme is an important mechanism of resistance in gram-positive bacteria. All the above types of resistance are plasmid mediated. Change in the 50S ribosome by chromosomal mutation reducing macrolide binding affinity occurs in some gram-positive bacteria.

Bacteria that develop resistance to erythromycin are cross resistant to other macrolides as well. Cross resistance with clindamycin and chloramphenicol also occurs, because the ribosomal binding sites for all these antibiotics are proximal to each other.

Pharmacokinetics Erythromycin base is acid labile. To protect it from gastric acid, it is given as enteric coated tablets, from which absorption is incomplete and food delays absorption by retarding gastric emptying. Its acid stable esters are better absorbed.

Erythromycin is widely distributed in the body, enters cells and into abscesses, crosses serous membranes and placenta, but not blood-brain barrier. Therapeutic concentration is attained in the prostate. It is 70–80% plasma protein bound, partly metabolized and excreted primarily in bile in the active form. Renal excretion is minor; dose need not be altered in renal failure. The plasma t½ is 1.5 hr, but erythromycin persists longer in tissues.

Preparations and dose

Dose: 250–500 mg 6 hourly (max. 4 g/day), children 30–60 mg/kg/day.

1. Erythromycin (base): ERYSAFE 250, mg tabs, EROMED 333 mg tab, 125 mg/5 ml susp.
2. Erythromycin stearate: blood levels produced are similar to those after erythromycin base. ERYTHROCIN 250, 500 mg tab, 100 mg/5 ml susp., 100 mg/ml ped. drops. ETROCIN, ERYSTER 250 mg tab, 100 mg/5 ml dry syr.
3. Erythromycin estolate (lauryl sulfate): it is relatively acid stable and better absorbed after oral administration. However, concentration of free and active drug in plasma may be the same as after administration of erythromycin base.

ALTHROCIN 250, 500 mg tab, 125 mg kid tab, 125 mg/5 ml and 250 mg/5 ml dry syr, 100 mg/ml ped. drops, E-MYCIN 100, 250 mg tab, 100 mg/5 ml dry syr, EMTHROCIN 250 mg tab, 125 mg/5 ml dry syr.

4. Erythromycin ethylsuccinate: well absorbed orally; ERYNATE 100 mg/5 ml dry syr, ERYTHROCIN 100 mg/ml drops, 125 mg/5 ml syr.

A 30% ointment (GERY OINTMENT) is marketed for topical treatment of boils, carbuncles and skin infections, but efficacy is doubtful.

Adverse effects Erythromycin base is a remarkably safe drug, but side effects do occur.

1. *Gastrointestinal* Mild-to-severe epigastric pain, nausea, anorexia is experienced by many patients, especially children, on oral ingestion. Diarrhoea is occasional.

Erythromycin stimulates motilin (an upper gastrointestinal peptide hormone) receptors in the g.i.t.—thereby induces gastric contractions, hastens gastric emptying and promotes intestinal motility without significant effect on colonic motility. On the basis of this action erythromycin has been occasionally used to afford short-term symptomatic relief in diabetic gastroparesis.Contribution of this action to the g.i. side effects of erythromycin is not known.

2. Very high doses of erythromycin have caused reversible hearing impairment.

3. *Hypersensitivity* Rashes, eosinophilia and fever are infrequent. Other allergic manifestations are rare with erythromycin base or esters other than estolate.

Hepatitis with cholestatic jaundice resembling viral hepatitis or extrahepatic biliary obstruction occurs with the estolate ester (rarely with ethyl succinate or stearate ester) after 1–3 weeks. Incidence is higher in pregnant women. The reaction clears on discontinuation of the drug, and is probably due to hypersensitivity to the estolate ester. Erythromycin base or other esters can be given to these patients without recurrence. Though the estolate is acid stable, tasteless and better absorbed, it has been banned in some countries (but not in India).

Interaction Erythromycin inhibits hepatic oxidation of many drugs. The clinically significant interactions are—rise in plasma levels of theophylline, carbamazepine, valproate, ergotamine and warfarin.

Several cases of Q-T prolongation, serious ventricular arrhythmias and death have been reported due to inhibition of CYP3A4 by erythromycin/clarithromycin resulting in high blood levels of concurrently administered terfenadine/astemizole/cisapride (*see* p. 181 and 715), because of which the latter drugs have been banned.

Uses

A. As an alternative to penicillin

1. Streptococcal pharyngitis, tonsillitis, mastoiditis and community acquired respiratory infections caused by pneumococci and *H. influenzae* respond to erythromycin as they do to penicillin. However, many bacteria resistant to penicillin are also resistant to erythromycin.
2. Diphtheria: For acute stage as well as for carriers—7 day treatment is recommended. Some prefer erythromyain over penicillin. Antitoxin is the primary treatment.
3. Tetanus: Erythromycin maybe used as an adjuvant to antitoxin, toxoid therapy.
4. Syphilis and gonorrhoea: Erythromycin is indicated only if other alternative drugs, including tetracyclines also cannot be used.
5. Leptospirosis: Erythromycin 250 mg 6 hourly for 7 days in patients allergic to penicillins.

B. As a first choice drug for

1. Atypical pneumonia caused by *Mycoplasma pneumoniae*: rate of recovery is hastened.
2. Whooping cough: a 1–2 week course of erythromycin is the most effective treatment for eradicating *B. pertussis* from upper respiratory tract. However, effect on the symptoms depends on the stage of disease when treatment is started.
   (a) Prophylactic: during the 10 day incubation period—disease is prevented.
   (b) Catarrhal stage: which lasts for about a week—erythromycin may abort the next stage or reduce its duration and severity.
   (c) Paroxysmal stage: lasting 2–4 weeks—no effect on the duration and severity of 'croup' despite eradication of the causative organism.
   (d) Convalescent stage: during which 'croup' gradually resolves (4–12 weeks)—is not modified.

Azithromycin, clarithromycin, and chloramphenicol are the alternative antimicrobials. Cough sedatives are not very effective. Corticosteroids may reduce the duration of paroxysmal stage but increase the risk of superinfections and carrier stage; they should be reserved for severe cases only. Adrenergic β_2 stimulants may reduce the severity of paroxysms, and are more useful in infants.

3. Chancroid : erythromycin 2 g/day for 7 days is one of the first line drugs, as effective as single dose azithromycin or ceftriaxone (*see* p. 813).

C. As a second choice drug in

1. *Campylobacter* enteritis: duration of diarrhoea and presence of organisms in stools is reduced. However, fluoroquinolones are superior.
2. Legionnaires' pneumonia: 3 week erythromycin treatment is effective, but azithromycin/ciprofloxacin are preferred.
3. *Chlamydia trachomatis* infection of urogenital tract: erythromycin 500 mg 6 hourly for 7 days is an effective alternative to single dose azithromycin (*see* p. 813).

NEWER MACROLIDES

In an attempt to overcome the limitations of erythromycin like narrow spectrum, gastric intolerance, gastric acid lability, low oral bioavailability, poor tissue penetration and short half-life, a number of semisynthetic macrolides have been produced, of which clarithromycin, azithromycin, roxithromycin and telithromycin are available.

Clarithromycin The antimicrobial spectrum of clarithromycin is similar to that of erythromycin; in addition, it includes *Mycobact. avium* complex (MAC), other atypical mycobacteria, *Mycobact. leprae* and some anaerobes but not *Bact. fragilis*. It is more active against *Helicobacter pylori*, *Moraxella*, *Legionella*, *Mycoplasma pneumoniae* and sensitve strains of gram-positive bacteria. However, bacteria that have developed resistance to erythromycin are resistant to clarithromycin as well.

Clarithromycin is more acid-stable than erythromycin, and is rapidly absorbed; oral bioavailability is ~50% due to first pass metabolism; food delays but does not decrease absorption. It has slightly larger tissue distribution than erythromycin and is metabolized by saturation kinetics—t½ is prolonged from 4–6 hours at lower doses to 6–9 hours at higher doses. An active metabolite is produced, so that clarithromycin can be given twice daily. About 1/3 of an oral dose is excreted unchanged in urine, but no dose modification is needed in liver disease or in mild-to-moderate kidney failure.

CHAPTER 55

Clarithromycin is indicated in upper and lower respiratory tract infections, sinusitis, otitis media, whooping cough, atypical pneumonia, skin and skin structure infections due to *Strep. pyogenes* and some *Staph. aureus*. Used as a component of triple drug regimen (*see* p. 705–06) it eradicates *H. pylori* in 1–2 weeks. It is a first line drug in combination regimens for MAC infection in AIDS patients and a second line drug for other atypical mycobacterial diseases as well as leprosy.

Dose: 250 mg BD for 7 days; severe cases 500 mg BD up to 14 days.

CLARIBID 250, 500 mg tabs, 250 mg/5 ml dry syr; CLARIMAC 250, 500 mg tabs; SYNCLAR 250 mg tab, 125 mg/5 ml dry syr.

Side effects of clarithromycin are similar to those of erythromycin, but gastric tolerance is better. High doses can cause reversible hearing loss. Few cases of pseudomembranous enterocolitis, hepatic dysfunction or rhabdomyolysis are reported. Its safety in pregnancy and lactation is not known. Clarithromycin inhibits CYP3A4, and the drug interaction potential is similar to erythromycin.

Azithromycin This azalide congener of erythromycin has an expanded spectrum, improved pharmacokinetics, better tolerability and drug interaction profiles. Azithromycin is more active than other macrolides against *H. influenzae*, but less active against gram-positive cocci. High activity is exerted on respiratory pathogens—*Mycoplasma, Chlamydia pneumoniae, Legionella, Moraxella* and on others like *Campylobacter, Ch. trachomatis, H. ducreyi, Calymm. granulomatis, N. gonorrhoeae*. However, it is not active against erythromycin-resistant bacteria. Penicillinase producing *Staph. aureus* are inhibited but not ~~MRSA~~. Good activity is noted against MAC.

The improved pharmacokinetic properties are acid-stability, rapid oral absorption (from empty stomach), larger tissue distribution and intracellular penetration. Concentration in most tissues exceeds that in plasma. High concentrations are attained inside macrophages and fibroblasts; volume of distribution is ~30 L/kg. Slow release from the intracellular sites contributes to its long terminal t½ of >50 hr. It is largely excreted unchanged in bile, renal excretion is ~ 10%.

Because of higher efficacy, better gastric tolerance and convenient once a day dosing, azithromycin is now preferred over erythromycin as **first choice** drug for infections such as:

- *Legionnaires'* pneumonia: 500 mg OD oral/i.v. for 2 weeks. Erythromycin or a FQ are the alternatives.
- *Chlamydia trachomatis*: nonspecific urethritis and genital infections in both men and women —1 g single dose is curative, while 3 weekly doses are required for lymphogranuloma venereum (*see* p. 813). It is also the drug of choice for chlamydial pneumonia and is being preferred over tetracycline for trachoma in the eye.
- Donovanosis caused by *Calymmatobacterium granulomatis:* 500 mg OD for 7 days or 1.0 g weekly for 4 weeks is as effective as doxycycline.
- Chancroid and PPNG urethritis: single 1.0 g dose is highly curative; may be combined with ceftriaxone (*see* p. 813).

The other indications of azithromycin are pharyngitis, tonsillitis, sinusitis, otitis media, community-acquired pneumonia (CAP), acute exacerbations of chronic bronchitis. In combination with at least one other drug it is effective in the prophylaxis and treatment of MAC infection in AIDS patients. Other potential uses are in multidrug resistant typhoid fever in patients allergic to cephalosporins; and in toxoplasmosis.

Dose: 500 mg once daily 1 hour before or 2 hours after food (food decreases bioavailability); (children above 6 month—10 mg/kg/day) for 3 days is sufficient for most infections.

AZITHRAL 250, 500 mg cap and 250 mg per 5 ml dry syr; AZIWOK 250 mg cap, 100 mg kid tab, 100 mg/5 ml and 200 mg/5 ml susp. AZIWIN 100, 250, 500 mg tab, 200 mg/5 ml liq. Also AZITHRAL 500 mg inj.

Fixed dose combination of azithromycin with cefixime is banned in India.

Side effects are mild gastric upset, abdominal pain (less than erythromycin), headache and

dizziness. Azithromycin has been found not to affect hepatic CYP3A4 enzyme. Interaction with theophylline, carbamazepine, warfarin, terfenadine and cisapride is not likely, but caution may be exercised.

Roxithromycin It is a semisynthetic longer-acting acid-stable macrolide whose antimicrobial spectrum resembles closely with that of erythromycin. Good enteral absorption and an average plasma t½ of 12 hr makes it suitable for twice daily dosing. It is an alternative to erythromycin for respiratory, ENT, skin, soft tissue and genital tract infections.

Dose: 150–300 mg BD 30 min before meals, children 2.5–5 mg/kg BD.

ROXID, ROXIBID, RULIDE 150, 300 mg tab, 50 mg kid tab, 50 mg /5 ml liquid; ROXEM 50 mg kid tab, 150 mg tab.

Telithromycin It is a ketolide congener of erythromycin with similar antibacterial spectrum, but active against many penicillin and erythromycin resistant *Strep. pneumoniae*, as well as *B. fragilis* and some nontuberculous mycobacteria. Oral telithromycin is ~ 60% bioavailable, has good tissue penetration and is eliminated in both urine and bile with a t½ of 12 hours. It inhibits CYP3A4 and has potential to prolong QTc interval. Therefore, the drug interaction potential is similar to that of erythromycin. It should not be given with other drugs which prolong QTc. Common side effects are abdominal pain, nausea, diarrhoea and taste disturbance. Due to reports of serious hepatitis, the clinical use of telithromycin is restricted to CAP, sinusitis and exacerbations of chronic bronchitis caused by penicillin and erythromycin resistant *Strep. pneumoniae* and other streptococci.

Dose: 800 mg OD for not more than 7–10 days.

KETEK 400 mg tab.

Spiramycin This macrolide antibiotic, though available for more than two decades, has been employed only sporadically. It resembles erythromycin in spectrum of activity and properties. Distinctively, it has been found to limit risk of transplacental transmission of *Toxoplasma gondii* infection. Its specific utility is for toxoplasmosis and recurrent abortion in pregnant women; 3 week courses of 3 MU 2–3 times a day are repeated after 2 week gaps till delivery. Other indications are similar to erythromycin, for which 6 MU/day is given for 5 days. Side effects are gastric irritation, nausea, diarrhoea and rashes.

ROVAMYCIN 1.5 MU, 3 MU tabs, 0.375 MU/ 5 ml susp.

LINCOSAMIDE ANTIBIOTICS

Clindamycin

This chlorinated lincosamide antibiotic is similar in mechanism of action (inhibits protein synthesis by binding to 50S ribosome) and spectrum of activity to erythromycin with which it exhibits partial cross resistance. Modification of the ribosomal binding site by the constitutive methylase enzyme confirs resistance to both, but not the inducible methylase. Antibiotic efflux is not an important mechanism of clindamycin resistance. Clindamycin inhibits most gram-positive cocci (including most species of streptococci, penicillinase producing *Staph.*, but not MRSA), *C. diphtheriae*, *Nocardia*, *Actinomyces*, *Toxoplasma* and has slow action on *Plasmodia*. However, the distinctive feature is its high activity against a variety of anaerobes, especially *Bact. fragilis*. Aerobic gram-negative bacilli, enterococci, spirochetes, *Chlamydia*, *Mycoplasma* and *Rickettsia* are not affected.

Oral absorption of clindamycin is good. It penetrates into most skeletal and soft tissues, but not in brain and CSF; accumulates in neutrophils and macrophages. It is largely metabolized and metabolites are excreted in urine and bile. The t½ is 3 hr.

Side effects are rashes, urticaria, abdominal pain, but the major problem is diarrhoea and pseudomembranous enterocolitis due to *Clostridium difficile* superinfection which is potentially fatal. The drug should be promptly stopped and oral metronidazole (alternatively vancomycin) given to treat it. Liver damage is occasional. Thrombophlebitis of the injected vein can occur on i.v. administration.

Because of the potential toxicity, use of clindamycin is restricted to anaerobic and mixed infections, especially those involving *Bact. fragilis* causing abdominal, pelvic and lung abscesses, septic abortion, penetrating injuries. It is a first line drug for these conditions, and is generally combined with an aminoglycoside or a cephalosporin. Metronidazole and chloramphenicol are the alternatives to clindamycin for covering the anaerobes. Skin and soft tissue infections in patients allergic to penicillins can be treated with clindamycin. Anaerobic streptococcal and *Cl. perfringens* infections, especially those involving bone and joints respond well.

It has also been employed for prophylaxis of endocarditis in penicillin allergic patients with valvular defects who undergo dental surgery, as well as to prevent surgical site infection in colorectal/pelvic surgery.

In AIDS patients, it has been combined with pyrimethamine for toxoplasmosis and with primaquine for *Pneumocystis jiroveci* pneumonia. Clindamycin is an alternative to doxycycline for supplementing quinine/artesunate in treating multidrug resistant falciparum malaria. Topically it is used for infected acne vulgaris.

Clindamycin, erythromycin and chloramphenicol can exhibit mutual antagonism, probably because their ribosomal binding sites are proximal; binding of one hinders access of the other to its target site. Clindamycin slightly potentiates neuromuscular blockers.

Dose: 150–300 mg (children 3–6 mg/kg) QID oral; 200–600 mg i.v. 8 hourly; DALCAP 150 mg cap; CLINCIN 150, 300 mg cap; DALCIN, DALCINEX 150, 300 mg cap, 300 mg/2 ml and 600 mg/4 ml inj. ACNESOL, CLINDAC-A 1% topical solution and gel.

Lincomycin

It is the forerunner of clindamycin; has similar antibacterial and toxic properties, but is less potent and produces a higher incidence of diarrhoea and colitis—deaths have occurred. Thus, it has been largely replaced by clindamycin.

Dose: 500 mg TDS-QID oral; 600 mg i.m. or by i.v. infusion 6–12 hrly.

LINCOCIN 500 mg cap, 600 mg/2 ml inj; LYNX 250, 500 mg cap, 125 mg/5 ml syr, 300 mg/ml inj in 1, 2 ml amp.

GLYCOPEPTIDE ANTIBIOTICS

Vancomycin

It is a glycopeptide antibiotic discovered in 1956 as a penicillin substitute which assumed special significance due to efficacy against MRSA. *Strep. viridans, Enterococcus* and *Cl. difficile*. Bactericidal action is exerted only on gram-positive cocci, *Neisseria, Clostridia* and diphtheroids. However, in hospitals where it has been extensively used for surgical prophylaxis, etc., vancomycin-resistant *Staph. aureus* (VRSA) and vancomycin-resistant *Enterococcus* (VRE) have emerged. These nosocomial bacteria are resistant to methicillin and most other antibiotics as well. Gram-negative bacilli are inherently non-responsive to vancomycin.

Vancomycin acts by inhibiting bacterial cell wall synthesis. It binds to the terminal dipeptide 'D-Ala-D-Ala' sequence of peptidoglycan units—prevents its release from the bactoprenol lipid carrier so that assembly of the units at the cell membrane and their cross linking to form the cell wall cannot take place (*see* Fig. 52.2). Enterococcal resistance to vancomycin is due to a plasmid mediated alteration of the D-Ala–D-Ala dipeptide target site, reducing its affinity for vancomycin.

Vancomycin is not absorbed orally. After i.v. administration, it is widely distributed, penetrates serous cavities, inflamed meninges and is excreted mainly unchanged by glomerular filtration with a t½ of 6 hours. Dose reduction is needed in renal insufficiency.

Toxicity: Systemic toxicity of vancomycin is relatively high. It can cause concentration-dependent nerve deafness which may be permanent. Kidney damage is also dose-related. Other oto- and nephrotoxic drugs like aminoglycosides must be very carefully administered when vancomycin is being used. Skin allergy and fall in BP during i.v. injection can occur. Vancomycin has the potential to release histamine by direct action on mast cells. Rapid i.v. injection has caused chills, fever, urticaria and intense flushing—called 'Red man syndrome'.

Uses: Given orally (125–500 mg 6 hourly), it is the second choice drug to metronidazole for antibiotic associated pseudomembranous enterocolitis caused by *C. difficile*. However, some experts recommend vancomycin as the preferred drug over metronidazole for serious cases. Staphylococcal enterocolitis is another indication of oral vancomycin.

Systemic use (500 mg 6 hourly or 1 g 12 hourly infused i.v. over 1 hr) is restricted to serious MRSA infections for which it is the most effective drug, and as a penicillin substitute (in allergic patients) for enterococcal endocarditis along with gentamicin. It is an alternative drug

for serious skin, soft tissue and skeletal infections in which gram-positive bacteria are mostly causative. For empirical therapy of bacterial meningitis, i.v. vancomycin is usually combined with i.v. ceftriaxone/cefotaxime. It is also used in dialysis patients and those undergoing cancer chemotherapy. Penicillin-resistant pneumococcal infections and infection caused by diphtheroids respond very well to vancomycin.

Vancomycin is the preferred surgical prophylactic in MRSA prevalent areas and in penicillin allergic patients.

VANCOCIN-CP, VANCOGEN, VANCORID-CP 500 mg/vial inj; VANCOLED 0.5, 1.0 g inj. VANCOMYCIN 500 mg tab, VANLID 250 mg cap, 500 mg/vial inj.

Teicoplanin

This glycopeptide antibiotic is a mixture of 6 similar compounds, active against gram-positive bacteria only. The mechanism of action and spectrum of activity is similar to vancomycin. Notable features are:

- It is more active than vancomycin against enterococci, and equally active against MRSA.
- Some VRE but not VRSA are susceptible to teicoplanin.
- It can be injected i.m. as well; is largely excreted unchanged by kidney; dose needs to be reduced in renal insufficiency; has a very long t½ (2–3 days); suitable for once daily dosing.
- Renal toxicity is less than vancomycin. Adverse effects are rashes, itching, bronchospasm, fever, granulocytopenia and occasionally hearing loss. Reactions due to histamine release are rare (1 in 2500).

Teicoplanin is indicated in enterococcal endocarditis (along with gentamicin); MRSA and penicillin resistant streptococcal infections, osteomyelitis and as alternative to vancomycin for surgical prophylaxis, etc.

Dose: 400 mg first day—then 200 mg daily i.v. or i.m.; severe infection 400 mg × 3 doses 12 hourly—then 400 mg daily.

TARGOCID, TECOPLAN, TECOCIN 200, 400 mg per vial inj. for reconstitution.

OXAZOLIDINONES

Linezolid

This is the first member of a new class of synthetic AMAs 'Oxazolidinones' useful in the treatment of resistant gram-positive coccal (aerobic and anaerobic) and bacillary infections. Linezolid is active against MRSA and some VRSA, VRE, penicillin-resistant *Strep. pyogenes*, *Strep. viridans* and *Strep. pneumoniae*. Other sensitive bacteria are *Corynebacterium, Listeria, Clostridia, Bact. fragilis* and *M. tuberculosis*. It is primarily bacteriostatic, but can exert cidal action against some streptococci, pneumococci and *B. fragilis*. Gram-negative bacteria are not affected.

Linezolid inhibits bacterial protein synthesis by acting at an early step and a site different from that of other AMAs. It binds to the 23S fraction (P site) of the 50S ribosome (*see* Fig. 53.1) and interferes with formation of the ternary N-formylmethionine-tRNA ($tRNA^{fMet}$)-70S initiation complex. Linezolid stops protein synthesis before it starts. As such, there is no cross resistance with any other class of AMAs. Linezolid resistance due to mutation of 23S ribosomal RNA has been detected among enterococci.

Linezolid is rapidly and completely absorbed orally, partly metabolized nonenzymatically and excreted in urine. Plasma t½ is 5 hrs. Dose modification has not been necessary in renal insufficiency.

Linezolid given orally or i.v. is used for uncomplicated and complicated skin and soft tissue infections, hospital-acquired pneumonias (HAPs), bacteraemias and other drug-resistant gram-positive infections with high cure rates. However, in order to prevent emergence of resistance, use should be restricted to serious HAPs, febrile neutropenia, wound infections and others caused by multidrug-resistant gram-positive bacteria such as VRE, vancomycin resistant-MRSA, multi-resistant *S. pneumoniae*, etc. Being bacteriostatic, it is not suitable for treatment of enterococcal endocarditis. Linezolid is used as a reserve drug for extensively drug resistant (XDR) TB.

Dose: 600 mg BD, oral/ i.v.; LIZOLID 600 mg tab; LINOX, LINOSPAN 600 mg tab, 600 mg/300 ml i.v. infusion.

Side effects to linezolid have been few; mostly mild abdominal pain, nausea, taste disturbance and diarrhoea. Occasionally, rashes, pruritus and headache have been reported. The primary toxicity is haematologic. Thrombocytopenia, neutropenia and anaemia occur mostly after prolonged use (>2 weeks), but are generally mild and reversible on stoppage. Optic and peripheral neuropathy may develop when linezolid is given for >4 weeks. Serotonin syndrome (*see* p. 488) has occurred when linezolid was given to patients taking serotonergic drugs, like selective serotonin reuptake inhibitors (SSRIs), probably because linezolid is a weak MAO inhibitor. However, no cytochrome P450 enzyme related interactions have been reported.

Tedizolid It is a new oxazolidinone, approved by US-FDA in 2014 for the treatment of acute skin and skin structure infections caused by gram +ive bacteria, including MRSA. Tedizolid is active only against gram +ive bacteria and exerts strong inhibitory effect (4-8 fold more potent than linezolid) on *Staphylococci*, *Enterococci*, *Streptococci* including MRSA VRE as well as some linezolid-resistant phenotypes. Its mechanism of action (binding to 23S ribosome) is similar to that of linezolid. In clinical trials on patients with acute skin and soft tissue infections, tedizolid 200 mg once daily was found to be equally effective as linezolid 600 mg twice daily, both taken for 6 days. It has also been successfully used to treat HAP and ventilator-associated pneumonia (VAP) caused by gram +ive bacteria.

Administered as inactive phosphate salt, free and active tedizolid is released by phosphatases. Oral bioavilability is high (~90%), and it is excreted by liver as sulfate conjugate with a t½ of 12 hours. No dose adjustment is needed in hepatic or renal disease. In clinical trials, tedizolid was better tolerated than linezolid, and appears to have lower potential for causing haematological disorders or neuropathy. However, it is also a weak MAO inhibitor, but there is no data on drug interactions. Thus, the distinctive features of tedizolid are—enhanced activity against gram +ive bacteria, once daily dosing, oral as well as i.v. route of administration, and possibly favourable adverse effect profile.

MISCELLANEOUS ANTIBIOTICS

Spectinomycin It is a chemically distinct (aminocyclitol), narrow spectrum, bacteriostatic antibiotic which inhibits a limited number of gram-negative bacteria, notably *Neisseria gonorrhoeae*. Spectinomycin acts by binding to 30S ribosome and inhibiting bacterial protein synthesis, but the action is distinct from that of aminoglycosides. The single approved indication of spectinomycin is treatment of drug resistant gonorrhoea, or when the first line drugs (β-lactams/macrolides, etc.) can not be used due to allergy or other contraindication.

Dose: 2.0 g i.m. single dose; for less responsive cases 4.0 g (2.0 g at 2 sites).

SPECTIN, TROBICIN 2.0 g/vial inj.

The single dose produces pain at injection site; chills, fever and urticaria. Repeated doses may cause anaemia, renal and hepatic impairment.

Quinupristin/Dalfopristin This is a combination of two semisynthetic streptogramins in 30:70 ratio which together exerts rapid bactericidal effect on many gram +ive organisms. Quinupristin binds to the same site on bacterial 50S ribosome as erythromycin, while dalfopristin binds to an adjacent site to exert synergistic inhibition of protein synthesis. It is cidal against most gram +ive cocci including. MRSA, penicillin resistant *Strep. pneumoniae* and static against *E. faecium*, but not active on ~~*E. faecalis*~~.

Administered by i.v. infusion over 60 min in a dose of 7.5 mg/kg every 8–12 hours, it is used as a reserve drug for multidrug resistant nosocomial gram +ive infections, especially those caused by MRSA, VRSA, *Strep. pneumoniae*, VRE, but not *E. faecalis*. Both components are rapidly metabolized in the liver with a t½ of 40–50 min, and excreted in faeces. Dose reduction is needed in liver disease. Muscle, joint, and injection site pain is the common adverse effect. They inhibit CYP3A4 and can interact with drugs metabolized by this enzyme.

SYNERCID: Quinupristin 150 mg + dalfopristin 350 mg (total 500 mg) per vial inj.

Daptomycin It is a lipopeptide antibiotic which has a unique mechanism of action. The lipoidal tail of daptomycin molecules gets inserted in the bacterial cell membrane followed by aggregation of several molecules to form a pore through which K^+ and other ions leak out and the membrane gets depolarized. Synthesis of DNA, RNA and proteins is consequently inhibited, and the cell is killed. It is bactericidal against only gram +ive bacteria, including MRSA, VRSA, multidrug resistant streptococci, VRE and corynebacteria. Daptomycin is indicated for the treatment of complicated skin and soft tissue infections caused by *Staph. aureus* including MRSA, VRSA and staphylococcal bacteraemia, but not for ~~pneumonia~~ because the pulmonary surfactant binds and inactivates it. Daptomycin can be used for VRSA endocarditis, but efficacy against enterococcal endocarditis is not established. Resistance can develop during daptomycin therapy.

Administered i.v. daptomycin is mostly excreted unchanged in urine with a biological t½ of 7–11 hours. The t½ is prolonged in renal insufficiency. The specific toxicity daptomycin is myopathy and risk of rhabdomyolysis, especially if given with statins. It has also caused eosinophilic pneumonia when used for >2 weeks. Side effects are abdominal pain, arthralgia, insomnia, pruritus, dyspnoea and injection site reaction.

Dose: Skin and soft tissue infection 4 mg/kg i.v. OD; for bacteraemia and endocarditis 6 mg/kg OD i.v.
DAPTOCURE 350 mg/vial for slow i.v. injection after reconstitution.

Mupirocin This topically used antibiotic obtained from a species of *Pseudomonas* is active mainly against gram-positive bacteria, including *Strep. pyogenes* (penicillin sensitive/resistant), *Staph. aureus*, MRSA, etc. It inhibits bacterial protein synthesis by blocking the production of t-RNA for isoleucin. As such, no cross resistance with any other antibiotic is seen. Though primarily bacteriostatic, high concentrations applied topically may be bactericidal. It is indicated in furunculosis, folliculitis, impetigo, infected insect bites and small wounds. Local itching, irritation and redness may occur.
BACTROBAN, MUPIN, T-BACT 2% oint. for topical application thrice daily.

Fusidic acid It is a narrow spectrum steroidal antibiotic, blocks bacterial protein synthesis. It is active against penicillinase producing *Staphylococci* and few other gram-positive bacteria. It is used only topically for boils, folliculitis, sycosis barbae and other cutaneous infections.
FUCIDIN-L, FUCIBACT, FUSIDERM; 2% oint. and cream.

POLYPEPTIDE ANTIBIOTICS

These are low molecular weight cationic polypeptide antibiotics. All are powerful bactericidal agents, but not used systemically due to toxicity. All are produced by bacteria. Clinically used ones are:

Polymyxin B
Colistin
Bacitracin

Polymyxin B and Colistin Polymyxin and colistin are basic polypeptides which were obtained in the late 1940s from *Bacillus polymyxa* and *B. colistinus* respectively. They are active against gram-negative bacteria only; all except *Proteus*, *Serratia* and *Neisseria* are inhibited. Both have very similar range of activity, but colistin is more potent on *Pseudomonas, Salmonella* and *Shigella.*

Mechanism of action Polymyxin B and colistin are rapidly acting bactericidal agents. They have a detergent-like action on the cell membrane. Due to high affinity for phospholipids, the peptide molecules (or their aggregates) orient between the phospholipid and protein films in gram-negative bacterial cell membrane causing membrane distortion or pseudopore formation. As a result ions, amino acids, etc. leak out. Sensitive bacteria take up more of the antibiotic. These antibiotics may also inactivate the bacterial endotoxin.

They exhibit synergism with many other AMAs by improving their penetration into the bacterial cell.

Resistance Resistance to these antibiotics has never been a problem. There is no cross resistance with any other AMA.

Adverse effects Little or no absorption occurs from oral route or even from denuded skin (burn, ulcers). Applied topically, they are safe—no systemic effect or sensitization occurs. A rash is rare. Given orally, side effects are limited to the g.i.t.—occasional nausea, vomiting, diarrhoea.

Preparation and dose

Polymyxin B: (1 mg = 10,000 U)
NEOSPORIN POWDER: 5000 U with neomycin sulf. 3400 U and bacitracin 400 U per g.
NEOSPORIN EYE DROPS: 5000 U with neomycin sulf. 1700 U and gramicidin 0.25 mg per ml.
NEOSPORIN-H EAR DROPS: 10,000 U with neomycin sulf. 3400 U and hydrocortisone 10 mg per ml.

Colistin sulfate: 25–100 mg TDS oral
WALAMYCIN 12.5 mg (25000 i.u.) per 5 ml dry syr, COLISTOP 12.5 mg/5 ml and 25 mg/5 ml dry syr.

Uses

(a) *Topically* Usually in combination with other antimicrobials for skin infections, burns, otitis externa, conjunctivitis, corneal ulcer—caused by gram-negative bacteria including *Pseudomonas*.
(b) *Orally* Gram-negative bacillary (*E. coli, Salmonella, Shigella*) diarrhoeas, especially in infants and children; *Pseudomonas* superinfection enteritis.

Bacitracin It is one of the earliest discovered antibiotics from a strain of *Bacillus subtilis*. In contrast to polymyxin, it is active mainly against gram-positive organisms (both cocci and bacilli). *Neisseria, H. influenzae* and few other bacteria are also affected.

It acts by inhibiting cell wall synthesis at a step earlier than that inhibited by penicillin. Subsequently, it increases the efflux of ions by binding to cell membrane. It is bactericidal.

Bacitracin is not absorbed orally. It is not given parenterally because of high toxicity, especially to the kidney. Use is restricted to topical application for infected wounds, ulcers, eye infections—generally in combination with neomycin, polymyxin, etc.
NEBASULF Bacitracin 250 U + neomycin 5 mg + sulfacetamide 60 mg/g powder, skin oint, eye oint; in NEOSPORIN 400 U/g powder (1 U = 26 μg).

Bacitracin does not penetrate intact skin, therefore, is of little value in furunculosis, boils, carbuncles, etc.

URINARY ANTISEPTICS

These are orally administered AMAs which attain antibacterial concentration only in urine, with no systemic antibacterial effect. Like many other drugs, they are concentrated in the kidney tubules, and are useful in lower urinary tract

infection ((UTI). They have been called *urinary antiseptics* because this may be considered as a form of local therapy. Nitrofurantoin and methenamine are two such agents; infrequently used now.

Nitrofurantoin

It is primarily bacteriostatic, but may be cidal at higher concentrations and in acidic urine, because its activity is enhanced at lower pH. Many gram-negative bacteria except *Ps. aeruginosa* and *Proteus* were susceptible, but due to development of resistance over time, activity is now restricted largely to *E. coli*. Resistance to nitrofurantoin does not develop during continued therapy. No cross resistance with any other AMA is known, though it antagonizes the bactericidal action of nalidixic acid. Susceptible bacteria enzymatically reduce nitrofurantoin to generate reactive intermediates which damage DNA and affect protein synthesis.

Pharmacokinetics Nitrofurantoin is well absorbed orally; rapidly metabolized in liver and other tissues; less than half is excreted unchanged in urine; plasma $t_{1/2}$ is 30–60 min. Antibacterial concentrations are not attained in blood or tissues. Probenecid inhibits its tubular secretion and reduces the concentration attained in urine—may interfere with its urinary antiseptic action. Renal excretion is reduced in azotaemic patients; effective concentrations may not be reached in the urine, while toxicity increases. As such, it is contraindicated in renal failure; also during pregnancy and in neonates.

Adverse effects Commonest is gastrointestinal intolerance—nausea, epigastric pain and diarrhoea.

An acute reaction with chills, fever and leucopenia occurs occasionally.

Peripheral neuritis and other neurological effects are reported with long-term use. Haemolytic anaemia is rare, except in G-6-PD deficiency. Liver damage and a pulmonary reaction with fibrosis on chronic use are infrequent events.

Urine of patients taking nitrofurantoin turns dark brown on exposure to air.

Use The only indication for nitrofurantoin is uncomplicated lower UTI not associated with prostatitis, but it is used only as a reserve drug now. Acute infections due to *E. coli* can be treated with 50–100 mg TDS (5–7 mg/kg/day) given for 5–10 days. These doses should not be used for > 2 weeks at a time. Suppressive long-term treatment of chronic lower UTI has been successful with 50 mg BD or 100 mg at bed time. This dose can also be employed for prophylaxis of urinary tract infection following catheterization or instrumentation of the lower urinary tract and in women with recurrent cystitis.

FURADANTIN, URIFAST 50, 100 mg tab, URINIF 100 mg tab..
NEPHROGESIC: Nitrofurantoin 50 mg + phenazopyridine 100 mg tab.

Methenamine (Hexamine)

It is hexamethylene-tetramine, which is inactive as such; but decomposes slowly in acidic urine to release formaldehyde which inhibits all bacteria. This drug exerts no antimicrobial activity in blood and tissues, including kidney parenchyma. Acidic urine is essential for its action; urinary pH must be kept below 5.5 by administering an organic acid which is excreted as such, e.g. mandelic acid or hippuric acid or ascorbic acid.

Methenamine is administered in enteric coated tablets to protect it from decomposing in gastric juice. Mandelic acid, given as methenamine mandelate, is excreted in urine →lowers urinary pH and promotes decomposition of methenamine. Lower urinary pH itself disfavours growth of urinary pathogens.

MANDELAMINE : Methenamine mandelate 0.5 g, 1 g tab: 1 g TDS or QID with fluid restriction (daily urine volume between 1–1.5 L) to ensure adequate concentration of formaldehyde in urine.

Methenamine is not an effective drug for acute urinary tract infections or for catheterization prophylaxis. Its use is restricted to chronic, resistant type of urinary tract infections, not involving kidney substance. Resistance to formaldehyde does not occur, but methenamine is rarely used now.

Adverse effects Gastritis can occur due to release of formaldehyde in stomach—patient compliance is poor due to this. Chemical cystitis and haematuria may develop with high doses given for long periods. CNS symptoms are produced occasionally.

URINARY ANALGESIC

Phenazopyridine It is an orange dye which exerts analgesic action in the urinary tract and affords symptomatic relief of burning sensation, dysuria and urgency due to cystitis. It does not have antibacterial property. Side effects are nausea and epigastric pain.
Dose: 200–400 mg TDS: PYRIDIUM 200 mg tab.

TREATMENT OF URINARY TRACT INFECTIONS

The general principles of use of AMAs for UTIs remain the same as for any other infection. Some specific considerations are highlighted below.

Most UTIs are caused by gram-negative bacteria, especially coliforms. Majority of acute infections involve a single organism (commonest is *E. coli*); chronic and recurrent infections may be mixed infections. Acute infections are largely self limiting; high urine flow rates with frequent bladder voiding may suffice. Many single dose antimicrobial treatments have been

successfully tried, but a three day regimen is considered optimal for lower UTIs. Upper UTIs (pyelonephritis) require more aggressive and longer treatment. Since pyelonephritis may damage the kidney or give rise to septicaemia, it may be treated with a potent parenteral antibacterial such as cefuroxime, cefoperazone, ceftriaxone, gentamicin or levofloxacin. The usual duration of treatment is 10–14 days, but longer treatment may be required. Prostatitis may need to be treated for 3–6 weeks.

Bacteriological investigations are very important to direct the choice of drug. Though, treatment may not wait till report comes, urine sample must be collected for bacteriology before commencing empirical therapy. Most AMAs attain high concentration in urine, smaller than usual doses may be effective in lower UTIs, because antibacterial action in urine is sufficient, mucosa takes care of itself. In upper UTI antimicrobial activity in kidney tissue is needed. Therefore, doses are similar to those for any systemic infection.

The least toxic and cheaper AMA should be used, just long enough to eradicate the pathogen. It is advisable to select a drug which does not disrupt normal gut and perineal flora. If recurrences are frequent, chronic suppressive treatment with cotrimoxazole, nitrofurantoin or cephalexin may be given.

The commonly used antimicrobial regimens for empirical therapy of uncomplicated acute UTI are given in the box. Choice of drug from this list should depend on current local sensitivity patterns.

Empirical antimicrobial regimens for acute UTI (all given orally for 3–5 days)*

1. Ciprofloxacin 250–500 mg 12 hourly
2. Ofloxacin 200–400 mg 12 hourly
3. Cotrimoxazole 960 mg 12 hourly
4. Cephalexin 250–500 mg 6 hourly
5. Cefpodoxime proxetil 200 mg 12 hourly
6. Amoxicillin + clavulanic acid (500 + 125 mg) 8 hourly
7. Nitrofurantoin 50 mg 8 hourly or 100 mg 12 hourly × 5–7 days

* For upper UTI (pyelonephritis), the same drugs may be given for 2 weeks. Nitrofurantoin is not suitable for pyelonephritis.

The status of AMAs (other than urinary antiseptics) in urinary tract infections is summarized below:

1. *Cotrimoxazole* (*see* p. 759) Though response rate and use have declined, cotrimoxazole may be employed empirically in acute UTI without bacteriological data, because majority of urinary pathogens, including *Chlamydia trachomatis*, are covered by cotrimoxazole. Given once daily at bed time, cotrimoxazole 480 mg is often used for prophylaxis of recurrent cystitis in women, as well as in catheterized patients. Because trimethoprim penetrates prostate well, cotrimoxazole is often selected for prostatitis. It should not be used to treat UTI during ~~pregnancy~~.

2. *Quinolones* (*see* p. 761-62) The first generation FQs, especially ciprofloxacin and ofloxacin are highly effective and currently the most popular drugs, because of potent action against gram-negative bacilli and low cost. However, to preserve their efficacy, use should be restricted. FQs are particularly valuable in complicated cases, those with prostatitis or indwelling catheters and for bacteria resistant to cotrimoxazole/ampicillin. Norfloxacin given for upto 12 weeks may achieve cure in chronic UTI. The FQs should not be given to ~~pregnant~~ women.

3. *Ampicillin/Amoxicillin* (*see* p. 772) These antibiotics were frequently used in the past as first choice drug for initial treatment of acute infections without bacteriological data, but higher failure and relapse rates have made them unreliable for empirical therapy. Many *E. coli* strains are now ampicillin-resistant. Amoxicillin + clavulanic acid is more frequently employed. Parenteral coamoxiclav is often combined with gentamicin for initial treatment of acute pyelonephritis.

4. *Piperacillin/Ticarcillin* These antibiotics are used only in serious *Pseudomonas* infection in patients with indwelling catheters or chronic urinary obstruction (prostatic hypertrophy,

calculi), and in hospitalized patients on the basis of *in vitro* sensitivity.

5. *Cephalosporins* Use of cephalosporins has increased, especially in women with nosocomial *Klebsiella* and *Proteus* infections. They should normally be employed only on the basis of sensitivity report, but empirical use for community-acquired UTI is also common. Some guidelines recommend them as one of the option for empirical treatment of acute lower UTI. Cephalexin given once daily is an alternative drug for prophylaxis of recurrent cystitis, especially in women likely to get pregnant.

6. *Gentamicin* (*see* p. 797) It is very effective against most urinary pathogens including *Pseudomonas*. However, because of narrow margin of safety and need for parenteral administration, it is generally used only on the basis of *in vitro* bacteriological sensitivity testing. In acute pyelonephritis gentamicin + parenteral amoxicillin-clavulanate, may be initiated empirically before bacteriological report becomes available. The newer aminoglycosides may be needed for hospital-acquired infections.

7. *Chloramphenicol* Though effective in many cases, use of chloramphenicol should be restricted (for fear of toxicity) to pyelonephritis in cases where the causative bacteria is sensitive only to this antibiotic.

8. *Tetracyclines* Tetracyclines are seldom effective now, because most urinary pathogens have become resistant. Though broad spectrum, they are used only on the basis of sensitivity report and in *Ch. trachomatis* cystitis.

Urinary pH in relation to use of AMAs

Certain AMAs act better in acidic urine, while others in alkaline urine (*see* Box). However, specific intervention to produce urine of desired reaction (by administering acidifying or alkalinizing agents) is seldom required (except for methenamine), because most drugs used in UTI attain high concentration in urine and minor changes in urinary pH do not affect clinical outcome. In case of inadequate response or in complicated cases, measurement of urinary pH and appropriate corrective measure may help.

Favourable urinary pH for antimicrobial action

Acidic	*Alkaline*	*pH immaterial*
Nitrofurantoin	Cotrimoxazole	Chloramphenicol
Methenamine	Aminoglycosides	Ampicillin
Tetracyclines	(Gentamicin, etc.)	
Cloxacillin	Cephalosporins	
	Fluoroquinolones	

In certain urease positive *Proteus* (they split urea present in urine into NH_3) infections it is impossible to acidify urine. In such cases, acidification should not be attempted and drugs which act better at higher pH should be used.

Urinary infection in patients with renal impairment

This is relatively difficult to treat because most AMAs attain lower urinary concentration. in the presence of renal impairment. Methenamine mandelate, tetracyclines (except doxycycline) and certain cephalosporins are contraindicated.

Nitrofurantoin, nalidixic acid and aminoglycosides are better avoided. Every effort must be made to cure the infection, because if it persists, kidneys may be further damaged. Bacteriological testing and followup cultures are a must to select the appropriate drug and to ensure eradication of the pathogen. Potassium salts and acidifying agents are contraindicated.

Prophylaxis for urinary tract infection

Prophylaxis may be given when:

(a) Women of child bearing age have recurrent cystitis.

(b) Catheterization or instrumentation inflicting trauma to the lining of the urinary tract is performed; bacteremia frequently occurs and injured lining is especially susceptible.

(c) Indwelling catheters are placed.

(d) Uncorrectable abnormalities of the urinary tract are present.

(e) Inoperable prostate enlargement or other chronic obstruction causes urinary stasis.

Table 55.1: Regimens for the treatment of sexually transmitted diseases

DISEASE/CAUSATIVE ORGANISM	*TREATMENT*	
	1st Choice	*Alternatives*
1. Gonorrhoea Nonpenicillinase producing (Non PPNG) Penicillinase producing (PPNG)	Amoxicillin 3 g oral, or / Ampicillin 3.5 g oral } + Probenecid 1 g oral single dose Ceftriaxone 1.0 g i.m. or / Cefuroxime 1.5 g i.m or } + Probenecid 1 g oral single dose Azithromycin 1.0 g oral single dose	Cefixime 400 mg once oral, or Doxycycline 100 mg BD × 7 days oral or Erythromycin 500 mg QID × 5 days oral
2. Syphilis Early (Primary, Secondary and Latent <1 yr)	Benzathine Pen. 2.4 MU i.m., 1–3 weekly inj., or Proc. Pen.G 1.2 MU i.m. daily × 10 days	Doxycycline 100 mg BD oral × 15 days or Ceftriaxone 1 g i.m. daily × 7 days, or Erythromycin 500 mg QID oral × 15 days
Late (>1 yr)	Benzathine Pen. 2.4 MU i.m. weekly × 4 weeks, or Proc. Pen.G 1.2 MU i.m. daily × 20 days	Doxycycline 100 mg BD for 30 days, or Ceftriaxone 1 g i.m./i.v. daily × 15 days.
3. *Chlamydia trachomatis* Nonspecific urethritis/ endocervicitis	Azithromycin 1 g oral single dose or Doxycycline 100 mg BD oral × 7 days	Erythromycin 500 mg QID oral × 7 days Levofloxacin 500 mg OD oral × 7 days
Lymphogranuloma venereum	Doxycycline 100 mg BD oral × 3 weeks or Azithromycin 1.0 g oral weekly × 3 weeks (aspirate fluctuant lymph node)	Erythromycin 500 mg QID oral × 3 weeks
4. Granuloma inguinale/ Donovanosis *(Calymm. granulomatis)*	Doxycycline 100 mg BD oral × 3 weeks or Azithromycin 500 mg OD oral × 7 days or 1.0 g weekly oral × 4 weeks	Erythromycin 500 mg QID oral × 3 weeks Ciprofloxacin 750 mg BD × 3 weeks
5. Chancroid *(H. ducreyi)*	Ceftriaxone 0.25 g i.m. single dose or Azithromycin 1.0 g oral single dose or Erythromycin 0.5 g QID oral × 7 days	Ciprofloxacin 500 mg BD oral × 3 days or Doxycycline 100 mg BD oral × 7 days
6. Genital Herpes simplex First episode	Acyclovir 400 mg 5 times a day/800 mg TDS oral × 10 days or / Valacyclovir 1.0 g BD oral × 10 days or / Famciclovir 250 mg TDS oral × 7–10 days } Does not prevent recurrences	
	(Acyclovir 5% oint locally 6 times a day × 10 days may afford relief in mild cases)	
Recurrent episode	The above drugs are given for 3–5 days (Topical acyclovir is ineffective)	
Suppressive treatment	Acyclovir 400 mg BD oral × 6–12 months or / Valacyclovir 500 mg OD oral × 6–12 months or / Famciclovir 250 mg BD oral × 6–12 months } upto 5 years treatment has been given	
7. Trichomonas vaginitis	Metronidazole 2 g single dose or 400 mg TDS × 7 days or Tinidazole 2 g single dose or 600 mg OD × 7 days (treat the male partner also if recurrent)	Clotrimazole 100 mg intravaginal every night × 6 to 12 days

The most frequently used drugs for prophylaxis or long-term suppressive treatment of lower UTI are:

- Cotrimoxazole 480 mg*
- Nitrofurantoin 100 mg*
- Norfloxacin 400 mg*
- Cephalexin 250 mg*

* All drugs are given once daily at bed time.

TREATMENT OF SEXUALLY TRANSMITTED DISEASES (STDs)

The effectiveness of various AMAs in treating different STDs is described with the individual drugs. The preferred drugs and regimens for important STDs are summarized in Table 55.1.

☞ PROBLEM DIRECTED STUDY

55.1 A 35-year-old woman came to the OPD with complaints of urinary urgency, pain and burning during urination, suprapubic discomfort and low-grade fluctuating fever for the past 2 days. She had 3–4 similar episodes over the last year, for which she took treatment from a local doctor. She is married, has 3 children and her last menstrual period was 10 days back. She is neither using nor is willing to use a contraceptive. Physical examination reveals tenderness in the suprapubic region and body temperature 100.4°F. A diagnosis of acute cystitis is made and she is advised to get urine culture and blood tests done.

(a) Should empirical antimicrobial treatment be started after urine sample has been taken for testing? If so, which drug(s) would be appropriate?

(b) Can any drug be given to rapidly relieve urinary symptoms?

(c) Should long-term prophylactic drug be prescribed in her case? If so, which drug would be suitable for her?

(see Appendix-1 for solution)

Chapter 56 Antitubercular Drugs

Tuberculosis is a chronic granulomatous disease and a major health problem in developing countries. About 1/3rd of the world's population is infected with *Mycobact. tuberculosis,* out of which 10–15% develop the disease over their life time. As per WHO statistics for 2014,[$] there were 9.6 million new TB cases globally, to which India was the highest contributor with 2.2 million cases. India has the dubious distinction of being the highest TB burden country for the past many years; where about 600 people die from TB every day. Thus, TB kills more adults in India than any other infectious disease. In 2012 the Government of India has declared TB to be a notifiable disease, so that any doctor who treats a TB patient, has to notify it to the Govt. Control and treatment of TB in India is covered under a National programme which provides free treatment to all TB cases. The Revised National Tuberculosis Control Programme (RNTCP) was launched in 1997, and its treatment guidelines have been successively revised, the last time in 2016.[*]

A new dimension got added in the 1980s due to spread of HIV with high prevalence of tuberculosis and *Mycobact. avium* complex (MAC) infection among these patients. India has a large load of HIV infected subjects (estimated 2.1 million living with HIV in 2015), and these persons have 10% risk of developing TB every year. Moreover, they are especially vulnerable to severe forms of tubercular/MAC infection. Emergence of 'multidrug resistant' (MDR) TB which now accounts for ~ 20% of previously treated, and 3.3% of new TB cases worldwide is a major challenge in antitubercular chemotherapy. As per latest survey, in India ~ 3% of new cases and 12–17% of previously treated patients have MDR-TB.

Remarkable progress has been made over the last 70 years since the introduction of *Streptomycin* in 1947 for the treatment of tuberculosis. Its full therapeutic potential could be utilized only after 1952 when *isoniazid* was produced to accompany it. The discovery of *ethambutol* in 1961, *rifampin* in 1962, and redefinition of the role of *pyrazinamide* has changed the strategies in the chemotherapy of tuberculosis. Since 1970 efficacy of short course (6–9 months) and domiciliary regimens has been demonstrated and clear-cut treatment guidelines have been formulated.

Fluoroquinolones (FQs) and some rifampin congeners are the later additions to the antimycobacterial drugs. Two novel drugs, *bedaquiline* and *delamanid* have been recently approved, and bedaquiline is being used as reserve drug.

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[*] RNTCP: Technical and operational guidelines for tuberculosis control in India, 2016; www.tbcindia. gov.in.

[$] Global tuberculosis report 2015; WHO, Geneva.

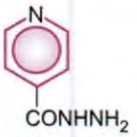
According to their clinical utility the anti-TB drugs can be divided into:

First line: These drugs have high antitubercular efficacy as well as low toxicity; are used routinely.

Second line: These drugs have either low antitubercular efficacy or higher toxicity or both; and are used when first line drugs cannot be used, or to supplement them.

Isoniazid (Isonicotinic acid hydrazide, H)

Isoniazid is an excellent antitubercular drug, and an essential component of all antitubercular regimens, unless the patient is not able to tolerate it or bacilli are resistant. It is primarily tuberculocidal. Fast multiplying organisms are rapidly killed, but quiescent ones are only inhibited. It



ISONIAZID

ANTITUBERCULAR DRUGS

First line drugs	Second line drugs		
	Fluoroquinolones	Other oral drugs	Injectable drugs
Isoniazid	Ofloxacin	Ethionamide	Kanamycin
Rifampin	Levofloxacin	Prothionamide	Amikacin
Pyrazinamide	Moxifloxacin	Cycloserine	Capreomycin
Ethambutol	Ciprofloxacin	Terizidone	
Streptomycin		Paraamino-salicylic acid (PAS)	
		Rifabutin	
		Rifapentine	

An alternative grouping of antitubercular drugs reflecting hierarchy in efficacy/priority in use has also been done.

ALTERNATIVE GROUPING*

ANTITUBERCULAR DRUGS

Group I First line oral drugs	Group II Injectable drugs	Group III Fluoroquinolones	Group IV Second line oral drugs	Group V Unclear efficacy drugs
Isoniazid	Streptomycin	Ofloxacin	Ethionamide	Bedaquiline
Rifampin	Kanamycin	Levofloxacin	Prothionamide	Clarithromycin
Pyrazinamide	Amikacin	Moxifloxacin	Cycloserine	Clofazimine
Ethambutol	Capreomycin	Ciprofloxacin	Terizidone	Linezolid
			Para amino-salicylic acid	Coamoxiclav
			Rifabutin	Imipenem/cilastatin
			Rifapentine	

*Adopted from: Treatment of tuberculosis guidelines; WHO (2010) and RNTCP: Technical and operational guidelines for tuberculosis control (2016)

Group I: are the most potent and best tolerated oral drugs used routinely.
Group II: are potent and bactericidal, but injectable drugs.
Group III: includes fluoroquinolones (FQs) which are well tolerated bactericidal oral drugs; all patients with drug resistant TB should receive one FQ.
Group IV: are less effective, bacteriostatic/more toxic oral drugs for resistant TB.
Group V: are drugs with uncertain efficacy; not recommended for MDR-TB; may be used as reserve drugs, and in extensively resistant TB (XDR-TB).

acts on extracellular as well as on intracellular TB (bacilli present within macrophages), and is equally active in acidic or alkaline medium. It is one of the cheapest antitubercular drugs. However, most nontubercular mycobacteria are not inhibited by INH.

The primary mechanism of action of INH is inhibition of synthesis of *mycolic acids* which are unique fatty acid components of mycobacterial cell wall. This may explain the high selectivity of INH for mycobacteria (it is not active against any other microorganism). The lipid content of mycobacteria exposed to INH is reduced. Two gene products labelled 'InhA' and 'KasA', which function in mycolic acid synthesis are the targets of INH action. INH enters sensitive mycobacteria which convert it by a catalase-peroxidase enzyme into a reactive metabolite. This then forms adduct with NAD that inhibits InhA and KasA. The reactive INH metabolite forms adduct with NADP as well which inhibits mycobacterial DHFRase resulting in interruption of DNA synthesis.

About 1 in 10^6 tubercle bacilli is inherently resistant to clinically attained INH concentrations. If INH is given alone, such bacilli proliferate selectively and after 2–3 months (sometimes even earlier) an apparently resistant infection emerges. The most common mechanism which confers high level INH resistance is by mutation of the catalase-peroxidase *(KatG)* gene so that the bacilli do not generate the reactive metabolite of INH. This type of resistance cannot be overcome; INH should be stopped. INH resistance may also involve mutation in the *inhA* gene. Low level INH resistance or that by inhA mutation resulting in overproduction of the carrier 'InhA; can be overcome by using 'high dose INH'. Resistance based on efflux of INH from the bacterial cell is also possible.

The incidence of primary INH resistance varies widely among different populations, depending on the extent of use and misuse of INH in that area. According to WHO, the global weighted mean of any INH resistance (excluding MDR) among new TB patients is 7.4%. In India resistance to INH alone or in combination with other anti-TB drugs is estimated to be 18%. No cross resistance with other antitubercular drugs occurs, and INH has good resistance preventing action when combined with other anti-TB drugs.

Pharmacokinetics INH is completely absorbed orally and penetrates all body tissues, tubercular cavities, placenta and meninges. It is extensively metabolized in liver; most important pathway being N-acetylation by NAT2. The acetylated metabolite is excreted in urine. The rate of INH acetylation shows genetic variation. There are either:

Fast acetylators
(30–40% of Indians) t½ of INH is 1 hr.
Slow acetylators
(60–70% of Indians) t½ of INH is 3 hr.

The proportion of fast and slow acetylators differs in different parts of the world. However, acetylator status does not matter if INH is taken daily, but biweekly regimens are less effective in fast acetylators. Isoniazid induced peripheral neuritis is more common in slow acetylators. A hepatotoxic minor metabolite is produced by CYP2E1 from acetylhydrazine.

Interactions Aluminium hydroxide inhibits INH absorption.

INH retards phenytoin, carbamazepine, diazepam, theophylline and warfarin metabolism by inhibiting CYP2C19 and CYP3A4, and may raise their blood levels. Since rifampin is an enzyme inducer, its concurrent use counteracts the inhibitory effect of INH. However, the net effect on metabolism of many drugs is unpredictable. PAS inhibits INH metabolism and prolongs its t½.

Dose of all first line drugs is given in Table 56.2.

Adverse effects INH is well tolerated by most patients. Peripheral neuritis and a variety of neurological manifestations (paresthesias, numbness, mental disturbances, rarely convulsions) are the most important dose-dependent toxic effects. These are due to interference with production of the active coenzyme pyridoxal

phosphate from pyridoxine, and its increased excretion in urine (*see* Ch. 69). Pyridoxine given prophylactically (10 mg/day) prevents the neurotoxicity even with higher doses. Prophylactic pyridoxine must be given to diabetics, chronic alcoholics, malnourished, pregnant, lactating and HIV infected patients, and when high dose INH is used. INH neurotoxicity is treated by pyridoxine 100 mg/day.

Hepatitis, a major adverse effect of INH, is rare in children, but more common in older people and in alcoholics (chronic alcoholism induces CYP2E1 which generates the hepatotoxic metabolite). INH must be stopped at the first sign of hepatotoxicity, which is due to dose-related damage to liver cells, and is reversible on stopping the drug.

Other side effects are lethargy, rashes, mild anaemia and arthralgia.

ISONEX 100, 300 mg tabs, ISOKIN 100 mg tab, 100 mg per 5 ml liq.

Rifampin (Rifampicin, R)

It is a semisynthetic derivative of rifamycin B obtained from *Streptomyces mediterranei*. Rifampin is bactericidal to *M. tuberculosis* and many other gram-positive and gram-negative bacteria like *Staph. aureus*, *N. meningitidis*, *H. influenzae*, *E. coli*, *Klebsiella*, *Pseudomonas*, *Proteus* and *Legionella*. Against TB bacilli, it is as efficacious as INH and better than all other drugs. The bactericidal action of rifampin covers all subpopulations of TB bacilli, but it acts best on slowly or intermittently dividing ones (spurters). *M. leprae* is also highly sensitive, while MAC and some other mycobacteria, but not *M. fortuitum*, are moderately susceptible. Both extra- and intracellular bacilli are affected, so that it has good sterilizing and resistance preventing actions.

Rifampin interrupts RNA synthesis by binding to β subunit of mycobacterial DNA-dependent RNA polymerase (encoded by *rpoB* gene) and blocking its polymerizing function. The basis of selective toxicity is that mammalian RNA polymerase does not avidly bind rifampin.

Mycobacteria and other organisms develop resistance to rifampin rather rapidly. However, the incidence of resistant bacilli is less than 10^{-7}, and it is quite unusual for a patient to have primary rifampin resistant tubercular infection. In India it is estimated to be 2%. Rifampin resistance is nearly always due to mutation in the *rpoB* gene reducing its affinity for the drug. No cross resistance with any other antitubercular drug, except rifampin congeners, has been noted.

Pharmacokinetics Rifampin is well absorbed orally (bioavailability is ~ 70%), but food decreases absorption; it is to be taken in empty stomach. It is widely distributed in the body: penetrates intracellularly, enters tubercular cavities, caseous masses and placenta. Though rifampin crosses meninges, it is largely pumped out from CNS by P-glycoprotein. It is metabolized in liver to an active deacetylated metabolite which is excreted mainly in bile, some in urine also. Rifampin and its desacetyl derivative undergo enterohepatic circulation. The t½ of rifampin is variable (2–5 hours).

Interactions Rifampin is a microsomal enzyme inducer—increases several CYP450 isoenzymes, including CYP3A4, CYP2D6, CYP1A2 and CYP2C subfamily. It thus enhances its own metabolism (area under the plasma concentration-time curve is reduced by ~35%) as well as that of many drugs including warfarin, oral contraceptives, corticosteroids, sulfonylureas, HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), theophylline, metoprolol, fluconazole, ketoconazole, clarithromycin, phenytoin, etc. Contraceptive failures have occurred. It is advisable to switch over to an oral contraceptive containing higher dose (50 μg) of estrogen or use alternative method of contraception.

Adverse effects The incidence of adverse effects is similar to that with INH.

- Hepatitis, a major adverse effect, generally occurs in patients with preexisting liver

disease and is dose-related. It is infrequent with ≤ 600 mg/day dose. Development of jaundice requires discontinuation of rifampin, after which it is reversible.

Minor reactions, usually not requiring drug withdrawal and more common with intermittent regimens, are:

- *Cutaneous*: flushing, pruritus + rash (especially on face and scalp), redness and watering of eyes.
- *Flu like symptoms:* chills, fever, headache, malaise and bone pain.
- Abdominal cramps, nausea, vomiting, diarrhoea.

Urine and secretions may become orange-red—but this is harmless.

Other serious but rare reactions are:

- Purpura, haemolysis, shock and renal failure.

Other uses of rifampin

1. Leprosy (*see* Ch. 57)
2. Prophylaxis of *Meningococcal* and *H. influenzae* meningitis and carrier state.
3. Second/third choice drug for MRSA, diphtheroids and *Legionella* infections.
4. Combination of doxycycline and rifampin is the first line therapy of brucellosis.

RCIN 150, 300, 450, 600 mg caps, 100 mg/5 ml susp. RIMACTANE, RIMPIN 150, 300, 450 mg caps, 100 mg/5 ml syr.; RIFAMYCIN 450 mg cap, ZUCOX 300, 450, 600 mg tabs; to be taken 1 hour before or 2 hour after meals.

Pyrazinamide (Z)

Chemically similar to INH, pyrazinamide (Z) was developed parallel to it in 1952. It is tuberculocidal but weaker than INH, and more active in acidic medium. It is more lethal to intracellularly located bacilli and to those at sites showing an inflammatory response, probably because pH is acidic at both these locations. Pyrazinamide, like INH, has no other use except in tuberculosis. It is highly effective during the first 2 months of therapy when inflammatory changes are present. By killing the residual intracellular bacilli it has good 'sterilizing' activity. Inclusion of pyrazinamide has enabled duration of treatment to be shortened and risk of relapse to be reduced. The mechanism of action of Z is not well established, but like INH it is also converted inside the mycobacterial cell into an active metabolite pyrazinoic acid by an enzyme (pyrazinamidase) encoded by the *pncA* gene. This metabolite gets accumulated in acidic medium and probably inhibits mycolic acid synthesis, but by interacting with a different fatty acid synthase than INH. Pyrazinoic acid also appears to disrupt mycobacterial cell membrane and its transport function. Resistance to Z develops rapidly if it is used alone, and is mostly due to mutation in the *pncA* gene.

Pyrazinamide is absorbed orally, widely distributed, has good penetration in CSF, because of which it is highly useful in meningeal TB; extensively metabolized in liver and excreted in urine; plasma t½ is 6–10 hours.

Hepatotoxicity is the most important dose-related adverse effect, but it appears to be less common in the Indian population than in western countries. Daily dose is now limited to 25–30 mg/kg which produces only a low incidence of hepatotoxicity. Pyrazinamide is contraindicated in patients with liver disease. It is now considered safe during pregnancy (*see* p. 827).

Hyperuricaemia is relatively common and is due to inhibition of uric acid secretion by kidney tubules: gout can occur.

Frequent adverse effects are abdominal distress and arthralgia. Flushing, rashes, fever and loss of diabetes control are occasional. Repeated blood glucose monitoring is warranted in diabetics.

PYZINA 0.5, 0.75, 1.0 g tabs, 0.3 g kid tab; PZA-CIBA 0.5, 0.75 g tabs, 250 mg/5 ml syr; RIZAP 0.75, 1.0 g tabs.

Ethambutol (E)

Ethambutol, a synthetic straight-chain compound, is selectively tuberculostatic and is active against MAC as well as some other mycobacteria, but not other types of bacteria. Fast multiplying bacilli are more susceptible. Added to the triple drug regimen of RHZ it has been found to hasten the rate of sputum conversion and to prevent development of resistance, the latter being the primary purpose of using it.

The mechanism of action of E is not fully understood, but it has been found to inhibit arabinosyl transferases (encoded by *embAB* genes) involved in arabinogalactan synthesis thereby interfering with mycolic acid incorporation in mycobacterial cell wall. Resistance to E develops slowly and is most commonly associated with mutation in *embB* gene, reducing the affinity of the target enzyme for E. No cross resistance with any other antitubercular drug has been noted.

About 3/4 of an oral dose of E is absorbed. It is distributed widely, but penetrates meninges incosistently; more when they are inflamed. Less than ½ of E is metabolized. It is excreted in urine by glomerular filtration and tubular secretion, as well as in faeces; plasma t½ is ~4 hrs. Caution is required in its use in patients with renal disease.

Patient acceptability of E is very good and side effects are few. Loss of visual acuity/colour vision, field defects due to retrobulbar neuritis is the most important dose and duration of therapy dependent toxicity. Patients should be instructed to stop the drug at the first indication of visual impairment. Because young children may be unable to report early visual impairment, it was contraindicated, but is now allowed with due precaution. With early recognition and stoppage of the drug, visual toxicity is largely reversible. Ethambutol produces few other symptoms: nausea, rashes, fever, rarely peripheral neuritis, and is safe during pregnancy. Ethambutol is used in MAC infection as well.

MYCOBUTOL, MYAMBUTOL, COMBUTOL 0.2, 0.4, 0.6, 0.8, 1.0 g tabs.

Streptomycin (S)

The pharmacology of streptomycin is described in Ch. 54. It was the first clinically useful antitubercular drug, and is tuberculocidal, but less effective than INH or rifampin. Streptomycin acts only on extracellular bacilli (because of poor penetration into cells). Thus, other drugs and host defence mechanisms are needed to eradicate the disease. It penetrates tubercular cavities, but does not cross to the CSF, and has poor action in acidic medium.

Resistance developed rapidly when streptomycin was used alone in tuberculosis—most patients had a relapse. Recent studies indicate worldwide increase in resistance to S. In case of S-resistant infection, it must be stopped at the earliest because of risk of S-dependence, in which case the infection flourishes when the drug is continued. Most nontubercular mycobacteria are unaffected by S.

Because of need for i.m. injections and lower margin of safety (ototoxicity and nephrotoxicity, especially in the elderly and in those with impaired renal function) S is used only in addition to other 1st line anti-TB drugs or as a reserve alternative. Use is restricted to a maximum of 2 months. It is thus also labelled as a 'supplemental' 1st line drug.

SECOND LINE ANTI-TB DRUGS

These are less effective and/or less well tolerated anti-TB drugs that are used only in case the bacilli are resistant to one or more 1st line drugs or when these are not tolerated/are contraindicated.

1. Kanamycin (Km), Amikacin (Am)

These aminoglycoside antibiotics (described in Ch. 54) are very similar to streptomycin in antitubercular activity, pharmacokinetic properties and types of adverse effects. Many S resistant and MDR strains of *M.tuberculosis* remain sensitive to them. One of these is mostly included in the regimen for MDR-TB during the intensive phase. The RNTCP standardized regimen for MDR-TB includes Km (probably because it is less expensive than Am), but in many countries Am is preferred, because it is considered less toxic. Cross resistance between Km and Am is very common. Both Km and Am produce less vestibular toxicity than hearing loss, but are equally nephrotoxic. Patients should be instructed to report vertigo and tinnitus. Audiometry and monitoring of renal function is recommended.

Dose: 0.75–1.0 g/day (10–15 mg/kg/day) i.m.

2. Capreomycin (Cm)

It is a cyclic peptide antibiotic, chemically very different from aminoglycosides, but with similar mycobactericidal activity, ototoxicity and nephrotoxicity. In addition, Cm often causes eosinophilia, rashes, fever and injection site pain. It has to be injected i.m. and is used only as alternative to aminoglycoside

antibiotics. Many *M.tuberculosis* isolates resistant to S and Am, as well as MDR-TB remain susceptible to Cm.
Dose: 0.75–1.0 g/day i.m.
KAPOCIN 0.5 g, 0.75 g, 1.0 g inj, CAPREOTEC 1.0 inj.

3. Fluoroquinolones (FQs)

Fluoroquinolones (FQs) like ofloxacin (Ofx), levofloxacin (Lfx), ciprofloxacin (Cfx) and moxifloxacin (Mfx) are relatively new potent oral bactericidal drugs for TB, that have gained prominence as well tolerated second line anti-TB drugs. They are active against MAC, *M. fortuitum* and some other atypical mycobacteria as well. Mfx is the most active FQ against *M.tuberculosis*, followed by Lvx, Ofx and Cfx in that order. On the other hand, Cfx is more active than Lfx against atypical mycobacteria, but is not used for *M. tuberculosis* now. The FQs penetrate cells and kill mycobacteria lodged inside macrophages as well.

The primary indication of FQs is for treatment of drug resistant TB (DR-TB). They have also been tried in 1st line regimens for new cases. Substitution of E with Mfx (but not with Lfx, Ofx or Cfx) to accompany RHZ in the four drug regimen has been found to enhance the rate of bacillary killing and cause faster sputum conversion. Thus, addition of Mfx to RHZ regimen holds the possibility of reducing the duration of treatments of TB from 6 months with RHZE used currently. However, to preserve the anti-TB efficacy of these valuable drugs, their use is restricted to DR-TB.

FQs are a key component of all regimens for MDR-TB, except when bacilli are found to be resistance to them. The RNTCP (2016) have included Lfx in the standardized regimen for MDR-TB. If used alone, mycobacterial resistance to Ofx, Lfx and Cfx develops rapidly by mutation of DNA gyrase gene. Interestingly, experimental data indicates that resistance against Mfx is slow to develop.
Dose: Ofloxacin 800 mg OD

Levofloxacin	1000 mg OD	For > 45 kg
Moxifloxacin	400 mg OD	body weight

4. Ethionamide (Eto)

It is an antitubercular drug of moderate efficacy, introduced in 1956, which acts on both extra- and intracellular bacilli. Few atypical mycobacteria including MAC are also susceptible. Chemically it resembles INH, but contains sulfur. The mechanism of action is also similar to INH: it is converted by mycobacteria into an active intermediate which interferes with mycolic acid synthesis. Resistance to Eto mosly results from mutation of the gene that encodes for the Eto activating enzyme. Eto is nearly completely absorbed orally, distributed all over and crosses into CSF. It is completely metabolized in liver and has a short t½ of 2–3 hours.

Tolerability of Eto is poor; frequent adverse effects are—anorexia, nausea, vomiting, salivation, metallic taste, epigastric discomfort, sulfurous belching and hepatitis. It also causes aches and pains, peripheral neuritis, behavioural changes, rashes, impotence, menstrual disturbances and goiter on prolonged use. To improve tolerance, dosing may initiated at 250 mg/day, and increased every 5–6 days to reach 750 mg/day (10–15 mg/kg/day). Pyridoxine (100 mg/day) can mitigate the neurological adverse effects.

Ethionamide is used only for drug-resistant TB. It is a component of the RNTCP standardized regimen for MDR-TB and an optional drug for inclusion into the treatment regimen of MAC infection in AIDS patients. It is also a reserve drug for leprosy.
ETHIDE, MYOBID, ETHIOKOX 250 mg tab.

5. Prothionamide (Pto)

A close congener of Eto to which it resembles in antimycobacterial property, mechanism of action, pharmacokinetics and adverse effects. Clinically it is considered interchangeable with Eto for use in MDR-TB, MAC infection, etc.
PROTHICID, PETHIDE 250 mg tab.

6. Cycloserine (Cs)

This antibiotic obtained from *S.orchidaceus* is an analogue of D-alanine. Accordingly, it inhibits bacterial cell well synthesis by inactivating the enzymes which racemize L-alanine and link two D-alanine residues. Cs is tuberculostatic; in addition inhibits MAC as well as some other gram-positive bacteria, *E.coli* and *Chlamydia*. Resistance to Cs develops slowly; no cross resistance with any other anti-TB drugs occurs.

Oral absorption of Cs is good; it diffuses all over the body; CSF concentration is equal to that in plasma. About 1/3 of a dose is metabolized; the rest is excreted unchanged in urine; plasma t½ is 9 hours. Adverse effects of Cs are primarily neurological; about half of the recipients experience neuropsychiatric symptoms, *viz.* sleepiness, headache, tremor, slurring of speech, altered behaviour, depression or frank psychosis. Seizures are infrequent. Pyridoxine 100 mg/day can reduce neurotoxicity and prevent convulsions. Fall in BP has been noted. Cs is contraindicated in patients with a history of mental illness or seizures. Cycloserine is used only for resistant TB, especially

MDR cases. It is included in the standardized regimen used by RNTCP for MDR-TB.

Dose: Start with 250 mg BD, increase if tolerated to 750 mg/day for patients with body weight >45 kg.

CYCLORINE, COXERIN, MYSER 250 mg cap.

7. Terizidone

It contains 2 molecules of cycloserine and has antibacterial properties as well as mechanism of action similar to it; but is believed to be less neurotoxic; reported incidence of adverse effects is lower. It is used as a substitute of Cs, especially in genitourinary TB, because it attains higher and longer lasting concentration in urine. Dosage are similar to Cs; 500–750 mg/day.

TERICOX 250 mg cap.

8. Para-amino salicylic acid (PAS)

Introduced in 1946, PAS is related to sulfonamides and acts probably by the same mechanism, i.e. inhibition of folate synthase. It is not active against other bacteria, and this selectivity may be due to difference in the affinity for folate synthase of *M.tuberculosis* compared to that of other bacteria. However, other mechanisms of action are also possible.

PAS is tuberculostatic and one of the least active drugs: does not add to the efficacy of more active drugs that are given with it; only delays development of resistance—probably by directly inhibiting episomal resistance transfer. Resistance to PAS is slow to develop. It is used as the sodium salt (large doses that are needed may cause Na^+ overload) or calcium salt (better gastric tolerance is claimed).

PAS is absorbed completely by the oral route and distributed all over except in CSF. About 50% PAS is acetylated; competes with acetylation of INH and prolongs its t½. It is excreted rapidly by glomerular filtration and tubular secretion; t½ is short, ~1 hour.

Patient acceptability of PAS is poor because of frequent anorexia, nausea and epigastric pain. Other adverse effects are rashes, fever, malaise, hypokalaemia, goiter, liver dysfunction and rarely blood dyscrasias.

PAS is used only in resistant TB. The RNTCP includes it in the standardized regimen for MDR-TB only when one of the tuberculocidal drugs (Km, Ofx, Z, Eto) or both the static drugs (E, Cs) cannot be used.

Dose: 10–12 g (200 mg/kg) per day in divided doses;

SODIUM-PAS 0.5 g tab, 80 g/100 g granules.

9. Rifabutin

It is related to rifampin in structure and mechanism of action, but is less active against *M.tuberculosis*, and more active against MAC. Majority of *M.tuberculosis* isolates resistant to R are cross resistant to rifabutin. Thus, it is not an option for treatment of MDR-TB. The only place of rifabutin in the treatment of TB is as a substitute for R to minimise drug interactions due to strong enzyme inducing property of R. Rifabutin is a much weaker inducer of CYP enzymes than R. This is especially needed in HIV coinfected patients of TB who receive a protease inhibitor (PI) and/or a non-nucleoside reverse transcriptase inhibitor (NNRTI) whose metabolism is markedly induced by R rendering them ineffective. The dose of rifabutin needs to be reduced when it is used to treat TB in a HIV patient receiving a protease inhibitor.

The primary indication of rifabutin is for prophylaxis and treatment of MAC infection in HIV-AIDS patients. For prophylaxis of MAC, rifabutin alone 300 mg/day is an alternative to azithromycin/clarithromycin, while for treatment of MAC infection, it is combined with 2–3 other anti-MAC drugs. Gastrointestinal intolerance, rashes, granulocytopenia, myalgia and uveitis have been reported with rifabutin. Reactions similar to those caused by R can also occur. Oral bioavailability of rifabutin is low (~20%), but t½ is much longer (>30 hours).

Dose: 300 mg (5 mg/kg) OD oral; RIBUTIN 150 mg tab.

Rifapentine It is a rifampin congener, very similar to it is mechanism of action as well as in activity against *M. tuberculosis* and MAC. Cross resistance between the two is complete. Toxicity as well as drug interaction profile is also similar. Rifapentine is as potent an enzyme inducer as rifampin. However, the t½ of rifapentine (13–15 hr) is longer than that of rifampin, so that it can be given once or twice weekly. The only indication of rifapentine (600 mg once/twice weekly) is in the continuation phase of treatment of TB, as a substitute of daily rifampin. It is not suitable for use during the intensive phase. Once weekly rifapentine combined with INH has also been employed to treat latent TB.

Bedaquiline (BDQ) Introduced recently, this diarylquinoline anti-TB drug acts by a novel mechanism. Bedaquiline (BDQ) inhibits mycobacterial ATP synthase, thereby limiting energy production within mycobacterial cell. The human ATP synthase is 20,000 fold less sensitive to BDQ than is the mycobacterial enzyme. It has exhibited strong bactericidal and sterilizing activity against *M. tuberculosis* in *in vitro* tests and in animal models by killing both rapidly multiplying as well as dormant bacilli. The MICs of BDQ are very low and similar for drug-sensitive as well as for MDR-TB and XDR-TB strains. Many nontubercular mycobacteria and *M. leprae* are also inhibited *in vitro*. *M. tuberculosis* develops resistance to BDQ primarily by mutation of ATP synthase enzyme, reducing its affinity for BDQ. Another mechanism is by acquisition of BDQ efflux from the bacilli. However, no cross resistance between BDQ and any 1st line or 2nd line anti-TB drug occurs.

Bedaquiline is well absorbed orally; fatty meal improves absorption. It is highly plasma protein bound and extensively distributed in tissues. Metabolism occurs in liver, mainly by CYP3A4, and the principal desmethyl metabolite is 20% as active as BDQ. Clinically significant drug interactions occur with CYP3A4 inducers and inhibitors. The terminal t½ of BDQ is very long (~ 160 days), probably due to redistribution from tissues. It is excreted mainly in faeces.

In clinical trials on pulmonary MDR-TB patients, addition of BDQ to WHO regimen for MDR-TB reduced the time for sputum to become culture negative. However, in 2 clinical trials, despite better microbiological outcome, more patients died in the BDQ group than in those receiving only background regimen. Since all deaths occurred after BDQ was stopped, the deaths did not appear to be related to BDQ use. The US-FDA approved BDQ in 2012, and it has been marketed internationally as SIRTURO 100 mg tab. The WHO in 2013 have issued guidelines for use of BDQ in drug resistant TB, following which the RNTCP (2016) has introduced BDQ in India for MDR-TB at selected centers through its 'conditional access programme'. The present recommendations regarding use of BDQ are:

- It should be used only for pulmonary MDR-TB in adults (>18 yr)
- Women patients should be nonpregnant and willing to remain so during BDQ use.
- It should be used only in combination with at least 3 other anti-TB drugs to which the bacilli of the patient are shown to be susceptible *in vitro*, or at least 4 other drugs to which the patient's isolate is likely to be sansitive.
- It should be used only when an effective regimen cannot otherwise be provided.
- BDQ should be given for a maximum of 24 weeks in a dose of 400 mg/day for 2 weeks followed by 200 mg 3 times a week for the next 22 weaks.
- Each BDQ tablet should be swalloed whole with meals.
- The background anti-TB drugs should be continued after stopping BDQ for the total 24 months treatment of MDR-TB. This is to ensure that any surviving bacilli are not expsed to BDQ alone, which persists in the body for > 5 months after stopping.
- BDQ is not to be used for drug-sensitive TB, or extrapulmonary TB or for nontubercular mycobacteria.

Adverse effects of BDQ are nausea, headache, arthralgia and prolongation of QTc interval. Caution is required in using BDQ in patients taking other QTc prolonging drugs. BDQ has the potential to cause hepatotoxicity.

TREATMENT OF TUBERCULOSIS

The therapy of tuberculosis has undergone remarkable changes.

The 'Conventional' 18–24 month treatment was abandoned in the 1990s and more effective as well as less toxic 6 month (short course) treatment was introduced, which also yielded higher completion rates. This has been possible due to better understanding of the biology of tubercular infection.

Biology of tubercular infection *M. tuberculosis* is an aerobic organism. In unfavourable conditions it grows only intermittently or remains dormant for prolonged periods. Several subpopulations of bacilli, each with a distinctive metabolic state, could exist in an infected patient, e.g.:

(a) *Rapidly growing with high bacillary load* as in the wall of a cavitary lesion where oxygen tension is high and pH is neutral. These bacilli are highly susceptible to H and to a lesser extent to R, E and S.

(b) *Slow growing* located intracellularly (inside macrophages) and at inflamed sites where pH is low. They are particularly vulnerable to Z, while H, R and E are less active, and S is inactive.

(c) *Spurters* found mostly within caseous material where oxygen tension is low but pH is neutral: the bacilli grow intermittently with occasional spurts of active metabolism. R is most active on this subpopulation.

(d) *Dormant* some bacilli remain totally inactive for prolonged periods. No antitubercular drug (except probably bedaquiline) is significantly active against them.

However, there is continuous shifting of bacilli between these subpopulations.

The goals of antitubercular chemotherapy are:

(a) *Kill dividing bacilli* Drugs with early bactericidal action rapidly reduce bacillary load in the patient and achieve quick sputum negativity. This makes the patient non-contagious and affords quick symptom relief.

(b) *Kill persisting bacilli* To effect cure, sterilize the patient and prevent relapse.

(c) *Prevent emergence of resistance* So that the bacilli remain susceptible to the drugs.

The relative activity of the first line drugs in achieving these goals differs, e.g. H and R are the most potent bactericidal drugs active against all populations of TB bacilli, while Z acts best on intracellular bacilli and those at inflamed sites. It thus has very good sterilizing activity. On the other hand S is active only against rapidly multiplying extracellular bacilli. E is bacteriostatic—mainly serves to prevent resistance and may hasten sputum conversion.

The general principles of antitubercular chemotherapy are:

- Use of any single drug in tuberculosis results in the emergence of resistant organisms and relapse in almost 3/4th patients. A combination of two or more drugs must be used. The rationale is: the incidence of resistant bacilli to most drugs ranges from 10^{-8} to 10^{-6}. Because an average

patient of pulmonary tuberculosis harbours 10^8 to 10^{10} bacilli, the number of organisms that will not respond to a single drug is high and cannot be dealt by the host defence. During protracted treatment, these bacilli multiply and become dominant in 3–4 months. Because insensitivity to one drug is independent of that to another, i.e. incidence of H resistance among bacilli resistant to R will be 10^{-6} and *vice versa*; only few bacilli will be resistant to both; these can be handled by host defence. By the same rationality, massive infection ($>10^{10}$ organisms) has to be treated by 3 or more drugs; and a single drug is sufficient for prophylaxis, because the number of bacilli is small.

- Isoniazid and R are the most efficacious drugs; their combination is clearly synergistic, so that duration of therapy is shortened from > 12 months to 9 months. Addition of Z for the initial 2 months further reduces duration of treatment to 6 months.
- A single daily dose of all first line antitubercular drugs is preferred. The 'directly observed treatment short course' (DOTS) was recommended by the WHO in 1995.
- Response is fast in the first few weeks as the fast dividing bacilli are eliminated rapidly. Symptomatic relief is evident within 2–4 weeks. The rate of bacteriological, radiological and clinical improvement declines subsequently as the slow multiplying organisms respond gradually. Bacteriological cure takes much longer. The adequacy of any regimen is assessed by sputum smear/culture conversion rates and 2–5 year relapse rates after completion of treatment.

SHORT COURSE CHEMOTHERAPY

The WHO introduced 6–8 month multidrug 'short course' regimens in 1995 under the DOTS programme. An expert group framed clearcut treatment guidelines in 1997 for different categories of TB patients.

The dose of all first line drugs was standardized on body weight basis. These guidelines were implemented by India and other WHO member countries, making major progress in global TB control. The 'Stop TB strategy' of WHO was launched in 2006 and the spread of MDR-TB was taken into account. On the basis of experience gained, new guideline with revised categorization of patients was brought out in 2010, in which patients of TB were classified as 'New case' or 'Previously treated' patients and 'Drug resistant TB' (DR-TB) including MDR-TB patients. From 2016 the WHO has enhanced its goal and launched 'End TB strategy'. The RNTCP have broughtout their latest guidelines in 2016, in which extensive use of drug-sensitivity testing has been incorporated to effectively treat DR-TB. Both liquid culture and drug susceptibility tests' (LC-DST) and the faster genotypic tests, e.g. 'line probe assay' (LPA) for R and H resistance, and 'Cartridge based nucleic acid amplification test' (CBNAAT) for R resistance are now widely utilized.

All anti-TB regimens have an initial *intensive phase (IP)* with 4–6 drugs aimed to rapidly kill the bacilli, bring about sputum conversion and afford fast symptomatic relief. This is followed by a *continuation phase (CP)* with 3–4 drugs during which the remaining bacilli are eliminated, so that relapse does not occur. For devising drug regimens, the RNTCP (2016) has classified TB cases into:

1. *Drug-sensitive TB:* The patient's bacilli are susceptible to all 5 first line anti-TB drugs (ATDs). All new TB patients who have never taken any ATD or have taken them for less than one month are presumed to have drug-sensitive TB.
2. *Multidrug resistant TB (MDR-TB)*: The patient's bacilli are resistant to both R and H with or without resistance to any number of other 1st line drugs.
3. *Rifampin resistant TB (RR-TB)*: The patient's bacilli are resistant to R but not to H, with or without resistance to other ATDs. These patients are to be treated as if they have MDR-TB.
4. *Mono-resistant TB*: The bacilli are resistant to one 1st line ATD, but not R-resistant.
5. *Poly-drug resistant TB (PDR-TB)*: The patient's bacilli are resistant to more than one 1st line ATD, except both R and H resistance.
6. *Extensive drug resistant TB (XDR-TB)*: A MDR-TB case whose bacilli are additionally resistant to a FQ and one 2nd line injectable ATD.

Drug-sensitive TB This is treated by 1st line ATDs as per regimens summarized in Table 56.1. For *new patients*, the initial treatment with

Table 56.1: Treatment regimens* for new patients and previously treated patients of pulmonary TB presumed to be drug sensitive

Type of patient	*Intensive phase*	*Continuation phase*	*Total duration*
New	2[£] HRZE	4 HRE	6 [£]
Previously treated	2 HRZES + 1 HRZE	5 HRE	8

* Based on RNTCP guidelines 2016.
[£] Duration of the phase/total duration in months.
H,R,Z,E,S—Standard codes for Isoniazid, Rifampin Pyrazinamide, Ethambutol, Streptomycin.

4 drugs including 3 bactericidal drugs (RHZ) and one bacteriostatic drug (E) rapidy brings down the bacillary load and reduces the risk of selecting resistant bacilli, especially in the face of increasing primary H resistance which is now upto 18%. After 2 months Z is discontinued and the remaining 3 (RHE) are continued for another 4 months to eliminate all bacilli from the body. While in the 2010 RNTCP regimen, the continuation phase had only 2 drugs (RH), the 2016 regimen includes E as well. This is in consonence with the suggestion of WHO to include E in the continuation phase for areas with high incidence of primary H resistance. In the new guidelines, the frequency of dosing during both IP and CP has been changed from 3 times a week to daily administration, which is considered optimal. The thrice weekly dosing was a compromise in the face of operational constraints of the programme, which have now been overcome.

For *previously treated* patients of TB who are presumed not to have DR-TB, all 5 1st line ATDs are administered daily for 2 months. Injected S is then stopped and remaining 4 (RHZE) are continued for 1 more month. The IP thus lasts 3 months. The CP is longer, i.e. 5 months with RH and E administered daily.

In case of severe forms of extrapulmonary TB, the CP in both new as well as previously treated patients may be extended by 3–6 months on clinical grounds.

The WHO has standardized the daily dose of all 1st line ATDs on body weight basis as given in Table 56.2. However, it is advisable to use fixed dose combinations (FDCs) of oral ATDs, because this ensures that the patient takes all the drugs; risk of bacilli being exposed to only 1 or 2 ATDs is eliminated, and resistance is not fostered. For operational ease the RNTCP provides separate FDC tablets of 1st line drugs for use during IP and CP. The number of such FDC tablets for different body weight bands is given in Table 56.3.

Table 56.2: Daily dose of 1st line antitubercular drugs on body weight basis[$]

Drug	*Daily dose (mg/kg)*
1. Isoniazid (H)	5 (4-6)
2. Rifampin (R)	10 (8-12)
3. Pyrazinamide (Z)	25 (20-30)
4. Ethambutol (E)	15 (15-20)
5. Streptomycin (S)*	15 (12-18)

[$] Based on WHO (2010) guidelines
* In patients above 50 years age, the maximum dose of streptomycin is 0.75 g/day

Multidrug-resistant (MDR) TB

MDR-TB has a more rapid course with worse outcomes. Its treatment requires complex multiple 2nd line drug regimens which are longer in duration, more expensive and more toxic. In India MDR-TB accounts for 3% of all new TB cases and 12–17% of retreatment cases in different states. These figures are close to the

Table 56.3: Daily dose of 1st line oral antitubercular drugs as number of fixed dose combination (FDC) tablets (based on RNTCP guidelines 2016)

Body weight category	*Intensive phase*	*Continuation phase*
	HRZE*	HRE[$]
25–39 kg	2	2
40–54 kg	3	3
55–69 kg	4	4
≥ 70 kg	5	5

* Intensive phase: each tablet contains H (75 mg) + R (150 mg) + Z (400 mg) + E (275 mg)
[$] Continuation phase: each tablet contains H (75 mg) + R (150 mg) + E (275 mg).

global average incidence. As per WHO global TB report 2015, India has the highest number of MDR-TB cases and an estimated 71,000 cases of MDR-TB emerge annually from the notified cases of pulmonary TB in India. The general principles of treatment of MDR-TB are:

- The regimen should have at least 4 drugs certain to be effective. Often 6 drugs are included, since efficacy of some may be uncertain.
- Reliance about efficacy may be placed on DST results, and the anti-TB drugs used previously in that individual.
- Avoid combining cross resistance drugs, e.g. two FQs, Km with Am or Eto with Pto, or Cs with terizidone.
- Include drugs from group I to group IV in a hierarchial order. Group I drugs (Z, E) can be included, add one injectable drug (group II), one FQ (group III) and two group IV drugs.

The RNTCP initiated the DOTS-plus programme in the year 2000 to cover the diagnosis and treatment of MDR-TB. It updated its strategy in 2010 according to the WHO recommendations, and has further revised its guidelines in 2016. The 'standard' RNTCP regimen for MDR-TB consists of 6 drugs intensive phase lasting 6–9 months and 4 drugs continuation phase of 18 months (*see* box). This regimen is used in all confirmed or suspect MDR-TB cases, unless DST results or other specifics (intolerance, etc.) of an individual case necessitate use of an 'individualized regimen', which is constructed taking into account these individual specific features.

Standard RNTCP regimen for MDR-TB*

Intensive phase	*Continuation phase*
(6–9 months)	*(18 months)*
1. Kanamycin (Km)	1. Levofloxacin
2. Levofloxacin (Lfx)	2. Ethionamide
3. Ethionamide (Eto)	3. Cycloserine
4. Cycloserine (Cs)	4. Ethambutol
5. Pyrazinamide (Z)	
6. Ethambutol (E)	
+ Pyridoxine 100 mg/day	

*Revised National Tuberculosis Control Programme Guidelines (2016).

The minimal 6 month intensive phase is extended by 1 month each time till a maximum of 9 months, if the sputum culture put up at the end of 4th, 5th and 6th month respectively are positive. Pyridoxine 100 mg/day is given to all patients during the whole course of therapy to prevent neurotoxicity of the anti-TB drugs. This standard regimen has been found to be highly successful.

Rifampin resistant TB (RR-TB) According to both WHO and RNTCP, a case of RR-TB is treated as MDR-TB. However, because the bacilli are sensitive to H, this 1st line drug is added to the MDR-regimen, both in the intensive phase as well as in the continuation phase, without changing the duration or the other drugs. Thus, for RR-TB, the intensive phase of 6 months has 7 drugs (Km, Lfx, Eto, Cs, Z, E and H), and the continuation phase (18 months) has 5 drugs (Lfx, Eto, Cs, E and H).

Monodrug resistant TB When the liquid culture drug sensitivity test (LC-DST) or line probe assay (LPA) reports resistance to one first line drug, other than R resistance, the treatment regimen according to RNTCP-2016 consists of:

- R + two of the 1st line drugs to which bacilli are sensitive + one injectable second line drug + one FQ to make a total of 5 drugs given daily in the intensive phase of 3–6 months.

Polydrug resistant TB When the bacilli are resistant to more than one first line drugs, other than R resistance, the initial regimen is:

R + one injectable 2nd line drug + one FQ + any 1st line drug to which the bacilli are sensitive + one of the oral 2nd line drugs (Eto/Cs/PAS). The duration of intensive phase is 3–6 months.

In the continuation phase for both mono and poly drug resistant TB, the injectable drug is stopped while the remaining 4 oral drugs are continued for a fixed duration of 6 months. Thus, the total duration of regimens for mono and poly drug resistant TB is 9–12 months.

Isoniazid resistant TB It has been observed that when H resistance is of low level (in LC-DST) or is due to *inhA* mutation (in LPA), high dose of INH (900 mg/day for 46–70 kg body weight) in place of 300 mg/day, is effective and should be added to the regimen (along with pyridoxine). However, in case of high level H resistance or that due to *Kat G* mutation, it is ineffective and should not be given.

Extensive drug-resistant TB As already defined, these are MDR-TB cases that are resistant to at least 4 most effective cidal drugs, *viz.* H,R,FQ and one of Km/Am/Cm.

The WHO estimated that 9.7% of MDR-TB patients had XDR-TB in 2015. The exact incidence of XDR-TB in India is not known, but with expanding laboratory facilities to conduct sensitivity tests for 2nd line drugs, more XDR-TB cases are likely to be confirmed.

The XDR-TB is very difficult to treat, has a rapid course and high mortality. However, to prevent further amplification of resistance, the standard MDR regimen must be immediately stopped when XDR-TB is detected or suspected. An expert panel may decide on instituting a regimen including the group V drugs which are difficult to tolerate and expensive. The RNTCP (2016) has recommended a treatment regimen for XDR-TB consisting of 7 drugs in the intensive phase (6-12 months) and 6 drugs in the continuation phase (18 months). The drugs and their adult daily doses (for 46–70 kg body weight) are:

Capreomycin	1000 mg
Moxifloxacin	400 mg
High dose isoniazid	900 mg
PAS	12 g
Clofazimine	200 mg
Linezolid	600 mg

Amoxicillin/clavulanate (875+125 mg tab) 2 tab morning + one tab evening.

In the continuation phase, injection capreomycin is stopped and the remaining 6 drugs are continued for another 18 months.

Tuberculosis in pregnant women The WHO and British Thoracic Society consider H, R, E and Z to be safe to the foetus and recommend the standard 6 month (2HRZE + 4HRE) regimen for pregnant women with TB. S is contraindicated because it is ototoxic to the foetus. In india, the current (2016) RNTCP guidelines also consider the 4 oral 1st line drugs to be safe, and recommend full course of TB treatment as in nonpregnant. Treatment of TB should not be withheld or delayed because of pregnancy. All pregnant women being treated with INH should receive pyridoxine 10–25 mg/day.

Treatment of breastfeeding women All 1st line ATDs are compatible with breastfeeding; full course should be given to the mother, and breastfeeding should be continued. The infant should receive 6 month isoniazid preventive treatment after ruling out active TB followed by BCG vaccination. Breast-fed infants whose mothers are taking INH, and those on INH preventive therapy should be supplemented with pyridoxine 5 mg/day.

Management of patients with adverse drug reactions to antitubercular drugs The 1st line ATDs are generally well tolerated, but minor side effects do occur, and should be managed symptomatically without altering medication; e.g. nausea, anorexia—give the drugs with small meals; drowsiness—give drugs before bed time; Z induced arthralgia can be treated by analgesic-NSAIDs; peripheral neuritis due to H can be mitigated by pyridoxine. If more severe reactions like skin rashes, itching develop, all drugs should be stopped promptly. After resolution of the reaction, the drugs are to be reintroduced one at a time by challenging with small doses and increasing every 3 days. When the offendng drug is identified, it should be stopped and the regimen reconstituted. However, R should never be reintroduced in case of severe reaction such as haemolysis, thrombocytopenia or renal failure. Ethambutol should be discontinued at the first sign of optic neuritis.

Hepatotoxicity is the most common problem with antitubercular drugs. Any one or more of H, R and Z could be causative and the reaction

occurs more frequently when, as per standard protocol, combination of these drugs is used. In case hepatitis develops, all drugs should be stopped and the reaction allowed to subside. If TB is severe, nonhepatotoxic drugs S + E + one FQ should be started while the reaction clears. Subsequently, the discontinued drugs are restarted one at a time. Generally, R is resumed first followed 7 days later by H. If hepatitis recurs, the last added drug is stopped permanently and the regimen is reconstructed. In case both R and H are tolerated—do not restart Z but prolong therapy with R, H and E to 9 months. If R is the culprit, HES may be given for 2 months followed by HE for 10 months. If H is implicated, REZ may be given for 9 months.

Latent tubercular infection (Chemoprophylaxis) The purpose is to prevent progression of latent tubercular infection to active disease. This is indicated only in subjects at high risk of developing active TB, *viz.*:

(a) Contacts of open cases who show recent Mantoux conversion.

(b) Children with a sputum positive TB patient in the family.

(c) Neonate of tubercular mother.

(d) Patients of leukaemia, diabetes, silicosis or those receiving immunosuppressant medication or those on long-term corticosteroid therapy.

(e) HIV infected contacts of sputum positive index cases.

The standard drug for chemoprophylaxis of TB is INH 300 mg (10 mg/kg in children) daily for 6 months. This is as effective in HIV patients as in those with normal immune function. The WHO have recently (2014) reviewed the evidence on treatment of latent tubercular infection, and have concluded that 6 month INH preventive treatment is optimal. Extending it by another 3 months does not afford additional protection. Another regimen of once a week rifapentine (10 mg/kg) + high dose INH (15 mg/kg) given for 3 months is equally effective.

Due to lack of quality evidence about the most appropriate drug(s) or duration of prophylaxis that should be used in case of subjects exposed to MDR-TB, the WHO expert panel (2014) recommend that MDR-TB contacts should be watched closely without giving any prophylactic medication, and treated promptly if they develop active disease. Nevertheless, TB experts may institute individually tailored preventive regimens based on the drug susceptibility profile of the MDR-TB case from whom infections is likely to have been contacted (index case).

Role of corticosteroids Corticosteroids should not be ordinarily used in tubercular patients. However, they may be used under adequate chemotherapeutic cover:

- In seriously ill patients (miliary TB or severe pulmonary TB) to buy time for drugs to act.
- When hypersensitivity reactions occur to antitubercular drugs.
- In meningeal/renal/pericardial TB or pleural effusion—to reduce exudation, prevent its organisation and strictures, etc.
- In AIDS patients with severe manifestations of tuberculosis.

Corticosteroids are contraindicated in intestinal tuberculosis because silent perforation can occur.

Corticosteroids, if given, should be gradually withdrawn when the general condition of the patient improves.

Tuberculosis in AIDS patients The association of HIV and TB infection is a serious problem. Risk of developing TB in HIV positive subjects increases by about 8 times. HIV positive cases have a higher incidence of extrapulmonary, more severe, more lethal and more infectious TB. HIV infection is the strongest risk factor for unmasking latent TB. Moreover, adverse reactions to anti-TB drugs are more common in HIV patients. It is estimated that 2.1 million Indians are currently living with HIV, and that 1.1 lac HIV associated TB cases occurred in 2014 and 31,000 died countrywide. About 1/4 of deaths among AIDS patients in India is due to TB. India thus ranks 2nd in the global burden of HIV-associated TB.

On the other hand, institution of 'antiretroviral therapy' (ART) and improvement in CD4 cell

count of the subject markedly reduces the incidence of TB among HIV-AIDS patients. When CD4 count is <150 cells/μL, extrapulmonary and dual TB is more commonly encountered. Risk of recurrent TB among cured TB subjects is also high in HIV patients.

In case of *M. tuberculosis* infection, drugs used are the same as in non-HIV cases, and at least 4 drugs are used. Initial intensive phase therapy with daily HRZE for 2 months is started immediately on the diagnosis of TB, and is followed by a continuation phase of HRE for 4–7 months (total 6–9 months). Thrice weekly regimen should not be used, because it is associated with 2–3 times higher rate of relapse and failure among HIV positive patients. Risk of acquiring resistance to R is increased compared to daily treatment. Pyridoxine 25–50 mg/day is routinely given along with H to counteract its neurological side effects, which are more likely in AIDS patients. All HIV positive TB patients should also receive cotrimoxazole preventive therapy at least throughout the anti-TB regimen. This has been found to reduce mortality, probably by preventing *Pneumocystis jirovecii* and other infections.

Consideration also has to be given to possible drug interactions between anti-TB and antiretroviral (ARV) drugs. Rifampin, a potent inducer of CYP isoenzymes, markedly enhances the metabolism of protease inhibitors (PIs, *viz.* indinavir, nelfinavir, ritonavir) and of NNRTIs, *viz.* nevirapine, making them ineffective. In patients receiving these drugs, rifabutin (a less potent enzyme inducer) given for 9–12 months may be substituted for rifampin. The metabolism of nucleoside reverse transcriptase inhibitors (NRTIs, zidovudine, etc.) is not induced by rifampin, and no dose adjustment is needed. An alternative regimen of 3 NRTIs (zidovudine + lamivudine + abacavir) has been advocated for patients who are to be treated by rifampin. If 2 NRTI + NNRTI is to be used, efavirenz should be selected as the NNRTI because its metabolism is induced to a lesser extent.

MDR-TB in HIV-AIDS patients should be treated in the same way as that in non-HIV infected patient for a total of 24 months.

Mycobacterium avium complex (MAC) infection

MAC is an opportunistic pathogen which causes disseminated and multifocal disease in immunocompromized (HIV-AIDS) patients. The disease develops when cell mediated immunity is markedly depressed, i.e. when CD4 count drops to <50 cells/μL, HIV-RNA load is high and other opportunistic infections (*P. jirovecii*, etc.) are also present. The newer macrolide antibiotics are particularly active drugs against MAC.

Clarithromycin and azithromycin have weak activity against *M.tuberculosis* but are the most active drugs against MAC, *M. fortuitum, M. kansasii* and *M. marinum*. Clarithromycin has lower MICs against these mycobacteria than azithromycin, but the latter may be equally efficacious due to its higher tissue and intracellular levels as well as longer stay in the body.

Therapy of MAC infection Eradication of MAC has not been achieved by any drug or regimen. Therapy is directed to suppress the disease and afford symptomatic relief untill immune status of the patient improves by ART. A favoured regimen consists of 3 or 4 drug intensive phase followed by 2 drug maintenance phase as outlined in the box. The benefit of adding a FQ as the 4th drug is not clear.

Regimen for treatment of MAC infection

Intensive phase

1. Clarithromycin 500 mg twice daily or Azithromycin 500 mg once daily
2. Ethambutol 1000 mg (15 mg/kg) per day
3. Rifabutin 300 mg per day

±

Ciprofloxacin 500 mg twice daily or
Levofloxacin 500 mg once daily or
Moxifloxacin 400 mg once daily

Maintenance phase*

1. Clarithromycin/Azithromycin
2. Ethambutol/Rifabutin/One fluoroquinolone

* Doses in the maintenance phase are the same as in intensive phase

The duration of intensive phase is dependent on the response, *viz.* till CD4 count rises > 100 cells/μL and symptomatic relief is obtained, which may take 2–6 months. The maintenance therapy is continued till a minimum of 12 months, or till the patient becomes asymptomatic for MAC infection and CD4 count stays > 100 cell/μL for at least 6 months. All patients must simultaneously receive ART for the HIV infection. However, if efavirenz is being used as a component of ART, the dose of rifabutin should be increased from 300 mg/day to 450 mg/day or 600 mg/day, because efavirenz induces rifabutin metabolism. Despite therapy, mortality remains high.

Prophylaxis of MAC infection

This is aimed at protecting the AIDS patient from developing active MAC disease during the period CD4 count remains below 75 cell/μL. A single drug is used—azithromycin 1200 mg/week (preferred due to better compliance) or clarithromycin 500 mg twice a day are the recommended drugs. Rifabutin 300 mg/day is used if either of these drugs cannot be given. This is continued till the simultaneously instituted ART achieves complete suppression of HIV replication, CD4 count rises above 100 cell/μL and stays there for at least 3 months.

PROBLEM DIRECTED STUDY

56.1 A 45-year-old male factory worker weighing 60 kg reports to the hospital with cough and expectoration, mild chest pain, weakness and fatigue for the last one month. In addition he has developed low grade fever for the last one week. He gives history of having suffered from TB of the lung one year back for which he took treatment from the hospital and became all right in 2 months. He stopped taking the medicines after another 1 month, though he was told by the doctor to continue treatment. The sputum was found to be positive for AFB and X-ray chest showed a 5 cm cavitary lesion in the right middle lobe and fibrotic changes in the upper lobe. He was diagnosed to be a previously treated and defaulted patient of pulmonary TB.

(a) Given that rapid genotypic drug-sensitivity tests are not available, should any other laboratory test be ordered in this case; if so, should the treatment start immediately or after the report is available?

(b) What should be the regimen of antitubercular drugs for this patient?

(*see* Appendix-1 for solution)

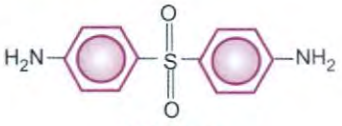
Chapter 57 Antileprotic Drugs

Leprosy, caused by *Mycobacterium leprae*, has been considered incurable since ages and bears a social stigma. Due to availability of effective antileprotic drugs, it is entirely curable now, but deformities/defects already incurred may not reverse.

Chaulmoogra oil with weak antileprotic property was used in Indian medicine for centuries. Shortly after the demonstration of antibacterial property of sulfonamides, congeners were tested and dapsone, the parent sulfone, was found to be an active antileprotic drug. Since the 1940s it is the sheet-anchor of treatment of leprosy. Few other sulfones were added, but none could excel dapsone. Clofazimine was inducted in the early 1960s as a useful adjunct, and soon rifampin, developed for TB, was found to be a rapidly acting cidal drug for *M.leprae* as well. Lately good antileprotic activity has been detected in some fluoroquinolones, macrolides and minocycline.

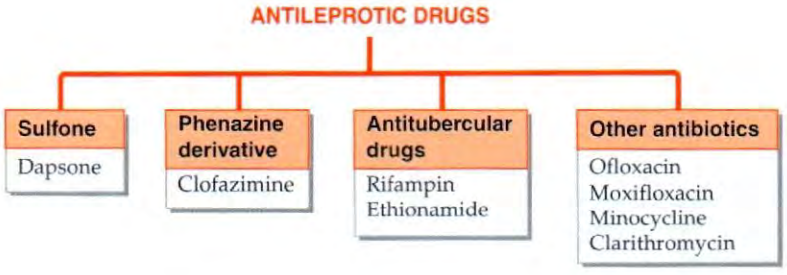
Dapsone (DDS)

It is diamino diphenyl sulfone (DDS), the simplest, oldest, cheapest, most active and most commonly used member of its class. All other sulfones have become obsolete.



DAPSONE

Activity and mechanism Dapsone is chemically related to sulfonamides and has the same mechanism of action, i.e. inhibition of PABA incorporation into folic acid by folate synthase. The antibacterial action of dapsone is antagonized by PABA. It is leprostatic at very low concentrations, while growth of many other bacteria sensitive to sulfonamides is arrested at higher concentrations. Specificity for *M. leprae* may be due to difference in the affinity of its folate synthase enzyme. Doses of dapsone needed for treatment of acute pyogenic bacterial infections are too toxic, hence not used.



Dapsone-resistance among *M. leprae*, first noted in 1964, has spread and has necessitated the use of multidrug therapy (MDT). When dapsone resistance is encountered in an untreated patient, it is called '*primary*', and indicates that the infection was contacted from a patient harbouring resistant bacilli. Resistance which develops during monotherapy with dapsone is called '*secondary*'.The incidence of primary dapsone resistance reported from different parts of the world, from time-to-time, has been variable; whereas secondary dapsone resistance developed in upto 20% patients treated with monotherapy. The mechanism of secondary resistance appears to be the same as for *M. tuberculosis,* i.e. selective propagation of resistant bacilli over time. Dapsone resistant *M. leprae* have mutated folate synthase which has lower affinity for dapsone. However, the peak serum concentration of dapsone after 100 mg/day dose exceeds MIC for *M. leprae* by nearly 500 times. Therefore, dapsone continues to be active against low to moderately resistant bacilli, and the risk of relapse due to dapsone resistance is reported to be only 2–3%. In addition to resistance, there is the problem of '*persisters*', that are drug sensitive bacilli which become dormant, hide in some tissues and are not affected by any drug. They may stage a comeback after the drug is withdrawn.

Dapsone is active against certain protozoa as well. Combined with pyrimethamine, it is an alternative to sulfadoxine-pyrimethamine for *P. falciparum* and *Toxoplasma gondii* infections, as well as for the fungus *Pneumocystis jirovecii*. Antiinflammatory property has been detected in dapsone.

Pharmacokinetics Dapsone is completely absorbed after oral administration and is widely distributed in the body, though penetration in CSF is poor. It is 70% plasma protein bound, but more importantly it is concentrated in the skin (especially lepromatous skin), muscle, liver and kidney.

Dapsone is acetylated as well as glucuronide and sulfate conjugated in liver. Metabolites are excreted in bile and reabsorbed from intestine, so that ultimate excretion occurs mostly in urine. The plasma t½ of dapsone is variable, though often > 24 hrs. The drug is cumulative due to retention in tissues and enterohepatic circulation. Elimination takes 1–2 weeks or longer.

DAPSONE 25, 50, 100 mg tab.

Adverse effects Dapsone is generally well tolerated at doses 100 mg/day or less.

Mild haemolytic anaemia is common. This is a dose-related toxicity—reflects oxidising property of the drug. Patients with G-6-PD deficiency are more susceptible; doses > 50 mg/day produce haemolysis in such subjects.

Gastric intolerance—nausea and anorexia are frequent in the beginning, decrease later.

Other side effects are methaemoglobinaemia, headache, paresthesias, mental symptoms and drug fever.

Cutaneous reactions include itching, allergic rashes, fixed drug eruption, hypermelanosis, phototoxicity and rarely exfoliative dermatitis.

Hepatitis and agranulocytosis are rare complications.

Sulfone syndrome It is the reaction which develops 4–6 weeks after starting dapsone treatment: consists of fever, malaise, lymph node enlargement, desquamation of skin, jaundice and anaemia. It is generally seen in malnourished patients, and has become more frequent after the introduction of MDT. Some or all of the above symptoms may occur. Its treatment consists of stopping dapsone and instituting corticosteroid therapy along with supportive measures.

Contraindications Dapsone should not be used in patients with severe anaemia (Hb < 7 g/ dl), G-6-PD deficiency and in those showing hypersensitivity reactions.

Other use In combination with pyrimethamine, dapsone can be used for chloroquine-resistant malaria, toxoplasmosis and *P. jirovecii* infection.

Clofazimine (Clo)

It is a dye with leprostatic and antiinflammatory properties. The putative mechanisms of antileprotic action of clofazimine are:

- Interference with template function of DNA in *M.leprae*
- Alteration of membrane stucture and its transport function.
- Disruption of mitochondrial electron transport chain.

When used alone, the clinical response to clofazimine is slower than that to dapsone, and resistance develops in 1–3 years. Dapsone-resistant *M. leprae* respond to clofazimine, but apparently after a lag period of about 2 months.

Clofazimine is orally active (40–70% absorbed). It accumulates in macrophages and gets deposited as needle shaped crystals in many tissues including subcutaneous fat. However, entry in CSF is poor. The t½ is 70 days so that intermittent therapy is possible.

CLOFOZINE, HANSEPRAN 50, 100 mg cap.

Clofazimine is used as a component of multidrug therapy (MDT) of leprosy. Because of its antiinflammatory property, it is valuable in lepra reaction.

Occasionally, it is used as a component of combination regimen for extensive drug resistant TB (XDR-TB).

Adverse effects In the doses employed for MDT, clofazimine is well tolerated.

Skin The major disadvantage is reddish-black discolouration of skin, especially on exposed parts. Discolouration of hair and body secretions may also occur, but is harmless. Dryness of skin, itching and scaling is often troublesome. Acneform eruptions and phototoxicity have been noted. Conjunctival pigmentation may create cosmetic problem.

GI symptoms Nausea, anorexia, abdominal pain, weight loss and enteritis with intermittent loose stools can occur, particularly when higher doses are used to control lepra reaction. It subsides with dose adjustment and by taking the drug with meals. Deposition of clofazimine crystals in the intestinal submucosa may produce late start g.i. symptoms.

Clofazimine is to be avoided during early pregnancy and in patients with liver or kidney damage.

Rifampin (R)

This important tuberculocidal drug is also the most potent cidal drug for *M.leprae*. It rapidly renders leprosy patients noncontagious. Upto 99.99% *M.leprae* are killed in 3–7 days by 600 mg/day dose. Clinical effects of rifampin are very rapid; nasal symptoms in lepromatous leprosy subside within 2–3 weeks and skin lesions start regressing by 2 months. However, nerve damage already incurred is little benefited. Moreover, it is not satisfactory if used alone; some bacilli persist even after prolonged treatment and resistance develops. Rifampin has been included in the MDT of leprosy whereby it shortens the duration of treatment, and prevents development of resistance. Persistence of dormant rifampin-sensitive bacilli, even after prolonged therapy has also been noted. However, relapse caused by such bacilli can be treated with the same MDT. Rifampin remains effective in leprosy even if given once a month. The 600 mg monthly dose used in MDT is practically nontoxic and does not cause enzyme induction to affect metabolism of other drugs. However, it should not be given to patients with hepatic or renal dysfunction, as well as during '*erythema nodosum leprosum*' (ENL) or '*reversal reaction*' in leprosy patients, because it can release large quantities of mycobacterial antigens by inducing rapid bacillary killing.

Ethionamide This antitubercular drug has significant antileprotic activity, but is poorly tolerated and causes hepatotoxicity in ~ 10% patients. It has been used as an alternative to clofazimine, but other substitutes are preferred. Ethionamide 250 mg/day may be used only when absolutely necessary.

Ofloxacin

Many fluoroquinolones (FQs) like ofloxacin, pefloxacin, moxifloxacin, sparfloxacin are highly active against *M.leprae*, but ciprofloxacin has poor activity. Clinically, ofloxacin has been used to the largest extent. As a component of MDT, it has been found to hasten the bacteriological and clinical response. It is cidal to *M.leprae*, and in one study, over 99.9% bacilli were found to be killed by 22 daily doses of ofloxacin monotherapy. However, it is not yet included in the standard treatment protocols, but can be used in alternative regimens in case rifampin cannot be used, or to shorten the duration of treatment and reduce chances of drug resistance.

However, safety during long-term use is not well documented. *Dose:* 400 mg/day.

Moxifloxacin is the most potent FQ against *M. leprae*. Recently, it has been tried in some combination regimens with good clinical and bacteriological results.

Minocycline

Because of high lipophilicity, this tetracycline penetrates into *M.leprae* and is active against them. A dose of 100 mg/day produces peak blood levels that exceed MIC against *M. leprae* by 10–20 times. Antileprotic activity of minocycline is less marked than that of rifampin, but greater than that of clarithromycin. In one trial monotherapy with minocycline 100 mg daily rendered all 8 patients of lepromatous leprosy negative for *M. leprae* after 8 weeks. A good clinical response in terms of relief of lepromatous symptoms has also been reported. Vertigo is the only serious complication of its long-term use. Minocycline is being tried in alternative MDT regimens.

Clarithromycin

It is the only macrolide antibiotic with significant activity against *M. leprae*. However, it is less bactericidal than rifampin. Monotherapy with clarithromycin 500 mg daily caused 99.9% bacterial killing in 8 weeks. Rapid clinical improvement also occurred in lepromatous patients. A synergistic action with minocycline has been demonstrated. It is being included in alternative MDT regimens.

TREATMENT OF LEPROSY

Leprosy is a chronic granulomatous infection caused by *Mycobacterium leprae*; primarily affecting skin, mucous membranes and nerves. It is more prevalent among the lowest socio-economic strata. Many patients exploit it for begging. In India, the National Leprosy Control Programme was launched in 1955, and was changed to National Leprosy Eradication Programme (NLEP) in 1982. Following the initiative under WHO Action Programme for Elimination of Leprosy, India introduced multidrug therapy (MDT) for leprosy through NLEP in 1982 and achieved elimination of leprosy as a public health problem (prevalence rate < 1 case per 10,000 population) in Dec. 2005, but some states still have >1 case per 10,000.*

Though the burden of leprosy has fallen drastically after introduction of MDT, both globally and in India, current WHO data show that India has the largest number of leprosy patients in the world. In 2015-16 a total of 1,27,326 new cases of leprosy were detected in India, accounting for ~ 60% of global total new cases; out of this 51% were multibacillary leprosy (MBL) cases.

Leprosy manifests in several clinical forms. The most widely used classification of leprosy is that of Ridley and Jopling (1966) who divided leprosy into Lepromatous (LL), Borderline lepromatous (BL), Borderline (BB), Borderline tuberculoid (BT), and Tuberculoid (TT). The important features of the two polar types are given in the box:

Tuberculoid leprosy	Lepromatous leprosy
Anaesthetic patch	Diffuse skin and mucous membrane infiltration, nodules
Cell mediated immunity (CMI) is normal	CMI is absent
Lepromin test—positive	Lepromin test—negative
Bacilli rarely found in biopsies	Skin and mucous membrane lesions teeming with bacilli
Prolonged remissions with periodic exacerbations	Progresses to anaesthesia of distal parts, atrophy, ulceration, absorption of digits, etc.

For operational simplicity WHO divided leprosy into:

1. *Paucibacillary leprosy (PBL)* Patient has few bacilli and is noninfectious. It includes the TT and BT types.
2. *Multibacillary leprosy (MBL)* Patient has large bacillary load and is infectious. It includes the LL, BL and BB types.

* National leprosy eradication programme–Annual report for the year 2015-16; nlep.nic.in > pdf > revised annual report 2015-16.

To further simplify the classification so that it may be applied at the field level, WHO reclassified leprosy in 1998 into:

- *Single lesion paucibacillary leprosy (SL PB)*: With a solitary cutaneous lesion.
- *Paucibacillary leprosy (PB):* With 2–5 skin lesions. Both SLPB and PB cases are skin smear negative for *M.leprae*.
- *Multibacillary leprosy (MB):* With ≥ 6 skin lesions, as well as all smear positive cases.

The classification being followed by NLEP since 2009 is given in the box below.

In the past, all forms of leprosy was treated with dapsone alone (monotherapy: MT) 100–200 mg daily, 5 days a week; duration of treatment depending on the type: TT–4 to 5 years, LL–8 to 12 years or lifelong. With this monotherapy symptomatic relief took few months, and bacteriological cure was delayed or did not occur. Emergence of dapsone resistance since 1964 threatened the efficacy of monotherapy, and upto 20% patients relapsed. Even primary dapsone resistance was increasingly encountered. Monotherapy is no longer given.

Multidrug therapy (MDT) of leprosy

To deal with dapsone resistant strains of *M. leprae* and to shorten the duration of treatment as well as to eliminate microbial persisters, i.e. dormant forms, multidrug therapy with rifampin, dapsone and clofazimine was introduced by the WHO in 1981. This was implemented under the NLEP in 1982. The MDT is the regimen of choice for all cases of leprosy. Its advantages are:

- It is effective in cases with primary dapsone resistance.
- It prevents emergence of dapsone resistance.
- It affords quick symptom relief, stops progression of disease, prevents further complications and renders MBL cases noncontagious within few days.
- It reduces total duration of therapy and chances of relapse to < 1%.
- The efficacy, safety and acceptability of MDT for both PBL and MBL is excellent.
- No resistance to rifampin has developed after use of MDT, and *M. leprae* isolated from relapse cases have remained sensitive to it. Clofazimine resistance has also not been reported. Relapse cases have been successfully treated by the same MDT.

Initially under the standard MDT, the PBL cases were treated with dapsone + rifampin for 6 months, while the MBL cases were treated with dapsone + rifampin + clofazimine for a minimum of 2 years or till disease inactivity/skin smear negativity was achieved. The MBL cases were kept under surveillance without treatment for the next 5 years.

Due to operational reasons, NLEP in India experimented with 'fixed duration therapy of 24 months' (FDT-24) for MBL cases without extending for smear negativity to be achieved, and found that relapse rates were similar to that with the standard protocol. The WHO expert group (1994) also recommended FDT-24 for all MBL cases whether disease inactivity or skin smear negativity was attained or not. The 6 months FDT continues for PBL cases.

MBL Encouraged by the very low relapse rates with 2 yrs FDT-24, studies were undertaken under the aegis of WHO to compare short-duration 12 months (FDT-12) with standard 24 months FDT-24. In the field situation the two were found to yield similar relapse rates over 3–5 yr follow up. Accordingly, a WHO expert committee on leprosy (1997) recommended shortening of MDT to 12 months. This was implemented globally

NLEP (2009) Classification of Leprosy

Paucibacillary leprosy (PBL)	*Multibacillary leprosy (MBL)*
• 1-5 skin lesions	• 6 or more skin lesions
• No nerve or only one nerve involvement, ± 1–5 skin lesions.	• > 1 nerve involved irrespective of number of skin lesions
• Skin smear negative at all sites	• Skin smear positive at any one site

including India.* The currently used MDT (FDT-12) for MBL and 6 months MDT for PBL is given in the box:

Multidrug therapy (MDT) of leprosy

	Multibacillary	*Paucibacillary*
Rifampin	600 mg once a month supervised	600 mg once a month supervised
Dapsone	100 mg daily self administered	100 mg daily self administered
Clofazimine	300 mg once a month supervised + 50 mg daily self administered	—
Duration	12 months	6 months

Child dose

Rifampin	:	10 mg/kg once monthly
Clofazimine	:	1 mg/kg daily + 6 mg/kg once monthly
Dapsone	:	2 mg/kg daily

- *Relapse of leprosy* The same MDT (12 months for MBL and 6 months for PBL) is started on confirmation of relapse.
- *Leprosy and TB coinfection* MDT for leprosy is continued, but rifampin is given daily as for treatment of TB.
- *Leprosy in HIV patients* No association of leprosy with HIV infection has been found. MDT for leprosy can be given safely to HIV +ive patients and to those receiving anti-retroviral therapy.

A few studies, (mostly institutional) have shown that despite 2 yr MDT, some patients continue to harbour viable *M. leprae* (persisters). Relapse rates are higher in the later years of follow up and in the subgroup of patients with large bacillary load, i.e. bacillary index (BI) ≥ 4+.

The primary purpose of mass programmes (WHO Action Programme for the Elimination of Leprosy, or NLEP-India) is to render patients non-contagious so as to cut down transmission. For this, 1 yr FDT may be considered adequate. Even if some patients relapse later, they can be treated by reinstituting MDT, because the dormant bacilli remain sensitive to the same drugs. This is more cost-effective than treating all patients with a longer MDT to prevent a few relapses. Moreover, case reports and prolonged follow-ups show that some patients relapse upto 15 years after being cured of MBL by extended-MDT till smear negativity. Thus, few relapses cannot be prevented irrespective of the duration of regimen or the drugs used in the regimen, probably reflecting invincibility of the 'persister' bacilli.

On the other hand, in private or institutional care, the aim is cure of every individual patient. Upto 4 years may be needed for this, particularly in highly bacillated patients (BI ≥4+). In the USA more intensive (daily rifampin) and longer lasting (12 months for PBL and 24 months for MBL cases) regimens are used.

PBL For PBL, 6 months 2 drug therapy has now been used for > 30 yrs with very encouraging results. Field studies from various parts of the world suggest that this is adequate, provided that the patient is kept on follow up for the subsequent 1–2 years. Some reports indicate that proportion of patients staying active can be reduced by 12 months MDT for PBL. Independent leprologists prefer to extend therapy of PBL to 12 months or longer till disease inactivity is achieved.

It may be concluded that, where feasible, treatment till cure of individual patient should be ensured both in MBL and in PBL. However, in mass programmes FDT-12 for MBL cases and FDT-6 for PBL cases may be the more practical approach to cover every leprosy patient.

Alternative regimens Many alternative regimens incorporating newer antileprotic drugs have been investigated. However, these are used only in case of rifampin-resistance or when it is impossible/inadvisable to employ the standard MDT regimen. Some of these are:

- *Intermittent ROM*: Rifampin 600 mg + ofloxacin 400 mg + minocycline 100 mg are given once a month for 3–6 month for PBL and for 12 or 24 month for MBL cases, without any drug in between.
- Cloflazimine 50 mg + any two of ofloxacin 400 mg/ minocycline 100 mg/clarithromycin 500 mg daily for 6 month, followed by clofazimine 50 mg + any one of ofloxacin 400 mg/minocycline 100 mg daily for additional 18 months.
- Four drug regimen of rifampin 600 mg + sparfloxacin 200 mg + clarithromycin 500 mg + minocycline 100 mg daily for 12 weeks has yielded equivalent clinical improvement in MBL cases to standard 12 month MDT.
- In case of refusal to accept clofazimine: ofloxacin 400 mg or minocycline 100 mg daily can be substituted for it in the standard MDT. Use of ethionamide as a substitute is not recommended.

* Short Course Treatment of Leprosy: present status; ICMR Bulletin 2002; 32(2): 13–19.

Highlights of multidrug therapy (MDT) of leprosy*

- Worldover the case load of leprosy was ~ 12 million before introduction of MDT, whereas little over 0.2 million new cases were detected during 2015.
- In India a total of 13.05 million patients of leprosy have been treated and cured by MDT, with very few relapses, from the introduction of MDT in 1982 till March 2016.
- In 1981 India recorded a total of 3.95 million leprosy cases. With institution of MDT in 1982, it has fallen to 0.127 million new cases detected during 2015–16.
- India achieved elimination of leprosy as a public health problem (prevalence rate < 1 case per 10,000 population) in Dec. 2005, by the use of MDT.
- In 2015–16 a total of 1.28 lakh (92.8%) cases of leprosy have been treated and cured by MDT in India. During this period, only 276 cases of relapse were confirmed.
- The prevalence of leprosy in India was 57.6 cases per 10,000 population in 1981. It has fallen to 0.66 cases per 10,000 in 2016
- Prevalence of lepra reaction has not increased due to use of MDT.

* The figures are based on WHO and NLEP data

- *Intermitent RMMx*: Moxifloxacin 400 mg + minocycline 200 mg + rifampin 600 mg is administered once a month: 6 doses given for PBL and 12 doses given for MBL cases have produced rapid and marked clinical response.

Reactions in leprosy

Lepra reaction This occurs in LL, usually coincides with institution of chemotherapy and/or intercurrent infection. It is a Jarish Herxheimer (Arthus) type of reaction due to release of antigens from the killed bacilli, and may be mild, severe or life-threatening, i.e. erythema nodosum leprosum (ENL).

Lepra reaction is of abrupt onset; existing lesions enlarge, become red, swollen and painful; several new lesions may appear. Malaise, fever and other constitutional symptoms generally accompany and may be marked.

Temporary discontinuation of dapsone is recommended only in severe cases. Clofazimine (200 mg daily) is effective in controlling the reaction (except the severe one), probably because of its antiinflammatory property. For severe reaction, prednisolone 40–60 mg/day is started immediately and continued till the reaction subsides. The dose is then tapered over 2–3 months.

Thalidomide It is an antiinflammatory, cytokine (TNF_α, ILs, interferon) modulating drug with anxiolytic, antiemetic property. Thalidomide can be used in ENL as an alternative to prednisolone. It was introduced in 1958 for morning sickness was found to be highly teratogenic (*see* p. 100), and withdrawn in 1961. It has been reintroduced for ENL as well as a variety of other conditions in which cytokines play an important role like cancer-associated cachexia; also used in multiple myeloma.

Dose: For ENL 100–300 mg OD at bed time.

THAANGIO, THALODA 50, 100 mg cap.

Other drugs used in lepra reactions are—analgesics, antipyretics, antibiotics, etc. according to symptoms and need. Chloroquine also suppresses lepra reaction.

Reversal reaction This is seen in TT and BL cases, and is a manifestation of delayed hypersensitivity to *M. leprae* antigens. Cutaneous ulceration, multiple nerve involvement with swollen, painful and tender nerves occur suddenly even after completion of therapy. Reversal reaction is treated with clofazimine or corticosteroids in the same way as ENL, but thalidomide is ineffective.

PROBLEM DIRECTED STUDY

57.1 A 50-year-old male attends the hospital OPD with multiple, diffusely raised nodules over the face and arms which have appeared over the past 1 month. The skin over the lesions is reddish and glossy. Sensation over face and arms is diminished and the ulnar nerve is thickened. He informs that 6 years back he had suffered from similar lesions and had taken regular medication for the same for one year and was declared cured. The treatment records revealed that he was given the standard multidrug therapy with rifampin, clofazimine and dapsone and had successfully completed the one year course. The skin smear is positive for *M. leprae*.
(a) What could be the cause of relapse of leprosy in this case? What treatment should be prescribed?
(*see* Appendix-1 for solution)

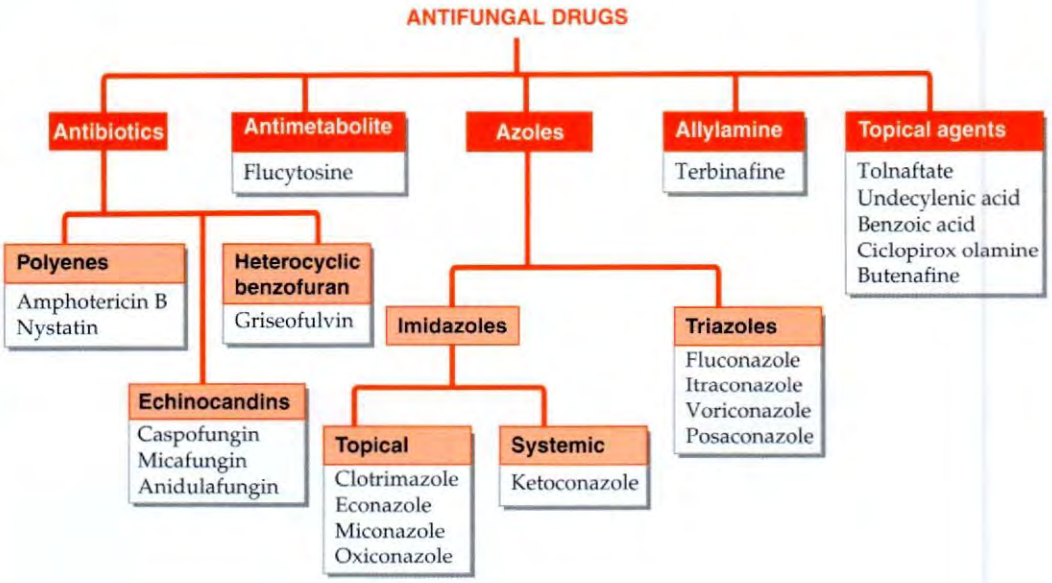
CHAPTER 57

Chapter 58 Antifungal Drugs

These are drugs used for superficial and deep (systemic) fungal infections.

A disquietening trend after 1950s is the rising prevalence of more sinister type of fungal infections which are, to a large extent, iatrogenic. Fungal infections are mostly associated with the use of broad-spectrum antibiotics, corticosteroids, anticancer/immunosuppressant drugs, dentures, indwelling catheters and implants, and emergence of AIDS. As a result of breakdown of host defence mechanisms by the above agents, saprophytic fungi easily invade living tissue.

Many topical antifungals have been available since the antiseptic era. Two important antibiotics *viz. amphotericin B*—to deal with systemic mycosis, and *griseofulvin*—to supplement attack on dermatophytes were introduced around 1960. Antifungal property of flucytosine was noted in 1970, but it could serve only as a companion drug to amphotericin. The development of *imidazoles* in the mid 1970s and *triazoles* in 1980s provided safer and more convenient alternatives to amphotericin B and griseofulvin. *Terbinafine* is a novel antifungal. A group of



potent semisynthetic antifungal antibiotics, the *Echinocandins* are the latest addition.

POLYENE ANTIBIOTICS

The name *polyene* is derived from their highly double-bonded structure. Amphotericin B is described as the prototype.

Amphotericin B (AMB)

It is obtained from *Streptomyces nodosus*.

Chemistry and mechanism of action The polyene antibiotic molecule is a macrocyclic ring, one side of which has several conjugated double bonds and is highly lipophilic, while the other side is hydrophilic with many OH groups. A polar aminosugar and a carboxylic acid group are present at one end in some. All polyenes are insoluble in water and unstable in aqueous medium.

Polyene antibiotics have high affinity for ergosterol present in fungal cell membrane. They combine with it, get inserted into the membrane and several polyene molecules together orient themselves in such a way as to form a 'micropore' (*see* Fig. 58.1). The hydrophilic side forms the interior of the pore through which ions, amino acids and other water-soluble substances move out. The micropore is stabilized by membrane sterols which fill up the spaces between the AMB molecules on the lipophilic side—constituting the outer surface of the pore. Thus, cell permeability is markedly increased.

Cholesterol, present in host cell membranes, closely resembles ergosterol; the polyenes bind to cholesterol as well, though with lesser affinity. Thus, the selectivity of action of polyenes is low, and AMB is one of the most toxic systemically used antibiotics, though it is the least toxic polyene. Bacteria do not have sterols and are unaffected by polyenes.

It has been found that AMB enhances immunity in animals, and this action may aid immunocompromised individuals in handling fungal infection.

Antifungal spectrum AMB is active against the most wide range of yeasts and fungi—*Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Blastomyces dermatitidis, Coccidioides immitis, Torulopsis, Rhodotorula, Aspergillus, Sporothrix,* etc. Dermatophytes are inhibited *in vitro*, but concentrations of AMB attained in infected skin are low and ineffective. It is fungicidal at high and static at low concentrations.

Resistance to AMB during therapy has been rarely noted among *Candida* in a selected group of leucopenic cancer patients, but it is not a problem in the clinical use of the drug.

AMB is also active on various species of *Leishmania,* a protozoa.

Pharmacokinetics AMB is not absorbed orally, but can be given orally for intestinal candidiasis without systemic toxicity. Administered i.v. as a suspension made with the help of deoxycholate (DOC), it gets widely distributed in the body, but penetration in CSF is poor. It binds to sterols in tissues and to lipoproteins in plasma and stays in the body for long periods. The terminal elimination t½ is 15 days. About 60% of AMB is metabolized in the liver. Excretion occurs slowly both in urine and bile, but urinary concentration of active drug is low. No dose adjustment is needed in patients with kidney or liver disease.

Administration and dose Amphotericin B can be administered orally (50–100 mg QID) for intestinal moniliasis; also topically for vaginitis, otomycosis, etc.:
FUNGIZONE OTIC 3% ear drops.

Conventional formulation of AMB (C-AMB) For systemic mycosis, C-AMB is available as dry powder along with deoxycholate (DOC) for extemporaneous dispersion before use:
FUNGIZONE INTRAVENOUS, MYCOL 50 mg vial.

It is first suspended in 10 ml water and then diluted to 500 ml with glucose solution (saline makes the suspension coarse, should be avoided). Initially 1 mg test dose is injected i.v. over 20 minutes. If no serious reaction follows, 0.3 mg/kg is infused over 4–8 hours. Daily dose may be gradually increased to 0.7 mg/kg depending on tolerance of the patient. The total dose of AMB for majority of cases is 3–4 g given over 2–3 months.

Intrathecal injection of 0.5 mg twice weekly has been given in fungal meningitis.

Liposomal amphotericin B (L-AMB) It has been produced to improve tolerability of i.v. infusion of AMB, reduce its

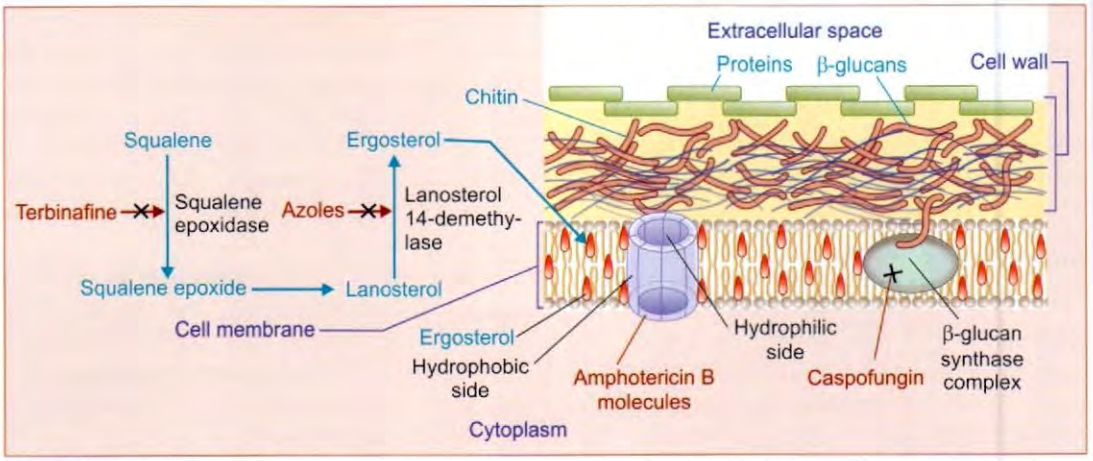


Fig. 58.1: Fungal cell wall and cell membrane along with schematic depiction of the mechanism of action of amphotericin B (AMB), caspofungin, azole antifungals and terbinafine
Note: The AMB molecules aggregate and orient in the fungal cell membrane to form a pore. The inner surface of the pore is formed by the hydrophilic side of AMB molecules through which ions, amino acids, etc. leak out. The outer surface of the pore is formed by the hydrophobic side of AMB molecules which are stabilized by interaction with ergosterol.

SECTION 12

toxicity and achieve targeted delivery. It consists of 10% AMB incorporated in uniform sized (60–80 nM) unilamellar liposomes made up of lecithin and other biodegradable phospholipids.

The special features of this preparation are:

- It produces milder acute reaction on i.v. infusion.
- It can be used in patients not tolerating infusion of conventional AMB formulation.
- It has lower nephrotoxicity.
- It causes minimal anaemia.
- It delivers AMB particularly to reticuloendothelial cells in liver and spleen—especially valuable for kala azar and in immunocompromised patients.

The *liposomal-AMB* produces equivalent blood levels, has similar clinical efficacy with less acute reaction and renal toxicity than conventional preparaton. It thus appears more satisfactory, can be infused at higher rates (3–5 mg/kg/day), but is many times costlier than conventional AMB. L-AMB is specifically indicated for empirical therapy in febrile neutropenic patients not responding to antibacterial antibiotics, critically ill deep mycosis cases and in kala azar. FUNGISOME (liposomal AMB) 10 mg, 25 mg, 50 mg per vial inj., AMPHOLIP 10 mg/2 ml, 50 mg/10 ml, 100 mg/20 ml inj.

Adverse effects The toxicity of AMB is high.

(a) *Acute reaction* This occurs with each infusion and consists of chills, fever, aches and pain all over, nausea, vomiting and dyspnoea lasting for 2–5 hour, probably due to release of cytokines (IL, TNFα). When the reaction is severe—the dose should be increased gradually. Usually the intensity of reaction decreases with continued medication. Injection of hydrocortisone 0.6 mg/kg with the AMB infusion may reduce the intensity of reaction.

Thrombophlebitis of the injected vein can occur.

(b) *Long-term toxicity* Nephrotoxicity is the most important. It occurs fairly uniformly and is dose-related. Manifestations are—azotemia, reduced g.f.r., acidosis, hypokalaemia and inability to concentrate urine. Nephrotoxicity reverses slowly and often incompletely after stoppage of therapy.

Anaemia: Most patients develop slowly progressing anaemia which is due to bone marrow depression. This is largely reversible.

CNS toxicity: occurs only on intrathecal injection—headache, vomiting, nerve palsies, etc.

Uses Amphotericin B can be applied topically for oral, vaginal and cutaneous candidiasis, fungal corneal ulcer and otomycosis.

It is the most effective drug for practically all types of *systemic mycoses* and is the gold standard of antifungal therapy. However, because of higher toxicity of AMB, the azole antifungals are now preferred in conditions where their efficacy approaches that of AMB (*see* Table 58.1).

In serious fungal infections, especially in immunocompromised patients, initial induction therapy with AMB may be replaced by the alternative safer azole antifungal drug for

Table 58.1: Choice of drugs for systemic mycoses

Disease	Drugs	
	1st Choice	*2nd Choice*
1. Candidiasis		
oral/vaginal/cutaneous	FLU/NYS/CLO	ITR
deep/invasive	AMB/VORI	FLU/CAS/POSA
2. Cryptococcosis	AMB ± 5-FC	FLU
3. Histoplasmosis	ITR/AMB	FLU
4. Coccidioidomycosis	AMB/FLU	ITR
5. Blastomycosis	ITR/AMB	FLU
6. Sporotrichosis (disseminated)	AMB	ITR
7. Paracoccidioidomycosis	ITR	AMB
8. Aspergillosis	VORI/AMB	ITR/CAS/POSA
9. Mucormycosis	AMB	POSA
10. Chromomycosis	ITR	TER/POSA

AMB—Amphotericin B; 5-FC—Flucytosine; KTZ—Ketoconazole; FLU—Fluconazole; ITR—Itraconazole; NYS—Nystatin; CLO—Clotrimazole; VORI—Voriconazole; CAS—Caspofungin; POSA—Posaconazole; TER—Terbinafine

continuation of therapy. Some properties of antifungal drugs used for systemic mycosis are compared in Table 58.2.

Febrile neutropenia: Empirical use of i.v. AMB is often made in neutropenic patients whose fever is not responding to i.v. bactericidal antibiotics.

Leishmaniasis: AMB is the most effective drug for resistant cases of kala azar and mucocutaneous leishmaniasis (*see* Ch. 62).

Interactions Flucytosine (5-FC) has supra-additive action with AMB in the case of fungi sensitive to both (AMB increases the penetration of 5-FC into the fungus).

Aminoglycosides, vancomycin, cyclosporine and other nephrotoxic drugs enhance the renal impairment caused by AMB.

Nystatin

Obtained from *S. noursei*, it is similar to AMB in antifungal action and other properties. However, because of higher systemic toxicity, it is used only locally for superficial candidiasis.

MYCOSTATIN 5 lakh U tab, 1 lakh U vaginal tab, 1 lakh U/g oint, NYSTIN EYE 1 lakh U/g ophthalmic oint.

Given orally, it is not absorbed; can be used for monilial diarrhoea (due to superinfection or otherwise), 5 lac U TDS (1 mg = 2000 U). Nausea and bad taste in mouth are the only side effects.

Nystatin can be used for monilial vaginitis—1 lac U tab is to be inserted twice daily. However, azole antifungals are more effective and preferred now.

As a suspension in glycerine, nystatin can be applied on oral thrush, but clotrimazole is preferred now. Cutaneous and corneal candidiasis can be treated by nystatin ointment. However, it is inefective in dermatophytosis.

ECHINOCANDINS

These are a new class of potent semisynthetic antifungal antibiotics with a complex cyclic lipopeptide structure, which stand out due to their low toxicity compared to AMB.

Caspofungin

It is the first and the prototype member of the class, active mainly against *Candida* and *Aspergillus*. Strains of candida that have become resistant to azoles are susceptible to caspofungin. The mechanism of action is different from other antifungals, *viz.* it inhibits the synthesis of β-1, 3-glucan, which is a unique component of the fungal cell wall. β-glucans are synthesized in the fungal plasma membrane by a complex

of β-glucan synthase enzymes which is inhibited by caspofungin (*see* Fig. 58.1). Cross linking between chitin (a fibrillar polysaccharide) and β-1, 3-glucan gives toughness to the fungal cell wall. Weakening of the cell wall by caspofungin leads to osmotic susceptibility of fungal cell, which then succumbs.

Caspofungin is not absorbed orally; has to be infused i.v. as freshly prepared aqueous solution. It is distributed into tissues, but does not enter CSF. Metabolism is extensive and metabolites are excreted in urine as well as faeces with a plasma t½ of 10 hours. Caspofungin is the preferred drug now for deep and invasive candidiasis. It is also indicated in esophageal candidiasis and salvage therapy of nonresponsive invasive aspergillosis. Because of good tolerability, it is now increasingly used in neutropenic immunocompromised patients whose fever is not responding to antibacterial antibiotics.

Dose: 70 mg loading dose infused i.v. over 1 hour, followed by 50 mg i.v. daily.

CANCIDAS, CASPOGIN 70 mg in 10 ml and 50 mg in 10 ml inj.

An acute febrile reaction some times attends the i.v. infusion of caspofungin, as does phlebitis of the injected vein. Rash, vomiting, dyspnoea, hypokalemia and joint pain may occur, but patient acceptability is good, and organ toxicity has not been noted.

Micafungin Another echinocandin that is approved in India, and has properties similar to caspofungin. Its t½ is some what longer (12–15 hours). In addition to esophageal candidiasis and candidaemia, micafungin (50 mg i.v./day) is indicated for prophylaxis of *Candida* infections in bone marrow transplant patients, but not for aspergillosis.

Anidulafungin is the third echinocandin with still longer t½ (~36 hours), but similar indications.

HETEROCYCLIC BENZOFURAN

Griseofulvin

It was one of the early antibiotics extracted from *Penicillium griseofulvum*. However, because of lack of antibacterial activity, little attention was paid to it: clinical utility in dermatophytosis was demonstrated only around 1960.

Griseofulvin is fungistatic for most dermatophytes, including *Epidermophyton, Trichophyton, Microsporum,* etc., but not against *Candida* and other fungi causing deep mycosis. Bacteria are also insensitive. Dermatophytes actively concentrate griseofulvin accounting for its selective toxicity. Resistance to griseofulvin during clinical use is rare.

Griseofulvin interferes with mitosis—multinucleated and stunted fungal hyphae are produced under its action. Metaphase arrest does not occur, but daughter nuclei fail to move apart or move only a short distance. It binds to polymerized microtubules and interferes with their function.

Pharmacokinetics The absorption of griseofulvin from g.i.t. is incomplete because of very low water solubility. Absorption is improved by taking it with fats and by microfining the drug particles.

Griseofulvin is keratophilic; gets deposited in keratin forming cells of skin, hair and nails. It is largely metabolized, primarily by methylation, and excreted in urine. Plasma t½ is 24 hrs, but it persists for weeks in skin and keratin.

Adverse effects Toxicity of griseofulvin is low and usually not serious. Headache is the commonest complaint, followed by g.i.t. disturbances. CNS symptoms and peripheral neuritis are occasional.

Rashes, photoallergy, hepatitis warrant discontinuation.

Use Griseofulvin is used orally only for dermatophytosis. On getting deposited in the skin through circulation, it prevents fungal invasion of keratin. Because it is fungistatic and not cidal, the newly formed keratin is not invaded by the fungus, but the fungus persists in already infected keratin, till it is shed off. Thus, the duration of treatment is dependent upon the site of infection, thickness of infected keratin and its turnover rate. It is ineffective topically. Systemic azoles and terbinafine are more efficacious, and are preferred now.

Dose: 125–250 mg QID with meals. Duration of therapy depends on the site of infection (turnover rate of keratin).

Scalp	4 weeks
Palm, soles	6 to 8 weeks
Finger nails	6 to 8 months
Toe nails	10 to 12 months

Majority of localized tinea infections are treated with topical agents. Griseofulvin should be reserved for cases with large body surface involvement, onychomycosis and tinea capitis. It is effective in athletes foot, but not in pityriasis versicolor.

GRISOVIN-FP, WALAVIN, GRISORAL 250 mg tab.

Interactions Griseofulvin induces CYP450 enzymes and hastens warfarin metabolism. Efficacy of oral contraceptives may be lost.

ANTIMETABOLITE

Flucytosine (5-FC)

It is a pyrimidine antimetabolite which is inactive as such. After uptake into fungal cells, it is converted into 5-fluorouracil and then to 5-fluorodeoxyuridylic acid which is an inhibitor of thymidylate synthesis. Thymidylic acid is a component of DNA. The fungal selectivity of 5-FC depends on the fact that mammalian cells (except some marrow cells) have low capacity to convert 5-FC into 5-fluorouracil. Therefore, 5-FC has no anticancer activity.

5-FC is a narrow spectrum fungistatic, active against *Cryptococcus neoformans, Torula, Chromoblastomyces*; and a few strains of *Candida*. Other fungi and bacteria are insensitive.

Adverse effects Toxicity of 5-FC is lower than that of AMB; consists of dose-dependent bone marrow depression and gastrointestinal disturbances, particularly enteritis and diarrhoea.

Liver dysfunction is mild and reversible.

Use Flucytosine is not employed as the sole therapy. Rapid development of resistance limits its utility in deep mycosis. In cryptococcosis (both meningeal and nonmeningeal) its synergistic action with AMB is utilized to reduce the total dose of the more toxic latter drug. Therapy with 5-FC is generally limited to first 2 weeks of AMB regimen to avoid its bone marrow toxicity.

IMIDAZOLES AND TRIAZOLES (AZOLES)

These are presently the most extensively used antifungal drugs.

Four imidazoles are entirely topical, while ketoconazole is used both orally and topically. Two triazoles fluconazole and itraconazole have largely replaced ketoconazole for systemic mycosis because of greater efficacy, longer t½, as well as fewer side effects. Voriconazole and posaconazole are the newer triazoles.

The azoles have broad-spectrum antifungal activity covering dermatophytes, *Candida*, other fungi involved in deep mycosis (except mucor), *Nocardia* and *Leishmania*.

The azoles act by inhibiting fungal cytochrome P450 enzyme 'lanosterol 14-demethylase' and thus impair ergosterol synthesis (*see* Fig. 58.1). This leads to a cascade of membrane abnormalities in the fungus. The lower host toxicity of triazoles compared to imidazoles has correlated with their lower affinity for mammalian CYP450 enzymes and lesser propensity to inhibit mammalian sterol synthesis.

Development of fungal resistance to azoles has been noted among *Candida* infecting advanced AIDS patients, but has not so far posed significant clinical problem in immunocompetent patients, except fluconazole resistance among *Candida* causing esophageal and other deep candidasis. Many of fluconazole-resistant *Candida* respond to itraconazole or to voriconazole. Mutation of the gene encoding for fungal 14-demethylase enzyme underlies azole resistance.

Clotrimazole It is the most commonly used topical imidazole effective in the treatment of tinea infections like ringworm: 60–100% cure rates are reported with 2–4 weeks application on a twice daily schedule. Athletes' foot, otomycosis and oral/cutaneous/vaginal candidiasis have responded in >80% cases. It is particularly favoured for vaginitis because of a long lasting residual effect after once daily application. A 7 day course is generally used. For oropharyngeal candidiasis 10 mg troche of clotrimazole is allowed to dissolve in the mouth 3–4 times a day, or the lotion/gel is applied/swirled in the mouth for as long as possible. It is also effective in skin infections caused by *Corynebacteria*, but like most topical antifungals, has poor efficacy in tinea capitis (scalp) and tinea unguium (nails).

Clotrimazole is well tolerated by most patients. Local irritation with stinging and burning sensation occurs in some. No systemic toxicity is seen after topical use.

SURFAZ, CLODERM 1% lotion, cream, powder; 1% ear drops with 2% lidocaine, 100 mg vaginal tab. CANDID 1% cream, mouth paint, powder, 1% ear drops with 2% lidocaine.

Econazole It is similar to clotrimazole; penetrates superficial layers of the skin and is highly effective in dermatophytosis, otomycosis, oral thrush, but is somewhat inferior to clotrimazole in vaginitis. No adverse effects, except local irritation in few is reported.

ECONAZOLE 1% oint, 150 mg vaginal tab; ECODERM 1% cream.

Miconazole It is a highly efficacious (>90% cure rate) drug for tinea, pityriasis versicolor, otomycosis, cutaneous and vulvovaginal candidiasis. Because of its good penetrating power,

single application on skin acts for a few days. Irritation after cutaneous application is infrequent, but a higher incidence of vaginal irritation is reported in comparison to clotrimazole.

DAKTARIN 2% gel, 2% powder and solution; GYNODAKTARIN 2% vaginal gel; ZOLE 2% oint, lotion, dusting powder and spray, 1% ear drops, 100 mg vaginal ovules.

Oxiconazole A newer topical imidazole antifungal effective in tinea and other dermatophytic infection, as well as in vaginal candidiasis. Local irritation can occur in some patients.

OXIZON, ZODERM: oxiconazole 1% with benzoic acid 0.25% cream/lotion; apply topically once or twice daily.

Ketoconazole (KTZ)

It is the first orally effective broad-spectrum antifungal drug, useful in both dermatophytosis and deep mycosis, but has been overshadowed by the newer triazoles. The oral absorption of KTZ is facilitated by gastric acidity. Hepatic metabolism is extensive; metabolites are excreted in urine and faeces with a variable t½ of 4–8 hours. The oral dose is 200 mg OD, but systemic use of KTZ is infrequent now.

FUNGICIDE, NIZRAL, KETOVATE 200 mg tab.

FUNGINOC 2% oint, 2% shampoo (for dandruff), KETOVATE 2% cream. NIZRAL 2% cream, 2% lotion; DANRUF 2% shampoo, HYPHORAL 2% lotion.

Adverse effects Ketoconazole produces more side effects than itraconazole or fluconazole.

The most common side effects are nausea and vomiting; others are—loss of appetite, headache, paresthesia, rashes and hair loss.

The major drawback of KTZ is its hormonal effects. It decreases androgen production from testes, and displaces testosterone from protein binding sites. Gynaecomastia, loss of hair and libido, and oligozoospermia may develop when the drug is used for a few weeks. Menstrual irregularities occur in some women due to suppression of estradiol synthesis.

A dose-dependent decrease in serum hydrocortisone due to synthesis inhibition has also been noted.

Interactions Ketoconazole (and most azoles) interact with several drugs. Due consideration must be given when azoles are coprescribed with other drugs.

- H_2 blockers, proton pump inhibitors and antacids decrease oral absorption of KTZ by reducing gastric acidity.
- Rifampin, phenobarbitone, carbamazepine and phenytoin induce KTZ metabolism and reduce its efficacy.
- Ketoconazole inhibits CYP450 enzymes, especially CYP3A4, CYP2C9; CYP2C19 and raises the blood levels of several drugs including:

Phenytoin	Digoxin
Carbamazepine	Omeprazole
Diazepam	Cyclosporine
Haloperidol	Nifedipine and other DHPs
Warfarin	HIV protease inhibitors
Sulfonylureas	Statins

Use Orally administered KTZ is effective in *dermatophytosis* because it is concentrated in the stratum corneum, but use is restricted due to potential adverse effects. Used as a lotion or shampoo, KTZ is quite effective in seborrhoea of scalp and dandruff. Pityriasis versicolor involving limited area of skin can also be treated by topical application of the lotion/shampoo formulation. Weekly treatment may be continued to prevent recurrences.

Though effective in *monilial vaginitis*, oral therapy (for 5–7 days) with KTZ is reserved for recurrent cases or those not responding to topical agents.

Oral KTZ is no longer used in systemic mycosis.

High-dose KTZ has been used in Cushing's syndrome to decrease corticosteroid production.

Fluconazole It is a water-soluble triazole having a wider range of activity than KTZ; indications include cryptococcal meningitis, systemic and mucosal candidiasis in both normal and immunocompromised patients, coccidioidal meningitis and some tinea infections.

Fluconazole is 94% absorbed; oral bioavailability is not affected by food or gastric pH. It is primarily excreted unchanged in urine with a t½ of 25–30 hr. Fungicidal concentrations are achieved in nails, vagina and saliva. It is the preferred azole for fungal meningitis because

Table 58.2: Properties of drugs used for systemic mycoses

Characteristic	*AMB*	*Caspo*	*5-FC*	*FLU*	*ITR*	*VORI*
Antifungal spectrum	Broad	Narrow	Narrow	Broad	Broad	Broad
Oral absorption	Nil	Nil	High	High	Variable	High
Administered i.v.	Yes	Yes	No	Yes	Yes	Yes
Elimination route	H, R	H, R	R	R	H	H
Half life	15 days	10 hr	3-4 hrs	24-30 hrs	24-40 hrs	6 hrs
Resistance (in vivo)	No	No	Yes	Limited	Minor	No
Nephrotoxicity	Yes	No	No	No	No	No
Anaemia	Moderate	No	Mild	No	No	No
Gastrointestinal upset	Brief	Mild	Moderate	Mild	Moderate	Mild
Overall toxicity	High	Low	Medium	Low	Low	Low

AMB—AmphotericinB; 5-FC—Flucytosine; FLU—Fluconazole; ITR—Itraconazole; Caspo—Caspofungin; VORI—Voriconazole; H—Hepatic; R—Renal.

of good penetration into brain and CSF. Dose reduction is needed in renal impairment.

Adverse effects The gastrointestinal tolerability of fluconazole is better than other azoles, but nausea, vomiting, abdominal pain, rash and headache are produced. Incidence and severity of these side effects increases with dose and duration of therapy.

Selectivity for fungal cytochrome P450 is higher. Unlike KTZ, it does not inhibit steroid synthesis in man: antiandrogenic and other endocrine side effects have not occurred.

Elevation of hepatic transaminase has been noted in AIDS patients.

Fluconazole is not recommended in pregnant and lactating women.

Interactions While fluconazole affects hepatic drug metabolism to a lesser extent than KTZ, increased plasma levels of phenytoin, cyclosporine, warfarin, zidovudine and sulfonylureas have been observed. The drug interaction potential of fluconazole is the lowest among azole antifungals, but caution needs to be applied in coadministering other drugs. Proton pump inhibitors and H_2 blockers do not affect its absorption.

Use Fluconazole can be administered orally as well as i.v. (in severe infections). A single 150 mg oral dose can cure vaginal candidiasis with few relapses.

Oral fluconazole (100 mg/day for 2 weeks) is highly effective in oropharyngeal candidiasis, but is reserved for cases not responding to topical antifungals. Fluconazole (100 mg/day) for 2–3 weeks is the first line treatment for candida esophagitis.

Most tinea infections including pityriasis versicolor involving large area of skin and cutaneous candidiasis can be treated with 150 mg weekly fluconazole for 4 weeks.

For disseminated candidiasis, cryptococcal or coccidioidal meningitis and other systemic fungal infections the dose is 200–400 mg/day for 4–12 weeks or longer. In candidemia, therapy may be initiated with i.v. fluconazole and continued orally. Long-term oral fluconazole maintenance therapy after initial treatment with i.v. AMB is used in AIDS patients with fungal meningitis to prevent relapse.

An eye drop is useful in fungal keratitis. Fluconazole is ineffective in aspergillosis and mucormycosis, and inferior to itraconazole for histoplasmosis, blastomycosis and sporotrichosis, as well as for tinea unguium.

SYSCAN, ZOCON, FORCAN, FLUZON 50, 100, 150, 200 mg caps, 200 mg/100 ml i.v. infusion.
SYSCAN 0.3% eye drops.

Itraconazole This orally active triazole antifungal has a broader spectrum of activity than KTZ or fluconazole; includes few moulds like

Aspergillus as well. Some fluconazole resistant *Candida* are susceptible. It is fungistatic, but effective in immunocompromised patients. Steroid hormone synthesis inhibition is absent in itraconazole, and serious hepatotoxicity is rare.

Oral absorption of itraconazole is variable. It is enhanced by food and gastric acid. Itraconazole is highly protein bound, has a large volume of distribution (10 L/Kg), accumulates in vaginal mucosa, skin and nails, but penetration into CSF is poor. It is largely metabolized in liver by CYP3A4; an active metabolite is produced which is excreted in faeces; t½ varies from 24–40 hours.

Itraconazole is well tolerated in doses below 200 mg/day, but doses > 400 mg/day are poorly tolerated. Dizziness, pruritus, headache and hypokalaemia are the other common side effects. Unsteadiness and impotence are infrequent. Plasma transaminase may rise and liver damage is reported. However, antiandrogenic and other hormonal adverse effects are not seen. Impaired left ventricular function has been worsened in some patients after prolonged treatment with itraconazole.

Drug interactions Oral absorption of itraconazole is reduced by antacids, H_2 blockers and proton pump inhibitors.

Rifampin, phenobarbitone, phenytoin and carbamazepine induce itraconazole metabolism and reduce its efficacy.

On the other hand, clarithromycin and HIV protease inhibitors reduce the metabolism of itraconazole and raise its blood levels.

Itraconazole inhibits CYP3A4, but the effect on metabolism of other drugs is less marked than that of KTZ. Nevertheless, phenytoin, digoxin, sulfonylureas, statins, dihydropyridines, protease inhibitors, warfarin and cyclosporine levels are increased by itraconazole.

Uses Itraconazole is the preferred azole antifungal for most *systemic mycosis* (*see* Table 58.1) that are not associated with meningitis. It is superior to fluconazole for histoplasmosis, blastomycosis, sporotrichosis and is the drug of choice for the rare fungal infections—paracoccidioidomycosis and chromomycosis. It also affords some relief in chronic aspergillosis, but voriconazole is superior. A dose of 200 mg OD/BD with meals is used for 3 months or more.

Vaginal candidiasis: 200 mg OD oral for 3 days is as effective as intravaginal clotrimazole.

Dermatophytosis: 100–200 mg OD for 7–15 days. Itraconazole is more effective than griseofulvin, but systemic therapy is resorted to only when topical antifungals fail or in patients with extensive involvement or scalp infection.

Onychomycosis: 200 mg/day for 3 months. An intermittent pulse regimen of 200 mg BD for 1 week each month for 3 months is equally effective. Relapses have occurred after itraconazole therapy, though it remains in the nail for few months after completion of the course.

Pityriasis versicolor: Oral itraconazole is the drug of choice when systemic therapy is needed for involvement of extensive area of skin.

SPORANOX, CANDITRAL, CANDISTAT, ITASPOR, FLUCOVER 100 mg cap. ITASPOR 100 mg cap, 200 mg/20 ml vial.

Voriconazole It is a second generation broad-spectrum triazole introduced for difficult to treat fungal infections. Voriconazole is the drug of choice for invasive *aspergillosis*, disseminated infections caused by fluconazole resistant *Candida*, *Fusarium* infections, and febrile neutropenia not responding to antibacterial therapy. It is also active against histoplasmosis and blastomycosis. Serious cases are first treated i.v. followed by oral voriconazole. It is completely absorbed orally, except when taken with a fatty meal, widely distributed into tissues and metabolized extensively by CYP2C19, CYP3A4, CYP2C9. Metabolites are excreted in urine. The t½ is 6 hours. Voriconazole is also an inhibitor of CYP isoenzymes and the drug interaction profile is similar to itraconazole. Rashes, photosensitivity, rise in liver enzymes and QTc prolongation can occur. Short lasting visual disturbances are common after i.v. injection, and an acute reaction is also possible.

Dose: 200 mg oral BD taken 1 hour before or 1 hour after meal. Begin i.v. infusion with 6 mg/kg 12 hourly infused over 2 hours twice followed by 3–4 mg/kg 12 hourly.

VFEND 50, 200 mg tabs, 40 mg/ml oral suspension; 200 mg/vial inj. , FUNGIVOR 200 mg tab.

Posaconazole This recently introduced broad-spectrum triazole has potent antifungal activity and is the only azole which has shown efficacy in mucormycosis. Posaconazole is indicated for salvage therapy of this difficult to treat fungal infection. Because of its high cost and limited experience, it is reserved for nonresponsive cases of aspergillosis and invasive candidiasis. Favourable results have been reported in febrile neutropenia and as a prophylactic in immunosuppressed patients. It has also been used as alternative to itraconazole for chromomycosis.

Side effects of posaconazole are common, but mostly limited to nausea, abdominal pain, loose motions, headache, dizziness and drowsiness. Anaemia, neutropenia, cardiac arrhythmias and visual disturbances are rare. Administered as an oral suspension, absorption of posaconazole is improved by low pH and fatty food. It is partly metabolized by CYP2C19 and glucuronidation, but excreted mostly unchanged in faeces. The t½ is > 24 hours. It can increase levels of drugs metabolized by CYP3A4.

Dose: 200 mg QID or 400 mg BD with meals.

NOXAFIL 200 mg/5 ml susp.

ALLYLAMINE

Terbinafine

This orally and topically active drug against dermatophytes and *Candida* belongs to a new allylamine class of antifungals. In contrast to azoles which are primarily fungistatic, terbinafine is fungicidal. It acts as a non-competitive inhibitor of 'squalene epoxidase', an early step enzyme which generates squalene epoxide that is converted to lanosterol and then to ergosterol by fungi (*see* Fig. 58.1). Accumulation of squalene within the fungal cells appears to be responsible for the fungicidal action. The mammalian enzyme is inhibited only by 1000-fold higher concentration of terbinafine.

Approximately 75% of orally administered terbinafine is absorbed, but only 5% or less from unbroken skin. First pass metabolism reduces oral bioavailability to < 50%. It is widely distributed in tissues, strongly plasma protein bound and has high affinity for keratin. Therefore, it is concentrated in sebum, stratum corneum of skin and into nail plates. Inactivation occurs by metabolism, and it is excreted mainly in urine, but about 20% in faeces as well. Elimination t½ after single dose is 11–16 hours, but is prolonged to 10 days after repeated dosing.

Oral terbinafine is usually well tolerated. Side effects are gastric upset, headache, rashes, taste disturbance. Some cases of hepatic dysfunction, haematological disorder and severe cutaneous reaction are reported. Terbinafine does not inhibit CYP450.

Topical terbinafine can cause erythema, itching, dryness, irritation, urticaria and rashes.

Use Terbinafine applied topically as 1% cream twice daily is indicated in localized tinea pedis/cruris/corporis and pityriasis versicolor; 2–4 weeks treatment is required according to the site, yielding high efficacy. Oral treatment with 250 mg OD is reserved for onychomycosis, tinea capitis and wide spread lesions, but is not effective in pityriasis versicolor. Duration of treatment varies from 3–6 months or more depending on the site. Efficacy in nail infection is ~90%, which is higher than with griseofulvin and itraconazole.

Terbinafine is less effective against cutaneous and mucosal candidiasis: 2–4 weeks oral therapy may be used as an alternative to fluconazole.

LAMISIL, SEBIFIN, DASKIL 250 mg tab, 1% topical cream. EXIFINE 125, 250 mg tabs, 1% cream; TERBIDERM 1% cream.

OTHER TOPICAL ANTIFUNGALS

All these drugs are used for dermatophytosis.

1. Tolnaftate It is an effective drug for tinea cruris and tinea corporis, and most cases respond in 1–3 weeks. Because of poor penetrability,

it is less effective in tinea pedis and other hyperkeratinized lesions. For the same reason, it is ineffective in tinea capitis (involving scalp) and tinea unguium (involving nails).

Symptomatic relief occurs early, but if applications are discontinued before the fungus bearing tissue is shed—relapses are common.

Tolnaftate causes little irritation, but is inferior in efficacy to imidazoles. It is not effective in candidiasis or other types of superficial mycosis.

TINADERM, TINAVATE 1% lotion, TOLNADERM 1% cream.

2. Ciclopirox olamine It is a newer drug effective in tinea infections, pityriasis versicolor and dermal candidiasis. High cure rates are reported. It penetrates superficial layers and reaches hair roots but systemic absorption is negligible. Local tolerance without irritation is good. Sensitization occurs occasionally. Formulated as nail lacquer (painted like nail polish), it has been used in onychomycosis, but cure rate is low. Vaginal candidiasis can be treated by 1% ciclopirox vaginal cream.

BATRAFEN 1% cream, 1% topical solution, 1% vaginal cream, OLAMIN 1% cream; ONYLAC NAIL LACQUER 8% nail lacquer.

3. Butenafine It is a benzylamine congener of terbinafine with the same mechanism of action. However, it is used only topically in dermatophytosis. Efficacy in tinea cruris/corporis/pedis is similar to that of topical terbinafine.

BUTOP, FINTOP 1% cream; apply locally once or twice daily.

4. Undecylenic acid It is fungistatic used topically, generally in combination with its zinc salt. It is inferior to the drugs described above; cure rates are low even after prolonged treatment. However, it is still used for tinea pedis, nappy rash and tinea cruris. Irritation and sensitization are infrequent.

TINEAFAX: Zinc undecenoate 8%, zinc naphthenate 8%, mesulphen 8%, methyl salicylate 2.5%, terpineol 2.5% oint.

5. Benzoic acid It has week antifungal and antibacterial property in slightly acidic medium. Eradication of the fungus needs prolonged application till infected keratin is totally shed.

On hyperkeratotic lesions, it is used in combination with salicylic acid (as Whitfield ointment: benzoic acid 5% or 6% + salicylic acid 3%). The latter, by its keratolytic action, helps to remove the infected tissue and promotes the penetration of benzoic acid into the lesion. Irritation and burning sensation are experienced by many patients.

RINGCUTTER, WHITEFIELDS oint/cream 20 g tube.

SECTION 12

☞ PROBLEM DIRECTED STUDY

58.1 A 50-year-old woman presents with complaints of constant pain in the retrosternal region for the past 2 weeks. The pain is markedly aggravated during swallowing. The condition has progressively worsened, and now even drinking water hurts. There is difficulty in swallowing as well. She informs that she is a diabetic and takes Tab. Glibenclamide 5 mg twice a day for the past two years, but has not checked her blood glucose for the last few months. Endoscopy reveals diffuse streaks of creamy yellow mucosal plaques and a few erosions in the esophagus. Scrapings from the plaque are sent for microbiological examination. Fasting blood glucose is found to be 180 mg/dl. She is diagnosed as a case of esophageal candidiasis with poorly controlled diabetes mellitus.

(a) What drug/drugs should be prescribed to treat her esophageal condition? What should be the duration of therapy?

(b) What are the aspects to be considered in view of the fact that the patient is a poorly controlled diabetic taking a sulfonylurea medication?

(*see* Appendix-1 for solution)

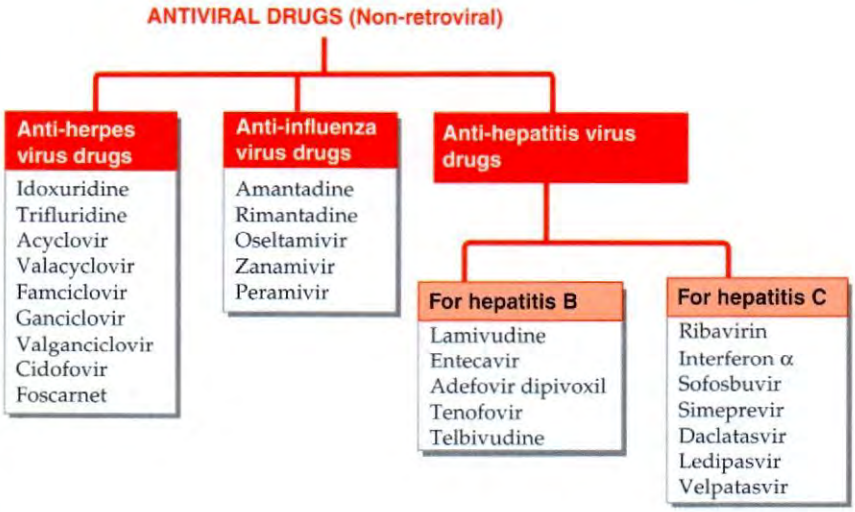
Chapter 59 Antiviral Drugs (Non-retroviral)

Viruses are the ultimate expression of obligate intracellular parasitism. They not only take nutrition from the host cell but also direct its metabolic machinery to synthesize new virus particles. Viral chemotherapy, therefore was considered impossible, as it would require interference with cellular metabolism in the host. However, in the past 50 years virus directed enzymes have been identified in the infected cell and some viruses have few enzymes of their own which may have higher affinities for some antimetabolites or inhibitors than the regular cellular enzymes. In addition, drugs have been developed which target virus specific steps like cell penetration, uncoating, reverse transcription, virus assembly or maturation and release from host cell, etc. Another stumbling block is that in majority of acute infections viral replication is already at its peak when symptoms appear. To be effective, therefore, therapy has to be started in the incubation period, i.e. has to be prophylactic or preemptive.

ANTI-HERPES VIRUS DRUGS

These are drugs active against the Herpes group of DNA viruses which include *Herpes simplex virus-1* (HSV-1), *Herpes simplex virus-2* (HSV2), *Varicella-Zoster virus* (VZV), *Epstein-Barr virus* (EBV), and *Cytomegalovirus* (CMV).

Idoxuridine It is 5-iodo-2-deoxyuridine (IUDR), which acts as a thymidine analogue. It was the first pyrimidine antimetabolite to be used as antiviral drug. It competes with thymidine, gets incorporated into viral DNA so that faulty DNA is formed which breaks down easily. Idoxuridine is



effective only against DNA viruses and clinical utility is limited to topical treatment of *Herpes simplex* keratitis. Because of low virus selectivity, higher local toxicity and rapid development of viral resistance, use of idoxuridine is restricted to superficial dendritic keratitis when rapid action is required. Idoxuridine eye drops act faster than acyclovir eye ointment, which is more effective when there is stromal involvement of the cornea. Ocular irritation occurs with idoxuridine eye drops.

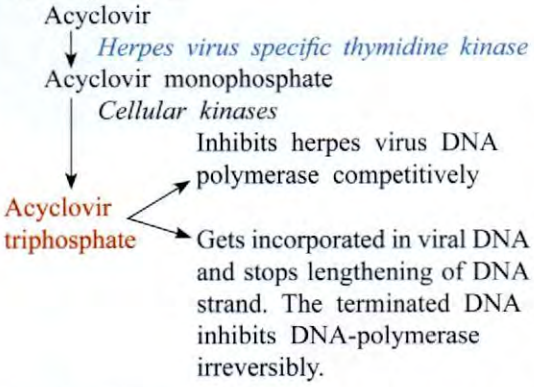
Dose: 0.1% eye drops to be instilled hourly, then 2 hourly and 4 hourly; apply 0.1% eye ointment at night.

IDURIN, TOXIL 0.1% eye drops and eye oint.

Trifluridine It is a fluorinated nucleoside which acts in the same way as idoxuridine, and inhibits HSV-1, HSV-2, CMV and related viruses. However, virus selectivity is low and DNA synthesis in host cells is also affected due to blockade of cellular kinases. Trifluridine eye drop is approved for use in *H. simplex* keratitis. Higher efficacy than idoxuridine eye drops is reported. Ocular irritation and lid edema can occur.

Acyclovir

This deoxiguanosine analogue requires a virus specific enzyme for conversion to the active metabolite that inhibits DNA synthesis and viral replication.



Acyclovir is preferentially taken up by the virus infected cells. Because of selective generation of the active inhibitor in the virus infected cell and its greater inhibitory effect on viral DNA synthesis, acyclovir has low toxicity for host cells: a several hundred-fold chemotherapeutic index has been noted.

Acyclovir is active only against herpes group of viruses; HSV-1 is most sensitive followed by HSV-2 > VZV=EBV, while CMV is practically not affected. HSV and VZV have been found to develop resistance to acyclovir during therapy; the former primarily due to mutants deficient in thymidine kinase activity and the latter primarily by change in specificity of virus directed enzyme so that its affinity for acyclovir is decreased.

Pharmacokinetics Only about 20% of an oral dose of acyclovir is absorbed. It is little plasma protein bound and is widely distributed attaining CSF concentration that is 50% of plasma concentration. After topical application systemic absorption is negligible, but it penetrates cornea well. Acyclovir is primarily excreted unchanged in urine, both by glomerular filtration and tubular secretion; plasma t½ is 2–3 hours. Renal impairment necessitates dose reduction. ZOVIRAX 200, 800 mg tab, 250 mg/vial for i.v. inj; CYCLOVIR 200 mg tab, 5% skin cream; HERPEX 200 mg tab, 3% eye oint, 5% skin cream; OCUVIR 200, 400, 800 mg tab, 3% eye oint, ACIVIR-DT 200, 400, 800 mg tab, 250 mg inj. ACIVIR EYE 3% oint.

Use Acyclovir is effective for herpes virus infection in patients with normal as well as deficient immune status. For better results, treatment should start as early as possible.

1. *Genital Herpes simplex* Generally caused by type-2 virus; can be treated by topical, oral or parenteral acyclovir depending on stage and severity of disease.

Primary disease: Topical treatment has low efficacy; 5% ointment is applied locally 6 times a day for 10 days. This is useful only if started early and in mild cases. Late and more severe cases should receive oral therapy (2 g/day in 5 divided doses or 800 mg TDS for 10 days) in addition to local therapy. Both local and oral therapies afford symptomatic relief and hasten healing of lesions, but do not prevent recurrences.

Recurrent disease: Topical therapy is totally ineffective. Response to oral treatment is slow and incomplete; severe cases may be treated parenterally—5 mg/kg i.v. infused over 1 hr, repeated 8 hourly for 10 days. Suppressive oral therapy with 400 mg BD has been shown

to prevent recurrences as long as given. It is recommended to stop treatment after 1 yr and ascertain whether the patient is still having recurrences; if so restart treatment. After prolonged therapy frequency of recurrences is reduced. Continuous acyclovir prophylaxis is generally advocated in patients with > 8 recurrences per year. However, suppressive therapy reduces, but does not toally prevent, disease transmission to sexual partner.

2. *Mucocutaneous H. simplex* It is a type-1 virus disease, remains localized to lips and gums; does not usually require specific treatment, but acyclovir skin cream may provide some relief. Spreading lesions may be treated with 10 day oral acyclovir. Prophylactic oral therapy may prevent sun exposure related recurrences. The disease often gets disseminated in immunocompromised individuals and may be treated with oral or i.v. acyclovir (15 mg/kg/day) for 7 days, but recurrences are not prevented.

3. *H. simplex encephalitis* (type-1 virus): Acyclovir 10 to 20 mg/kg/8 hr i.v. for ≥10 days is the drug of choice. Treatment is effective only if started early: delay precludes salutary effect on mortality and neurological complications.

4. *H. simplex (type I) keratitis*: Acyclovir is equally effective as idoxuridine in superficial dendritic corneal ulcer, and may be better for deep stromal infections because of good corneal penetration. Though acyclovir eye ointment acts slower than idoxuridine eye drops, blindness can be prevented. The eye ointment should be applied 5 times daily till 3 days after healing.

5. *Herpes zoster*: The varicella-zoster virus is less susceptible to acyclovir. As such, higher doses are needed and it should be used only in immunodeficient individuals or in severe cases: 10 mg/kg/8 hr i.v. for 7 days. Oral therapy with 800 mg 5 times daily is beneficial only if started early. It affords symptomatic relief and faster healing of lesions. Postherpetic neuralgia is not prevented, though its duration may be shortened. Acyclovir skin cream may be applied on herpetic ulcers.

6. *Chickenpox*: Specific therapy is indicated only in patients with immunodeficiency and in neonates. Acyclovir (15 mg/kg/day i.v. × 7 days) is the drug of choice. It reduces fever, eruptions, hastens healing and prevents visceral complications. Oral acyclovir is not advised in children.

In susceptible contacts, oral acyclovir 400 mg 4 times a day for 7 days given during the incubation period may abort chickenpox.

Adverse effects

Topical: Stinging and burning sensation after each application.

Oral: The drug is well tolerated; headache, nausea, malaise and some CNS effects are reported.

Intravenous: Rashes, sweating, emesis and fall in BP occur only in few patients.

Dose-dependent decrease in g.f.r. is the most important toxicity; occurs especially in those with kidney disease; normalises on discontinuation of the drug.

Reversible neurological manifestations (tremors, lethargy, disorientation, hallucinations, convulsions and coma) have been ascribed to higher doses.

No teratogenic potential has been noted.

Valacyclovir It is a valyl ester prodrug of acyclovir with improved oral bioavailability (55–70%) due to active transport by peptide transporters in the intestine. During passage through intestine and liver, it is completely converted to acyclovir in the first passage by esterases. Thus, >3 fold higher plasma levels of acyclovir are obtained improving clinical efficacy in certain conditions; e.g. it is the drug of choice in herpes zoster. Valaciclovir is excreted in urine as acyclovir with a t½ of 3 hours.

Dose: For genital herpes simplex—first episode 1.0 g BD × 10 days; recurrent episode 1.0 g BD × 3–5 days; suppressive treatment 0.5 g OD × 6–12 months (max 5 years).

For orolabial herpes 2 g BD × 1 day; in immunocompromised patient 1 g BD × 5 days.

For herpes zoster 1 g TDS × 7 days.

VALCIVIR 0.5 g, 1.0 g tabs.

Famciclovir It is an ester prodrug of a guanine nucleoside analogue *penciclovir*, which has good oral bioavailability and prolonged intracellular t½ (> 8 hrs) of the active triphosphate metabolite. Like acyclovir, it needs viral thymidine kinase for generation of the active DNA polymerase inhibitor. Famciclovir inhibits *H. simplex, H. zoster* but not acyclovir-resistant strains. Some activity against hepatitis B virus (HBV) has been noted. It is used as an alternative to acyclovir for genital or orolabial herpes and herpes zoster. Early treatment of herpes zoster reduces the duration of post herpetic neuralgia, but not its incidence.

Dose: Genital herpes (1st episode) 250 mg TDS × 5 days; recurrent cases 250 mg BD for up to 1 year. Herpes zoster and orolabial herpes 500 mg TDS for 7–10 days.

FAMTREX 250, 500 mg tabs.

Famciclovir is a less active alternative to lamivudine in chronic hepatitis B, but not in resistant cases. Side effects are headache, nausea, loose motions, itching, rashes and mental confusion.

Drugs for cytomegalovirus (CMV)

Ganciclovir It is an analogue of acyclovir which is most active against CMV, but also inhibits other herpes viruses, *viz. H.simplex, H. zoster* and EBV. Ganciclovir is also activated intracellularly by virus specific thymidine kinase and its triphosphate nucleotide preferentially inhibits viral DNA polymerase. This active metabolite attains much higher concentration inside CMV infected cells. The precursor cells in bone marrow are also quite sensitive to ganciclovir, and this may account for its bone marrow toxicity. Due to poor oral absorption, bioavailability of ganciclovir is low (<10%). Its prodrug *Valganciclovir*, which is better absorbed orally; has replaced it for oral therapy. Ganciclovir and its active metabolite are mostly excreted unchanged in urine. The plasma t½ of ganciclovir is 2–4 hrs, but that of its triphosphate inside CMV infected cells is > 24 hrs. CMV can develop ganciclovir resistance by mutation of viral phosphokinase and/or viral DNA polymerase.

Systemic toxicity of ganciclovir is high (bone marrow depression, rash, fever, vomiting, neuropsychiatric disturbances). Therefore, use is restricted to prophylaxis and treatment of severe CMV infections (pneumonia/colitis/retinitis) which occur in immunocompromised (AIDS, transplant recipient) patients. Treatment may be initiated with i.v. infusion of ganciclovir 10 mg/kg/day which can prevent blindness in AIDS patients with CMV retinitis. Systemic therapy can be supplemented by intravitreal injection of ganciclovir. Colitis or pneumonia caused by CMV in immune deficient patients has also been treated by i.v. ganciclovir.

GANGUARD 250, 500 mg tabs.

Valganciclovir It is the valyl prodrug of ganciclovir that is 60% bioavailable orally (about 8 fold higher than ganciclovir). Oral valganciclovir is nearly equally effective as i.v. ganciclovir in CMV retinitis, and has practically replaced the parent drug, except when vision is threatened. Valganciclovir is also suitable for long term suppressive therapy of CMV retinitis and other CMV infections. It is indicated for prophylaxis of CMV infections in organ transplant/immunosuppressed patients. Adverse effects of valganciclovir are similar to those of ganciclovir.

Dose: 900 mg OD, BD.

VALGAN, VALSTEAD 450 mg tab.

Cidofovir It is a monophosphate nucleotide analogue of cytidine which inhibits most DNA viruses including HSV, CMV, pox and adenoviruses. Many HSV resistant to acyclovir and many CMV resistant to ganciclovir are susceptible. Because it is a monophosphate, it does not require viral phosphokinase for activation, and is converted to the active diphosphate by cellular enzymes. Cidofovir diphosphate remains intracellularly for long periods in virus infected cells to inhibit viral DNA polymerase, as well as acts as its alternative substrate. Weekly therapy is, therefore, possible despite short plasma t½ (2–3 hours) of cidofovir itself. CMV develops cidofovir resistance by mutation of its DNA polymerase.

Very little cidofovir is absorbed orally. It is administered by i.v. infusion with pre and post dose oral probenecid which inhibits its tubular secretion and improves its availability for entering into cells, as well as reduces nephrotoxicity. Cidofovir 5 mg/kg i.v. weekly and then every 15 days is used for CMV retinitis in AIDS patients, particularly those who have failed ganciclovir therapy. It can also be used for acyclovir-resistant mucocutaneous herpes simplex in immunosuppressed patients. Cidofovir can be applied topically on anogenital warts. The primary toxicity of cidofovir is dose related kidney damage and it is contraindicated in patients with kidney disease. Gastric disturbances, constitutional symptoms, hypersensitivity reactions, neutropenia and uveitis are the other adverse effects.

Foscarnet It is a simple straight chain phosphonate unrelated to any nucleic acid precursor which inhibits viral DNA polymerase and reverse transcriptase. It is active against *H. simplex* (including strains resistant to acyclovir), CMV (including ganciclovir-resistant ones), other herpes group viruses and HIV. Viral resistance to foscarnet is minimal. However, viral selectivity of foscarnet is low. Oral absorption is poor. Its t½ is 4–8 hours, and it is not metabolised.

Toxicity of foscarnet is high: damages kidney—produces a renal diabetes like condition, acute renal failure can also

occur. Anaemia, phlebitis, tremor, convulsions and other neurological as well as constitutional symptoms due to hypocalcaemia are frequent. Administered by i.v. infusion, foscarnet has been used for:

1. CMV retinitis and other CMV infections in AIDS patients; efficacy is similar to ganciclovir, includes resistant cases, but produces more adverse effects.
2. Acyclovir-resistant mucocutaneous *H. simplex* type 2 and varicella-zoster infections in AIDS patients.

When used to treat associated CMV/*H. simplex*/VZV infection in AIDS patient, it decreases HIV viral titre, and may improve outcome in patients receiving antiretroviral therapy (ART).

ANTI-INFLUENZA VIRUS DRUGS

The anti-influenza virus drugs exert type and strain specific action on influenza virus.

Influenza virus is an RNA virus with segmented genome and core proteins which define its type (A, B or C). Majority of human infections and epidemics are caused by influenza A, while the B type produces sporadic seasonal cases. Several subtypes of influenza A characterized by its haemagglutinin (H) and neuraminidase (N) surface glycoproteins have produced epidemics and pandemics from time-to-time. Of particular importance are the H5N1 (bird flu) subtype which got transferred from poultry in 1997 and caused severe epidemics in east Asia, and the H1N1 subtype (swine flu) which produced a pandemic in 2009 and several epidemics there after.

Amantadine Introduced in the 1960s, it is a tricyclic amine unrelated to any nucleic acid precursor, which inhibits influenza A virus, but not influenza B or the H5N1 and H1N1 strains of influenza A. Amantadine acts by inhibiting the viral M2 protein (an ion channel), and prevents uncoating of the viral genome within the infected cell. Viral resistance to amantadine developed by mutation of the M2 protein. Due to the emergence of H5N1 and other strains (since the 1990s) which were unresponsive to amantadine, as well as due to availability of newer broad spectrum and more efficacious antiinfluenza drugs, like Osaltamivir, the use of amantadine declined. Currently it is seldom used for influenza. Its use for parkinsonism is also occasional now.

Dose: prophylactic 100 mg OD, therapeutic 100 mg BD for 5 days.

AMANTREL 100 mg tab.

Rimantadine It is the methyl derivative of amantadine; similar to it in mechanism of action, but longer acting and better tolerated. However, it exhibits complete cross-resistance with amantadine, and is inactive against N1H1, N5H1 strains of influenza A as well as influenza B viruses. As such, rimantadine has also gone into disuse.

Dose: prophylactic 100 mg OD, therapeutic 100 mg BD.

FLUMADINE 100 mg tab.

Oseltamivir This is the most commonly used anti-influenza virus drug now. It is a sialic acid analogue with broad spectrum activity covering influenza A (amantadine sensitive as well as resistant), H5N1 (bird flu), H1N1 (swine flu) strains and influenza B. Oseltamivir is an ester prodrug that is rapidly and nearly completely hydrolysed during absorption in intestine and by liver esterases to the active form *oseltamivir carboxylate* with an oral bioavailability of ~ 80%. The active metabolite is not further metabolized and is excreted by the kidney with a t½ of 6–10 hours. Dose reduction is needed in renal insufficiency. Oseltamivir acts by inhibiting influenza virus neuraminidase enzyme which is needed for release of progeny virions from the infected cell. Spread of the virus in the body is thus checked. Resistance can develop by mutation of the viral neuraminidase enzyme. In many areas oseltamivir-resistant influenza A (seasonal influenza) and H5N1 have been encountered, though swine flu (H1N1) is still mostly sensitive. Some oseltamivir-resistant strains remain susceptible to zanamivir.

Oseltamivir (as well as zanamivir) is the most effective drug for influenza A, including H5N1 and H1N1 strains, as well as influenza B. Started within few hours (maximum 48 hours) of symptom onset, it reduces severity, duration and complications of the illness. Early initiation of therapy is critical because viral replication is maximal during the first 2 days of symptom onset. Oseltamivir may not be effective in infants, because they may fail to generate the active metabolite. Prophylactic use within 2 days of exposure prevents illness in contacts of influenza patients.

Dose: therapeutic 75 mg oral BD for 5 days; prophylactic 75 mg OD.

TAMIFLU, ANTIFLU 75 mg cap, 12 mg/ml susp., FLUVIR 75 mg cap.

Side effects are nausea and abdominal pain due to gastric irritation (reduced by taking the drug with food), headache, weakness, sadness, diarrhoea, cough and insomnia. Skin reactions have been reported.

Zanamivir Another influenza A (including amantadine-resistant, H1N1, H5N1 strains) and influenza B virus neuraminidase inhibitor that is administered by inhalation as a powder due to very low oral bioavailability. Small amount that is absorbed after inhalation is excreted by the kidney with a t½ of 2–5 hours. The mechanism of action, clinical utility and efficacy of zanamivir are similar to that of oseltamivir. Some strains resistant to oseltamivir remain sensitive to zanamivir. Therefore, it should be reserved for oseltamivir-resistant cases, or when the latter cannot be given, or for severely immunocompromized patients. Prophylactic use may be made for 7–10 days in household contacts.

Dose: 10 mg through breath actuated inhaler or rotacaps, BD × 5 days for treatment, and OD for prophylaxis.

RELENZA, VIRENZA 5 mg/actuation powder inhaler rotacaps.

The inhaled powder can induce bronchospasm in some individuals. This may be severe in asthmatics, therefore contraindicated in them. Headache, dizziness, nausea and rashes are mild and infrequent side effects.

Peramivir It is a new single dose i.v. treatment for influenza in adults approved by the US-FDA in 2014. Peramivir is active against human influenza A and B, as well as bird flu (H5N1), swine flu (H1N1) and several emerging strains of influenza A virus, including those resistant to oseltamivir. Like oseltamivir, it inhibits influenza viral neuraminidase enzyme, prevents spread of the virus in host body, and is effective if administered soon after symptom onset (max. 48 hrs). Peramivir is more active *in vitro* against influenza B, which is intrinsically less susceptible to oseltamivir and zanamivir. In multicentric controlled study, single dose i.v. peramivir administered within 48 hours of symptom onset was found to be as effective as 5 day oseltamivir in reducing severity and duration of influenza illness.

Oral bioavailability of preramivir is very low (≤3%) in humans. It is almost entirely eliminated unchanged by glomerular filtration and its clearance parallels CLcr. Dose needs to be reduced in renal insufficiency, but not in liver disease. The elimination t½ in healthy adults is 20 hr. The long t½ allows single or infrequent dosing. Adverse effect of peramivir are mild and similar to those of oral oseltamivir. Self limiting diarrhoea, nausea and vomiting are the usual complaints. Decreased neutrophil count peaking on 3rd day with spontaneous recovery has been noted. Because of well tolerated and safe single dose i.v. use, peramivir appears to be a valuable option for treating severely ill influenza patients, or those unable to tolerate other drugs, as well as for oseltamivir resistant cases.

Dose: 600 mg to be diluted and injected i.v. over 15–20 min, within 48 hours of influenza symptom onset (internationally marketed as RAPIVAB 600 mg inj.).

ANTI-HEPATITIS VIRUS DRUGS

While hepatitis B virus (HBV) is a DNA virus which, like retroviruses, can integrate into host chromosomal DNA to establish permanent infection, the hepatitis C virus (HCV) is a RNA virus, which does not integrate into chromosomal DNA, does not establish noncurable infection, but frequently causes chronic hepatitis. Some antiviral drugs (e.g. ribavirin, interferon α) used primarily for hepatitis viruses are nonselective and inhibit several other viruses, including both RNA and DNA viruses.

DRUGS FOR HEPATITIS B

Since the hepatitis B virus cannot be eradicated from the body, the treatment is aimed as suppression of the virus and its inflammatory and hepatocyte damaging response. This results in improved liver function and reduction of risk for development of cirrhosis and hepatic carcinoma. Sudden stoppage of anti-HBV drugs can results in acute exacerbation of hepatitis. Most experts opine that unless loss of efficacy or toxicity limits use, the nucleoside/nucleotide anti-HBV drugs should be continued till 6 months after seroconversion. Combination therapy of HBV has not proven superior, and drugs are generally used sequentially.

Lamivudine This nucleoside analogue is active against HBV as well as HIV, and is described with antiretroviral drugs on p. 862.

Entecavir This newer guanosine nucleoside analogue is currently the most active and 1st line option for treating chronic hepatitis B. Like other nucleoside analogues, entecavir inhibits HBV-DNA polymerase after activation by intracellular phosphorylation. It brings down HBV titre more rapidly and more profoundly than lamivudine, and this is attended by clinical, biomechanical and histological improvement. The response is

well sustained and HBV-resistance to entecavir is rare upto 5 years of use, but is more likely in cases already resistant to lamivudine. It has weak anti-HIV activity as well.

Entecavir is nearly completely absorbed after oral dosing, but food decreases bioavailability; it should be taken in empty stomach. It is not metabolized, and is excreted unchanged by the kidney with a biologial t½ of 128-148 hours. Entecavir is well tolerated; side effects are mild dyspepsia, nausea, diarrhoea, fatigue, and disturbed sleep. Lactic acidosis can occur in patients with decompensated cirrhosis of liver.
Dose: 0.5 mg OD; for lamivudine resistant cases 1.0 mg OD.
ENTAVIR 0.5 mg, 1.0 mg tabs.

Adefovir dipivoxil *Adefovir* is a monophosphate analogue of AMP that is active against HBV and some other DNA as well as RNA viruses, but is used only for hepatitis caused by HBV. Esterases in the intestine and liver release the active drug during absorption to attain oral bioavailability of ~60% in terms of adefovir. On entering cells, adefovir is phosphorylated to the diphosphate which has high affinity for HBV DNA polymerase compared to host cell DNA polymerase. Adefovir itself gets incorporated in the viral DNA resulting in termination of the DNA chain. It is primarily excreted by the kidney. While adefovir plasma t½ is 7 hours, intracellular t½ of its diphosphate is upto 18 hours.

Adefovir is indicated in chronic hepatitis B, including lamivudine-resistant cases and those having concurrent HIV infection. Clinical, biochemical, histological, serological and virological response occurs in nearly 50% patients within 1 year. More cases respond with continued treatment. Virologic response to adefovir is slower than to lamivudine and tenofovir and it is the least active nucleotide analogue against HBV, therefore not a first line drug. Adefovir resistance occurs in about 30% patients.
Dose: 10 mg/day; ADESERA, ADFOVIR 10 mg tab.

At 10 mg/day dose adefovir is well tolerated. Side effects are sore throat, headache, weakness, abdominal pain and flu syndrome. Nephrotoxicity occurs at higher doses and in those with preexisting renal insufficiency.

Tenofovir disoproxil fumarate (TDF) It is a monophosphate nucleotide related to AMP, which is active against HBV as well as HIV. Due to very low oral absorption, it is used as the disoproxil ester prodrug, which not only improves bioavailability, but also intracellular passage of the active form. Tenofovir released from hydrolysis of the prodrug is diphosphorylated by cellular kinases into tenofovir diphosphate which preferentially inhibits HBV-DNA polymerase and HIV-reverse transcriptase (*see* p. 863). Affinity for host DNA-polymerase is very low. It also gets incorporated in the viral DNA to cause chain termination.

Tenofovir disoproxil is incompletely, but adequately absorbed after oral intake, and is largery excreted by the kidney with a plasma t½ of ~16 hours. It produces few side effects, which are mostly limited to the g.i. tract *viz.* nausea, flatulence, abdominal discomfort, loose motions and headache. Slight increase in serum creatinine is common and acute renal injury or chronic renal disease is possible. Drug interactions are not significant.

Administered in a dose of 300 mg daily, tenofovir disoproxil has produced good clinical and virological response in chronic hepatitis B. In a comparative study, higher percentage of patients responded within one year of use than with adefovir. A response rate of > 90% has been reported among HBe antigen negative patients. Tenofovir-resistance has not developed during treatment of chronic hepatitis B, and it is effective in lamivudine-resistant cases. Due to its high efficacy, good tolerability and low risk of resistance, tenofovir is one of the first line drugs for chronic hepatitis due to HBV.
TENTIDE, TENOF, TENVIR 300 mg tab; 1 tab OD.

Telbivudine This newer anti-HBV drug is a thymidine nucleoside analogue. Telbivudine is absorbed orally and its bioavailability is not affected by food. It is not metabolized and is excreted unchanged by the kidney with an average plasma t½ of 15 hours. Telbivudine

enters cells and is phosphorylated by cellular kinases to generate the active triphosphate nucleotide, which competitively inhibits HBV-DNA polymerase, and also gets incorporeted into HBV-DNA resulting in chain termination. Telbivudine causes faster and more complete suppression of HBV-DNA titre than lamivudine or adefovir, but resistance often develops resulting in return of viraemia. Telbivudine-resistance is more likely in lamivudine-resistant cases. As such, it not a first line drug for chronic hepatitis B. Tolerability of telbivudine is good; side effects are abdominal pain, diarrhoea, cough, headache, dizziness and myalgia, which are usually mild. Serum amylase may rise.

Dose: 600 mg OD; SEBIVOL 600 mg tab.

DRUGS FOR HEPATITIS C

The aim of treatment for chronic hepatitis C is to attain *sustained viral response (SVR)*, meaning undetectable HCV-RNA in blood for at least 6 months after completion of therapy. If this is achieved, only ~5% patients relapse. Oral ribavirin combined with injected PegINFα is conventionally the standard therapy for HCV infection, that is still widely used in India. However, several novel direct acting oral antiviral drugs have been developed over the past 5–10 years which have revolutionized the treatment of hepatitis C. These new drugs have largely replaced the older ones in the developed world, but are accessible only to few patients in India due to constraints of cost and other logistics.

Ribavirin This purine nucleoside analogue has broad-spectrum antiviral activity, including that against HCV, influenza A and B, respiratory syncytial virus and many other DNA and double stranded RNA viruses. Its mono- and triphosphate derivatives generated intracellularly by host kinases inhibit GTP synthesis and viral RNA synthesis. They have other sites of action as well. Viral resistance to ribavirin is rare.

Oral bioavailability of ribavirin is ~50%. It is partly metabolized and eliminated mainly by the kidney in a multiexponential manner. It accumulates in the body on daily dosing and persists for months after discontinuation; long term $t_{1/2}$ is > 10 days.

The most common therapeutic use of oral ribavirin is in chronic hepatitis C, but it is not used alone, and is traditionally combined with injected peginterferon for 6–12 months. This is active against all genotypes of HCV and achieves SVR in 50–80% cases. It is also used along with sofosbuvir based combination therapy in decompensated cirrhotics. Nebulized ribavirin is used for respiratory syncytial virus bronchiolitis in infants and children, particularly those with congenital heart disease, prematurity or other high risk conditions. Ribavirin has shown efficacy in some rare viral infections as well.

Dose: 200 mg QID; 400 mg TDS for body weight ≥ 75 kg (children 15 mg/kg/day).

VIRAZIDE, RIBAVIN 100, 200 mg caps, 50 mg/5 ml syr.

The major toxic effect is dose-dependent haemolytic anaemia. Others are bone marrow depression, CNS and g.i. symptoms. It is also teratogenic; female patients should practice contraception during and till 3 months after ribavirin treatment. The aerosol can cause irritation of mucosae and bronchospasm.

Interferon α

Interferons (IFNs) are low molecular weight glycoprotein cytokines produced by host cells in response to viral infections, TNFα, IL-1 and some other inducers. They have nonspecific antiviral as well as other complex effects on immunity and cell proliferation. Interferons bind to specific cell surface receptors and affect viral replication at multiple steps, *viz.* viral penetration, synthesis of viral mRNA, assembly of viral particles and their release, but the most widespread effect is direct or indirect suppression of viral protein synthesis, i.e. inhibition of translation. Interferon receptors are JAK-STAT tyrosine protein kinase receptors which on activation phosphorylate cellular proteins. The phosphorylated proteins then migrate to the nucleus and induce transcription of 'interferon-induced-proteins' which exert antiviral effects.

Interferons inhibit many RNA and DNA viruses, but they are host specific: those produced by another species have poor activity in man. Three types of human IFNs (α, β and γ) are known to have antiviral activity. Only $IFN\alpha_{2A}$ and $IFN\alpha_{2B}$ produced by recombinant technology are available and are clinically used. Both are nonglycosylated low MW proteins administered by i.m. or s.c. injection. Their pegylated (polyethylene glycol complexed) forms are meant for s.c. injection at weekly intervals. Plasma levels of $pegIFN\alpha_{2A}$ are sustained twice longer than those of $pegIFN\alpha_{2B}$.

After i.m./s.c. injection, interferon is distributed to tissues. It is degraded mainly in kidney and to some extent in liver, so that it remains detectable in plasma for < 24 hours. However, cellular effects are longer lasting because the interferon induced proteins persist, so that IFN is generally administered thrice weekly. Peginterferon is absorbed more slowly—exerts more sustained effects, permiting weekly administration and improving clinical efficacy. PegIFN has replaced IFN, except for consideration of cost.

ALFERON: Interferon α_{2A} 3MU/vial inj, ZAVINEX 3MU, 5MU vials for inj.

REALFA-2B, SHANFERON, VIRAFERON: Interferon α_{2B} 3MU, 5MU vials for inj.

PEGASYS: Peginterferon α_{2A} 135 µg/vial and 180 µg/vial for weekly s.c. injection.

Uses

1. *Chronic hepatitis B:* $IFN\alpha_{2A}$ 2.5–5 MU/m² or $IFN\alpha_{2B}$ 5–10 MU given 3 times per week for 4–6 months causes disappearance of HBV-DNA from plasma and improvement in liver function tests/histology in nearly half of the patients. High doses (10 MU) injected thrice weekly for 6 months often produce prolonged remission, but relapses do occur. $PegIFN\alpha_{2A}$ 180 µg s.c. once weekly for 24–48 weeks produces better and more sustained responses.

2. *Chronic hepatitis C:* $IFN\alpha_{2B}$ 3MU 3 times weekly for 6–12 months has produced remission in 50–70% patients. Viral RNA becomes undetectable and liver function tests return to normal. Histology improves if response is sustained. However, relapses occur in majority of patients. $PegIFN\alpha_{2A}$ 180 µg/week is more effective and induces longer lasting remissions. Combination with oral ribavirin increases number of responders, decreases chances of relapse and is the standard therapy.

3. *AIDS-related Kaposi's sarcoma:* IFN is used to treat AIDS-related Kaposi's sarcoma, but not to treat HIV as such. However, interferon accentuates haematological toxicity of zidovudine.

4. *Condyloma acuminata:* caused by papilloma virus is usually treated with topical podophyllin. Intralesional interferon injection may be used in refractory cases.

5. *H. simplex, H. zoster* and CMV: IFN may be added to acyclovir/ganciclovir as an adjuvant in immunocompromised patients.

6. Interferons are also used in chronic myeloid leukaemia, follicular lymphoma, cutaneous T-cell lymphoma and multiple myeloma.

Clinical utility of s.c. or i.m. injected interferon is limited by substantial adverse effects.

Adverse effects

Side effects of IFN/PegIFN are frequent and distressing. They are contraindicated during pregnancy, in decompensated cirrhotics and in autoimmune disease patients.

- Flu-like symptoms—fatigue, aches and pains, malaise, fever, dizziness, anorexia, nausea, taste and visual disturbances develop few hours after each injection, but become milder later.
- Neurotoxicity—numbness, neuropathy, altered behaviour, mental depression, tremor, sleepiness, rarely convulsions.
- Myelosuppression: dose dependent neutropenia, thrombocytopenia.
- Thyroid dysfunction (hypo as well as hyper).
- Hypotension, transient arrhythmias, alopecia and reversible liver dysfunction.

New direct acting anti-HCV drugs

As indicated above, several novel direct-acting antiviral drugs for HCV are now available. They target specific nonstructural (NS) viral proteins that play essential role in replication of HCV inside hepatocytes. All of them are used in combination, either among themselves or with ribavirin ± PegINFα, because of lower efficacy and development of resistance if used as monotherapy. Used in combination, the newer drugs have achieved SVR of upto 99%, and have shortened the duration of therapy to 12–24 weeks. They are also much less toxic than ribavirin or INFα, but most of them do have important drug interactions. Therapy of HCV infection is at present rapidly evolving. The newer drugs may be grouped according to their target NS protein.

1. *NS5B polymerase inhibitor:* Sofosbuvir.
2. *NS3 protease inhibitor:* Simeprevir.
3. *NS5A inhibitor:* Daclatasvir, Ledipasvir, Velpatasvir.

NS5B polymerase inhibitor

Sofosbuvir It is a uridine analogue prodrug which is converted into its triphosphate nucleotide within the hepatocytes and inhibits the HCV nonstructural protein 5B (NS5B) which is a HCV-RNA polymerase. The active metabolite also enters the viral RNA and serves as a chain terminator. Sofosbuvir is active against all (1–6) HCV genotypes, especially genotype 1, but is always used in combination, either with one of the NS5A inhibitors or with simeprevir, or with ribavirin ± PegINFα. Such combinations have achieved SVR of 85%–99% after 12 weeks therapy in noncirrhotics and upto 93% after 24 weeks therapy in cirrhotics. Remarkably, resistance to sofosbuvir does not develop easily. Recent studies have shown that it can be employed in patients with decompensated liver disease as well.

The oral bioavailability of sofosbuvir is ~80% and is improved if taken with fatty meal. It is rapidly metabolized in liver and excreted in urine with a t½ of 27 hr. It is a substrate for Pgp efflux transporter, therefore should not be used with Pgp inducers like phenytoin, rifampin, etc. and in patients with severe renal impairment. Adverse effects of sofosbuvir are abdominal pain, fatigue, agitation, joint pain and anaemia. Severe bradycardia and arrest has occurred in patients taking amiodarone.

Dose: 400 mg daily with meals.

MYHEP, SOFOCURE, SOVIHEP, HEPCINAT 400 mg tab.

NS3/4A Protease inhibitor

Simeprevir This newer drug is a HCV protease NS3 inhibitor which blocks the cleavage of HCV polyprotein complex, so that functional viral RNA is not formed and viral replication is halted. Simeprevir is active against HCV genotype 1 and 4 and is recommended for use along with sofosbuvir or with ribavirin + PegINFα. The simeprevir–sofosbuvir combination has achieved SVR in 83–97% noncirrhotic patients after 12 weeks therapy, and in cirrhotic patients after 24 weeks therapy. It is orally active and should be taken with food to increase absorption. The terminal t½ is 13 hours in normal subjects, but is increased upto 41 hrs in HCV infected patients. Simeprevir is metabolized by CYP3A4. It is a substrate for, as well as inhibitor of the efflux transporter Pgp. As such, clinically significant interactions occur with rifampin, statins, NNRTI and protease inhibitor antiretroviral drugs, which are an important limitation to simeprevir use. Its adverse effects are nausea, headache, dyspnoea, fatigue, rashes and photosensitivity.

Dose: 150 mg/day

OLYSIO, GALEXOS 150 mg cap.

NS5A inhibitors

The NS5A is a multifunctional protein that serves essential role in the replication of HCV.

Daclatasvir It is an orally active NS5A inhibitor which blocks HCV-RNA replication as well as assembly of progeny virions. Daclatasvir is metabolized by CYP3A and is a substrate for efflux transporter Pgp. It also inhibits Pgp and other transporters. The usual dose 60 mg/day needs to be halved in patients receiving CYP3A inhibitors and increased to 90 mg/day in those

taking CYP3A inducers. It is active against all genotypes of HCV. Coadministered with sofosbuvir, it is indicated in HCV genotypes 1–6 infection and has achieved SVR upto 90% after 12 week therapy in noncirrhotic patients, but the response rate is lower in cirrhotics. Addition of ribavirin to the regimen is recommended. In patients with HIV coinfection or with advanced liver disease, it can be employed regardless of the HCV genotype. The t½ of daclatasvir is 12–15 hr. It is generally well tolerated; adverse effects are headache, fatigue, abdominal pain, alopecia, anaemia and rarely allergy.

HEPECDAC, DACIHEP, MYDEKLA 60 mg tab.

Ledipasvir This NS5A inhibitor is approved for use in combination with sofosbuvir, and is marketed only as fixed-dose combination (LDV/SOF) tablets for once daily dosing. Ledipasvir is strongly active against HCV genotypes 1,4,5,6 with only week activity on genotypes 2 and 3. As such, LDV/SOF combination is indicated for genotypes 1,4,5,6 HCV, but can be used in HIV coinfected, as well as in those with decompensated cirrhosis. In noncirrhotic patients LDV/SOF combination has achieved SVR in 95–99% cases after 12 weeks therapy, and in cirrhotics after 24 weeks therapy. Addition of ribavirin to the regimen achieves the same SVR among cirrhotics in 12 weeks, and is effective in genotype 3 HCV infection as well. Ledipasvir absorption is dependent on gastric acid and is impaired in patients taking H_2 blockers or PPIs. Only ~30 ledipasvir is metabolized, and it is largely excreted unchanged in faeces. The t½ is 48 hr. The LDV/SOF combination should not be used in patients being treated with Pgp inducers.

HEPCINAT-LP, SOFAB-LP: ledipasvir 90 mg + sofosbuvir 400 mg tab; one tab OD.

Velpatasvir Available only as a fixed dose combination of velpatasvir 100 mg + sofosbuvir 400 mg (VEL/SOF), this NS5A inhibitor is indicated in all (1–6) genotypes of HCV hepatitis. In noncirrhotics it has achieved SVR of 95–99% after 12 weeks. The SVR rates were lower in decompensated patients and could be improved either by addition of ribavirin or by extending the therapy to 24 weeks. Like ledipasvir, the absorption of velpatasvir is also impaired in patients receiving acid suppressant drugs. It is partly metabolized and excreted mainly in faeces. The t½ is 15 hours and liver disease has modest effect on its clearance. Inducers of CYP3A and Pgp lower velpatasvir blood levels and should not be used with it. The usual adverse effects are headache, fatigue, weakness and nausea.

VELPANAT: Velpatasvir 100 mg + sofosbuvir 400 mg tab; one tablet/day.

Chapter 60 Antiviral Drugs (Anti-retrovirus)

These are drugs active against human immunodeficiency virus (HIV) which is a retrovirus. They are useful in prolonging and improving the quality of life and postponing complications of acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC), but do not cure the infection. The clinical efficacy of antiretrovirus drugs is monitored primarily by plasma HIV-RNA assays and CD4 lymphocyte count carried out at regular intervals.

HIV is a single stranded RNA retrovirus which uniquely carries out reverse transcription of proviral DNA from viral RNA (normally RNA is transcripted from DNA) with the help of a viral RNA-dependent DNA polymerase (reverse transcriptase). The primary cell type attacked by HIV is the CD4+ helper T-lymphocyte, but later macrophages and some other cell types may also be infected. When population of CD4 cells declines markedly (<200 cells/μL), cell mediated immunity (CMI) is lost and opportunistic infections abound, to which the victim ultimately succumbs, unless treated. Because the HIV genome integrates with the host DNA, eradication of the virus from the body of the victim appears impossible at present.

Over the past 35 years, a number of virus specific targets have been identified and drugs for these developed. We now have drugs which effectively suppress HIV replication and restore CMI for variable periods of time. The two established targets for anti-HIV attack are:
(a) *HIV reverse transcriptase*: Which transcripts HIV-RNA into proviral DNA.
(b) *HIV protease*: Which cleaves the large virus directed polyprotein into functional viral proteins.

In addition, some newer targets being exploited are:

- Fusion of viral envelope with plasma membrane of CD4 cells through which HIV-RNA enters the cell.
- Chemokine coreceptor (CCR5) on host cells which provide anchorage for the surface proteins of the virus.
- HIV-integrase: Viral enzyme which integrates the proviral DNA into host DNA.

The first anti-retrovirus (ARV) drug *zidovudine* was made available for use in 1987. Over the past 30 years a large number of drugs belonging to 3 classes *viz.* Nucleoside or Non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs) and HIV-protease inhibitors (PIs) have been produced and extensively used. Recently drugs for the newer targets have also become available for use in patients who have failed several regimens employing the 3 major groups of drugs, and have viral multiplication despite optimized background therapy.

The aim of anti-HIV therapy is to cause maximal suppression of viral replication for the maximal period of time that is possible. For this, ARV drugs are always used in combination of at least 3 drugs and regimens have to be changed over time due to development of resistance. Life long therapy is required.

Over the past 40 years, HIV infection has emerged as a major global health problem. Though, with the use of effective antiretroviral therapy (ART) the prevalence is declining in the present century, WHO has estimated that 36.7 million people worldwide were living with HIV (PL-HIV) at the end of 2016, out of which nearly 21 million were receiving ART.* About 1.8 million new HIV infections occurred in 2016. India is a relatively low HIV prevalence country (prevalence rate 0.26% in 2016), but the absolute number is huge (2.1 million PL-HIV in 2016, out of which 9.97 lakh are receiving free ART under the NACP).[£] Female sex workers, men who have sex with men, transgenders and injection drug abusers are at high risk of contacting HIV infection. India launched its National AIDS Control Programme (NACP) in 1992, but the prevalence and annual death rate has declined steadily only after 2004 when the National AIDS Control Organization (NACO) rolled-out

free combination ART to eligible patients. In 2015, an estimated 86000 new HIV infections occurred in India, which is a decline of 32% compared to new HIV cases in 2007. After 2007, AIDS related deaths have steadily declined in India, and the annual death rate in 2015 was 54% lower than that in 2007, which in large measure, is due to effective use of combination ART.

Nucleoside reverse transcriptase inhibitors (NRTIs)

Zidovudine (AZT) It is a thymidine analogue (azidothymidine), the first and prototype NRTI. After phosphorylation in the host cell—zidovudine triphosphate selectively inhibits viral reverse transcriptase in preference to cellular DNA polymerase.

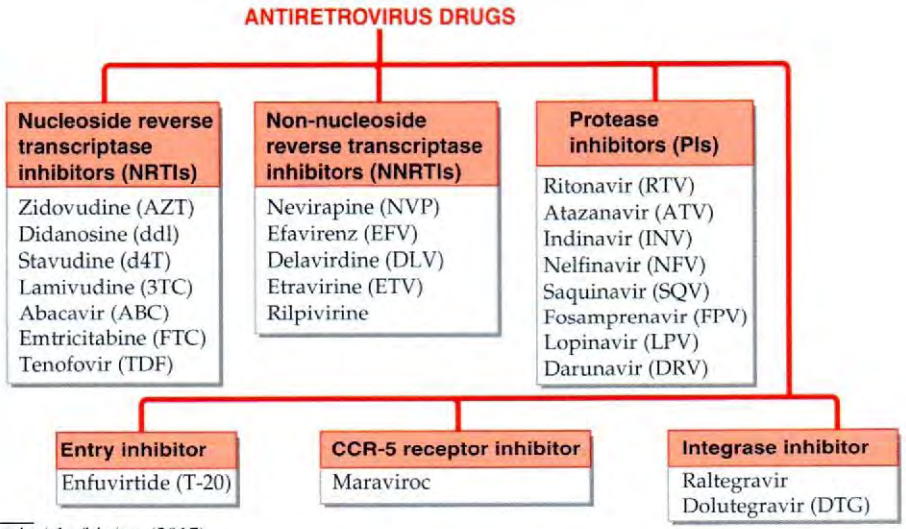
Single-stranded viral RNA

↓ Virus directed reverse transcriptase (*inhibited by zidovudine triphosphate*)

Double-stranded proviral DNA

On the template of single-stranded RNA genome of HIV, a double-stranded DNA copy is produced by viral reverse transcriptase. This proviral DNA translocates to the nucleus and is integrated with chromosomal DNA of the host cell (by viral integrase enzyme) which then starts transcribing viral genomic RNA as well as viral mRNA. Under the direction of viral mRNA, viral regulatory and structural proteins are produced in the form of a polyprotein. Finally, viral particles are assembled and matured after fractionation of the polyprotein by viral protease. Zidovudine thus prevents infection of new cells by HIV, but has no effect on proviral DNA that has already integrated into the host chromosome. It is effective only against retroviruses. Zidovudine itself gets incorporated into the proviral DNA and terminates chain elongation. Resistance to AZT occurs by point mutations which alter reverse transcriptase enzyme. In the past, when AZT was used alone, >50% patients became nonresponsive to AZT within 1–2 years therapy due to growth of resistant mutants.

Pharmacokinetics The oral absorption of AZT is rapid, but bioavailability is ~65%. It is quickly cleared by hepatic glucuronidation (t½ 1 hr); 15–20% of the unchanged drug along with



*www.who.int/gho/hiv/en (2017)
[f] www.naco.gov.in/documents/annual reports (July 2017)

the metabolite is excreted in urine. It crosses placenta and is found in milk.

Dose Adults 300 mg BD; Children 180 mg/m^2 (max 200 mg) 8 hourly.

RETROVIR, ZIDOVIR 100 mg cap, 300 mg tab, 50 mg/5 ml syr VIRO-Z, ZIDOMAX, ZYDOWIN 100 mg cap, 300 mg tab. (to be taken with plenty of water).

Adverse effects Anaemia and neutropenia are the most important and dose-related adverse effects.

Nausea, anorexia, abdominal pain, headache, insomnia and myalgia are common at the start of therapy, but diminish later. Myopathy, pigmentation of nails, lactic acidosis, hepatomegaly are infrequent.

Interactions Paracetamol increases AZT toxicity, probably by competing for glucuronidation. Azole antifungals also inhibit AZT metabolism. Other nephrotoxic and myelosuppressive drugs and probenecid enhance toxicity. Stavudine and zidovudine exhibit mutual antagonism by competing for the same activation pathway.

Use Zidovudine is used in HIV infected patients only in combination with at least 2 other ARV drugs. However, it is no longer included in the preferred 1st line WHO (2016) regimen, but is a component of one alternative regimen.

Didanosine (ddI) It is a purine nucleoside analogue which after intracellular conversion to didanosine triphosphate competes with ATP for incorporation into viral DNA, inhibits HIV reverse transcriptase and terminates proviral DNA. Mutational resistance develops, but only few AZT resistant mutants are non-responsive to didanosine also. It is infrequently used now due to higher toxicity than other NRTIs.

Dose: 400 mg/day (for ≥ 60 kg BW), 250 mg/day (< 50 kg BW) 1 hour before or 2 hour after meals.

DINEX EC, DDRETRO, VIROSINE DR 250 mg, 400 mg tabs.

In contrast to AZT, it does not cause myelosuppression. The major dose-related toxicity is peripheral (stocking and glove) neuropathy, which may be irreversible. Rarely acute pancreatitis occurs. Diarrhoea, abdominal pain, dry mouth and nausea are the side effects.

Stavudine (d4T) It is also a thymidine analogue which acts in the same way as AZT. Because of long term serious metabolic complications like lipodystrophy, lactic acidosis and peripheral neuropathy stavudine is no longer employed in WHO as well as NACO regimens, except in exceptional circumstances.

Dose: 30 mg BD

STAG, STAVIR, VIROSTAV 30 mg caps.

Lamivudine (3TC) This deoxycytidine analogue is phosphorylated intracellularly and inhibits HIV reverse transcriptase as well as HBV DNA polymerase. Its incorporation into viral DNA results in chain termination. Most human DNA polymerases are not affected and systemic toxicity of 3TC is low. Point mutation in HIV-reverse transcriptase and HBV-DNA polymerase gives rise to rapid lamivudine resistance.

Oral bioavailability of 3TC is high and plasma t½ longer (6–8 hours). Intracellular t½ is still longer (> 12 hr). It is mainly excreted unchanged in urine, and it can be employed in patients with hepatic insufficiency.

Lamivudine is used in combination with other anti-HIV drugs, and is as effective as AZT. It synergises with most other NRTIs for HIV, and is an essential component of most first line triple drug WHO and NACO regimens.

Lamivudine is also effective in chronic hepatitis B; in which lower doses are required than for HIV. This may be due to longer intracellular t½ of lamivudine in HBV infected cells than in HIV infected cells. HBV-DNA titre is markedly reduced and biochemical as well as histological indices of liver function improve. However, viral titres rise again after discontinuation. Even with continued medication HBV viraemia tends to return and lamivudine-resistance develops in upto 70% patients within 1–5 years. Because of this, it is no longer a 1st line drug for chronic hepatitis B. Lamivudine-resistant HBV remain responsive to tenofovir and adefovir, but usually not to entecavir or to telbivudine.

Dose: For chronic hepatitis B—100 mg OD

For HIV infection— 150 mg BD, or 300 mg OD.

LAMIVIR 150 mg tab, 150 mg/ 5 ml soln; LAMIVIR-HBV 100 mg tab; HEPTAVIR, LAMIDAC, LAMUVID, VIROLAM 100, 150 mg tabs;

Lamivudine is generally well tolerated and has good safety profile, because of which it is accorded high priority in use for HIV. Side effects are few—headache, fatigue, rashes, nausea, anorexia, abdominal pain. Pancreatitis and neuropathy are rare. Hematological toxicity does not occur.

Abacavir (ABC) This guanosine analogue is a clinically potent ARV drug that acts after

intracellular conversion to carbovir triphosphate, which gets incorporated in proviral DNA and terminates chain elongation. Rapid reduction in plasma HIV-RNA count and rapid rise in CD4 cell count has been noted when abacavir was given to AIDS patients. Resistance to ABC develops slowly, and it exhibits little cross resistance with other NRTIs. Its oral bioavailability is 80% and it is mainly eliminated by metabolism. The plasma t½ is 1–1.5 hour, but intracellular t½ of the active metabolite is >12 hours. Hypersensitivity reactions such as rashes, fever, abdominal pain, bowel upset, flu-like respiratory and constitutional symptoms occur in 2–5% adult patients and are the major problems. Abacavir must be promptly stopped when the reaction occurs, because fatalities are on record when patients developing the reaction were given further doses of ABC. A genetic basis and massive release of TNFα have been related to this reaction. Abacavir should never be given again to a patient who has developed this reaction. It should also be avoided in patients with cardiovascular risk factors. Other side effects are not serious. Lypodystrophy is least likely. Avoidance of alcohol is advised. Combination regimens including abacavir are frequently used, and it is a component of the preferred 1st line WHO regimen for children.

Dose: 300 mg BD or 600 mg OD.

ABAVIR, ABAMUNE 300 mg tab.

Tenofovir (TDF) This is the only nucleotide (not nucleoside) analogue that is a commonly used anti-HIV drug. It is also active against HBV, and its pharmacology is described on p. 855. Tenofovir was initially used only in previously treated patients, but because of good tolerability profile, it is now being included in first line regimens as well. Tenofovir containing regimens have been found at least as effective and less toxic as other first line regimens. It is included in the preferred 1st line WHO regimen for adults and adolescents. Renal toxicity is to be watched.

TENVIRAL-L: Tenofovir 300 mg + Lamivudine 300 mg tab

TRIO DAY: Tenofovir 300 mg + Lamivudine 300 mg + Efavirenz 600 mg tab.

Emtricitabine (FTC) It is a fluorinated cytidine analogue which is converted intracellularly by cellular kinases into its triphosphate which acts as the HIV reverse transcriptase inhibitor. Emtricitabine is well absorbed orally, little metabolized and largely excreted unchanged by the kidney with a t½ of 10 hrs. However, the intracellular t½ of the active triphosphate is much longer (~40 hrs), permitting once daily dosing. Dose reduction is needed in renal impairment. Some cross resistance with lamivudine occurs, but not with other NRTIs. Like lamivudine, it is also active against HBV, but should not be used in HIV-HBV coninfected patients because sudden stoppage of therapy can cause rebound exacerbation of hepatitis. Emtricitabine is one of the 1st line anti-HIV drugs, and is a component of the preferred WHO regimen for treating adults and adolescent HIV patients. In combination with tenofovir, it is advocated by WHO for pre-exposure prophylaxis of HIV in high risk adults. Emtricitabine is one of the least toxic ARV drugs; side effects are fatigue, headache, nausea, diarrhoea, and discoloration of exposed skin. It is marketed only as fixed dose combination tablets.

Dose: 200 mg OD, as FDC tablets.

TENVIR-EM, TAVIN-EM, TENOF-EM: Emtricitabine 200 mg + Tenofovir disoproxil fumarate (TDF) 300 mg tab.

TRUSTIVA, VIRADAY, VONAVIR: Emtricitabine 200 mg + tenofovir (TDF) 300 mg + Efaviranz 600 mg tab.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Nevirapine (NVP), Efavirenz (EFV) These are nucleoside unrelated compounds which directly inhibit HIV reverse transcriptase without the need for intracellular phosphorylation. Their locus of action on the enzyme is different from that of NRTIs, and they are non-competitive inhibitors. They are more potent than AZT on HIV-1, but do not inhibit HIV-2. Accordingly, they are not indicated in infections caused by HIV-2 (HIV-2 infections are infrequent and milder). If used alone, viral resistance to NNRTIs develops rapidly by point mutation of the enzyme; they should always be combined

with 2 other effective drugs. Cross-resistance between NVP and EFV is common, but not with NRTIs or PIs. A patient failing a regimen contaning NVP should not be treated with EFV and *vice versa*, but can be put on etravirine regimen.

NVP is well absorbed orally; is extensively metabolized, mainly by CYP3A4 and to a lesser extent by CYP2B6, with a t½ of ~ 30 hours. Oral absorption of EFV is ~ 50%, but the t½ is longer (48 hours). It is completely metabolized, mainly by CYP2B6 and a smaller fraction by CYP3A4. Both are enzyme inducers, and cause autoinduction of their own metabolism. However, EFV inhibits CYP3A4 as well. Nevirapine is started at a lower dose (200 mg/day); the dose is doubled after 2 weeks when its blood levels go down due to autoinduction. Such dose escalation is not required for EFV. Rifampin induces NVP metabolism and makes it ineffective, but has little effect on EFV levels. If a patient being treated with NVP develops TB and is put on rifampin, NVP should be replaced by EFV.

The NNRTIs are indicated in combination regimens for HIV. Either NVP or EFV is included in the first line triple drug regimen used by NACO, but the WHO (2016) regimen prefers EFV and advocates NPV as an alternative. These drugs have succeeded in reducing HIV-RNA levels when an earlier regimen (not including an NNRTI) has failed.

Nevirapine (NVP)

Dose: Initially 200 mg/day, to be increased after 2 weeks to 200 mg twice daily (because autoinduction reduces levels).
NEVIMUNE, NEVIVIR, NEVIPAN, NEVIRETRO 200 mg tab.

Rashes are the commonest adverse effect, followed by nausea and headache. Occasionally skin reactions are severe. Fever and rise in transaminases occurs dose dependently. NVP is potentially hepatotoxic. In patients developing NVP toxicity, it should be replaced by EFV which has low hepatotoxicity. NVP should not be used in patients with hepatic dysfunction.

Efavirenz (EFV) Its side effects are headache, rashes, dizziness, insomnia and a variety of neuropsychiatric symptoms. However, these symptoms decrease over time and discontinuation rate (due to adverse effect) is low. Gynaecomastia can occur. On the basis of animal studies, EFV was considered to be teratogenic, but recent human data have exonerated it; and the WHO (2016) regimen includes EFV in the preferred 1st line regimen for pregnant and breast-feeding women. Because of its longer plasma t½, occasional missed doses of EFV are less damaging.

Dose: 600 mg OD on empty stomach.
EFFERVEN, VIRANZ, EVIRENZ 200 mg cap, 600 mg tab.

Etravirine This is a second generation NNRTI which is active against HIV-1 mutants that are resistant to other NNRTIs. Etravirine is indicated in adults and children >6 yr who have already been treated and are resistant/intolerant to other NNRTIs. In one study, after 24 weeks etravirine containing regimen, 74% recipients achieved < 400 copies of HIV-RNA, compared to 51% of placebo recipients. The oral absorption of etravirine is enhanced by food and it is completely metabolized by CYP3A4, CYP2C9 and CYP2C19 with a plasma t½ of 40 hours. Metabolites are excreted in urine. Etravirine induces CYP3A4, but inhibits CYP2C9 and 2C19. As such it interacts with many drugs.

Etravirine is approved for use only in combination with a NRTI + one of PIs, e.g. darunavir/r or lopinavir/r or saquinavir/r, but not with fosamprenavir/r or atazanavir/r. Adverse effects are nausea and skin rashes, which can rarely be very serious.

Dose: 200 mg BD after meals.
INTRAVIR 100 mg tab.

Delavirdine and ***Rilpivirine*** are the other NNRTIs used infrequently.

Retroviral protease inhibitors (PIs)

An aspartic protease enzyme encoded by HIV is involved in the production of structural proteins and enzymes (including reverse transcriptase and integrase) of the virus from the large viral polyprotein synthesized in the infected cell. The polyprotein is broken into various functional components by this protease enzyme. It acts at

a late step in HIV replication, i.e. maturation of the new virus particles when the RNA genome acquires the core proteins and enzymes. Eight protease inhibitors—*Atazanavir (ATV), Indinavir (IDV), Nelfinavir (NFV), Saquinavir (SQV), Ritonavir (RTV), Lopinavir* (in combination with ritonavir *LPV/r*), *Fosamprenavir (FPV)* and *Darunavir (DRV)* are available for use against HIV. They bind to the active site of the protease molecule, interfere with its cleaving function, and are more effective viral inhibitors than AZT. The PIs do not need intracellular activation by phosphorylation. Because they act at a late step of viral cycle, they are effective in both newly as well as chronically infected cells. Under their influence, HIV-infected cells produce immature noninfectious viral progeny—hence prevent further rounds of infection.

Oral bioavailability of PIs is variable (IDV and RTV ~65%, NFV >20%, SQV 15%) and their plasma t½ ranges from 2–8 hours. All are extensively metabolized mainly by CYP3A4, except NFV which is mainly a substrate of CYP2C19. All PIs (especially ritonavir and lopinavir) are potent inhibitors of CYP3A4, while some other CYP isoenzymes are induced. The PIs interact with many drugs. Nelfinavir, lopinavir and ritonavir induce their own metabolism.

The PIs are not used as monotherapy, because resistance develops over months due to selection of resistant mutants. Combination of NRTIs with PIs is more effective than either drug given alone, and triple therapy is more effective than double therapy. Current recommendation is to use a PI in combination with either two NRTIs or one NRTI + one NNRTI. However, PIs are avoided in 1st line regimens, because their use in initial regimens markedly restricts second line regimen options. Most guidelines, including that of WHO and NACO, reserve them for failure cases.

Because different PIs inhibit as well as induce specific CYP isoenzymes to different extents, drug interactions with them are common and often unpredictable. Manufacturer's package inserts should be consulted while coprescribing any other drug. Specifically, metabolism of PIs is induced by rifampin and other enzyme inducers rendering them ineffective. Another problem in their use is the large tablet load. In case of different PIs, 6–18 tablets are to be taken daily, some on empty stomach, but others with meals; and this has to go on for months and years. Therefore, patient acceptability and compliance are often low. One of the strategies adopted to reduce the dose of PIs (except that of NFV) is to combine them with a low and subtherapeutic dose (100 mg) of ritonavir. By reducing first pass metabolism, ritonavir increases the bioavailability and by slowing systemic metabolism decreases clearance of the companion PI. This 'boosted PI regimen' permits reduction in the number/frequency of tablets to be taken each day. Nelfinavir is not to be combined with ritonavir because it is metabolized mainly by CYP2C19 that is not inhibited. All other PIs are mostly administered with low dose RTV.

The most prominent adverse effects of PIs are gastrointestinal intolerance, asthenia, headache, dizziness, limb and facial tingling, numbness and rashes. Of particular concern are lipodystrophy (abdominal obesity, buffalo hump with wasting of limbs and face), dyslipidaemia (raised triglycerides and cholesterol) which may necessitate restriction of lipids in diet. Insulin resistance occurs and diabetes may be exacerbated. Indinavir crystalises in urine and increases risk of urinary calculi.

Atazanavir (ATV) This PI is administered with light meal which improves absorption, while acid suppressant drugs decrease its absorption. ATV is metabolized primarily by CYP3A4, which is also moderately inhibited by it. Bioavailability and efficacy of ATV is improved by combining with RTV. The t½ is 6–8 hours. Loose motions, nausea and abdominal pain are the side effects. Dyslipidaemia and other metabolic complications are minimal with ATV, but jaundice occurs in some patients without liver damage due to inhibition of hepatic glucuronyl transferase.

Dose: 300 mg OD with ritonavir 100 mg taken at meal time.

ATAZOR 100, 150, 200, 300 mg caps.

Indinavir (IDV) It is to be taken on empty stomach; g.i. intolerance is common; excess fluids must be consumed to avoid nephrolithiasis. Hyperbilirubinaemia occurs. It is infrequently used now.

Dose: 800 mg TDS (BD if taken with 100 mg RTV).

INDIVAN, INDIVIR, VIRODIN 400 mg cap.

Nelfinavir (NFV) It is to be taken with meals, since food increases absorption, but bioavailability is erratic. NFV is mainly metabolized by CYP2C19. Often produces diarrhoea and flatulence; clinical efficacy is lower than other boosted PIs; less popular now.

Dose: 750 mg TDS; NELFIN, NELVIR, NEIVEX 250 mg tab.

Ritonavir (RTV) It is a potent PI; also a potent CYP3A4 inhibitor. Drug interactions, nausea, diarrhoea, paresthesias, fatigue and lipid abnormalities are prominent. Though RTV (600 mg twice daily) can be used as an antiretroviral drug, it is more commonly employed in a low dose (100 mg BD) to boost all other PIs except NFV. Low dose RTV produces no additional side effect.

RITOMUNE, RITOMAX 100 mg cap; RITOVIR 250 mg tab.

Saquinavir (SQV) Its oral bioavailability is low, the tablet load is large and side effects are frequent; photosensitivity can occur. Importantly, it is a weak inhibitor of CYP3A4.

Dose: 1200 mg TDS on full stomach; 1000 mg BD (with RTV 100 mg).

SAQUIN 200 mg tab.

Lopinavir It is available only in combination with RTV to improve bioavailability, though it is itself a CYP3A4 inhibitor. Diarrhoea, abdominal pain, nausea and dyslipidaemias are more common. ECG abnormalities have been noted. Its dose needs to be increased by 1/3rd if either NVP or EFV is used concurrently.

Dose: 400 mg (with ritonavir 100 mg) BD with food.

RITOMAX-L: V-LETRA: lopinavir 133.3 mg + ritonavir 33.3 mg cap.

Darunavir It is a potent newer PI active against both HIV-1 and HIV-2, including several strains resistant to other PIs. Oral bioavailability of darunavir is improved by coadministering ritonavir, which retards its 1st pass metabolism as well as systemic clearance by inhibiting CYP3A4. It is metabolized extensively by CYP3A4 and excreted in urine with a t½ of 15 hrs. Rifampin and other CYP3A4 inducers render it ineffective. Darunavir is approved for use only in combination with ritonavir or another booster *Cobicistat*. Side effects are nausea, diarrhoea, rise in hepatic enzymes, rashes and allergic reactions, particularly in those with sulfonamide allergy, but overall tolerability is good.

Dose: 600 mg BD along with ritonavir 100 mg BD.

DARUVIR 300 mg tab.

Fosamprenavir It is a phosphorylated prodrug of amprenavir that has better oral bioavailability and better tolerability than the parent drug. As such, it has replaced amprenavir. Fosamprenavir is active against both HIV-1 and HIV-2, and is effective in treatment-naive as well as previously PI treated patients. It is extensively metabolized, mainly by CYP3A4 and is a moderate inhibitor of CYP3A4. The plasma t½ is ~8 hours. Side effects are nausea, diarrhoea, fatigue and rashes, but lipid abnormalities are less marked.

Dose: 1400 mg twice daily, or 1400 mg once daily with ritonavir 200 mg daily.

Integrase inhibitors

The HIV integrase enzyme enters the host cell alongwith the genomic RNA. After the HIV-proviral DNA is transcripted in the cytoplasm of host cell, this enzyme translocates to the nucleus alongwith the proviral DNA, nicks host chromosomal DNA, integrates the proviral DNA with it and reseals it. Thus the proviral DNA becomes a part of the chromosomal DNA, and the cell gets permanently infected. Interference with this virus specific function provides an important target for action of ARV drugs.

Raltegravir It is the first integrase inhibitor to become available for treating HIV infection. Raltegravir prevents the integration of proviral DNA into the host chromosome and thus interrupts the viral cycle. It is active against both HIV-1 and HIV-2, and there is no cross resistance with other classes of ARV drugs. Its clinical efficacy in rapidly clearing HIV-RNA from circulation and in improving CD4 cell count has been demonstrated in treatment-naive as well as previously treated patients.

Raltegravir is rapidly absorbed orally and extensively glucuronide conjugated in liver. The terminal plasma t½ is ~12 hours. Rifampin induces metabolism of raltegravir; its dose needs to be doubled. Administration of Ca^{2+} and Mg^{2+} containing antacids and Ca^{2+} or iron supplements should be avoided with raltegravir

or staggered from it, because of its chelating property. Raltegravir produces few side effects like nausea, headache, diarrhoea, and weakness; myopathy is a potential toxicity.

Dose: 400 mg BD (along with 2 NRTIs).

ISENTRESS, ZEPODOM 400 mg tab.

Dolutegravir This is a second generation integrase inhibitor, which like raltegravir, is active against both HIV-1 and HIV-2, exhibits no cross resistance with other classes of ARV drugs. In addition it retains some activity against raltegravir-resistant viruses. Dolutegravir combined with 2NRTIs has yielded superior results than raltegravir-containing regimens.

It is absorbed rather slowly, glucuronide conjugated and eliminated with a t½ of 12 hours. The dose of dolutegravir should be doubled when given with enzyme inducers like rifampin and efavirenz, but its combination with nevirapine and etravirine should be avoided. Cationic medication (Ca^{2+}, Mg^{2+} salts) should be avoided or staggered with dolutegravir. It has good tolerability profile with rashes and hypersensitivity as the infrequent adverse effects. Hepatotoxicity is occasional. Given its potent activity, good tolerability, once a day dosing, dolutegravir alongwith 2 NRTIs is gaining popularity as a 1st line regimen for treatment-naive HIV patients, if cost is not a consideration. By doubling the dose, it is also advocated for patients who have been treated with raltegravir, when integrase-resistance is suspected.

Dose: 50 mg once daily; 50 mg twice daily with enzyme inducers, or if integrase-resistance is suspected.

INSTGRA, NAIVEX 50 mg tab.

Entry (fusion) inhibitor

Enfuvirtide This HIV-derived synthetic peptide acts by binding to HIV-1 envelope transmembrane glycoprotein (gp41) which is involved in fusion of viral and cellular membranes. Fusion of the two membrances is thus prevented and entry of the virus into the cell is blocked. It is not active against HIV-2. No cross resistance with other classes of ARV drugs occurs. Administered s.c. twice daily, it is used as add-on drug to an optimized regimen in selected patients who have failed many earlier regimens or have multidrug resistant HIV, and for whom there is no other treatment option. The injections are painful and cause local nodules/cysts. The cost and inconvenience are prohibitive.

CCR5 receptor inhibitor

Maraviroc The globular glycoprotein gp120 of the HIV envelope anchors to the CD4 site of host cell by binding to a cell membrane receptor, which mostly is the CCR5 chemokine receptor (most HIV are CCR5-tropic). Maraviroc is a novel anti-HIV drug which targets the host cell CCR5 receptor and blocks it. Attachment of the virus and subsequent entry of viral genome into the cell is thus interfered. It has no effect on HIV strains that are CXCR4 receptor tropic (CXCR4 is an alternative chemokine receptor which also can bind gp 120), or dual CCR5/CXCR4 tropic.

Added to optimized background therapy in patients who have already been treated with several regimens and who have CCR5-tropic HIV infection, maraviroc has resulted in marked reduction in HIV-RNA load, and improvement in CD4 count. It is active orally and there is no cross resistance with any other ARV drug. However, CCR5-tropism must be proven before using it.

Side effects are cough, fever, abdominal pain, rashes and postural hypotension, but tolerability of maraviror in general is satisfactory.

Some antiretroviral combinations

1. Tenofovir disoproxil fumarate 300 mg + Emtricitabine 200 mg tab: TENVIR-EM, TAVIN-EM, TENOF-EM tab.
2. Tenofovir disoproxil fumarate 300 mg + Emtricitabine 200 mg + Efavirenz 600 mg tab: TRUSTIVA, VIRADAY, VONAVIR tab.
3. Tenofovir disoproxil fumarate 300 mg + Lamivudine 300 mg tab: TENVIR-L tab.
4. Tenofovir disoproxil fumurate 300 mg + Lamivudine 300 mg + Efavirenz 600 mg tab: TRIODAY tab.
5. Lamivudine 150 mg + Zidovudine 300 mg tab (1 tab BD); COMBIVIR, CYTOCOM, DUOVIR, LAMUZID tab.
6. Lamivudine 150 mg + Zidovudine 300 mg + Nevirapine 200 mg tab (1 tab BD); DUOVIR-N, CYTOCOM-N, NEXIVIR-Z.
7. Lamivudine 150 mg + Stavudine 30 mg + Nevirapine 200 mg tab (1 tab BD); LAMOSTAD-N, TROMUNE, VIROLANS.
8. Lamivudine 150 mg + Zidovudine 300 mg 2 tab and Efavirenz 600 mg 1 tab kit; CYTOCOM-E kit.

HIV TREATMENT PRINCIPLES AND GUIDELINES

The treatment of HIV infection and its complications is complex, life-long, needs expertise, strong motivation and commitment of the patient, resources and is expensive. Antiretroviral therapy (ART) is only 30 years old, and is still evolving. Initially, anti-HIV drugs were used singly one after the other as each failed in a patient

due to emergence of resistance. Understanding the biology of HIV infection and availability of several potent drugs belonging to different classes has mandated 'highly active antiretroviral therapy' (HAART) with combination of 3 or more drugs whenever indicated. Monotherapy is contraindicated.

It has been realized that even with 3 drug ART, which rapidly kills > 99% virions, a small number survive within the resting CD4 lymphocytes and invariably give rise to relapse when treatment is discontinued despite complete absence of detectable viraemia and normal CD4 cell count for years. Relapses occur even if the same ART is continued after disappearance of viraemia and immune reconstitution. This is because HIV-reverse transcriptase and other enzymes are highly copying error prone, implying that viral replication produces changes at some base pairs (and codons) with high frequency—rate of mutation is high. Some mutations confer resistance to one or the other antiretroviral drugs. The resistant mutants are selected by ART and in time an apparently sensitive population is replaced by resistant virions. As the disease progresses in the individual (and several ARV regimens are used) the HIV population becomes genetically complex and diverse with respect to susceptibility to drugs. Each failing regimen limits future treatment options. Even primary drug resistance (i.e. in untreated patients) is being detected in 5–20% HIV patients. In developed countries, drug resistance studies are being recommended before initiating ART.

Since none of the currently available regimens can eradicate HIV from the body of the patient, the goal of therapy is to maximally and durably inhibit viral replication so that the patient can attain and maintain effective immune response towards potential microbial pathogens. Greater the suppression of viral replication, lesser is the chance of emergence of drug resistant virus. Effective ART prevents sexual transmission of HIV. Therapy in the infected partner nearly eliminates risk of transmission to the uninfected partner. It also reduces infectivity of the patient for other persons, thus serves to limit transmission.

Initiating antiretroviral therapy Till recently, various professional bodies and health organizations like WHO and NACO recommended delaying start of ART in asymptomatic HIV infected subjects untill the CD4 count fell to <350 cells/μL (or < 500 cells/μL in some guidelines) or untill symptoms/opportunistic infections appeared. However, strong evidence has emerged in the past few years, particularly after 2013, to show that early institution of ART is associated with better clinical outcomes in people living with HIV (PL-HIV) compared to late start ART. It is also realized that HIV infection starts damaging the immune system from the very beginning, though early damage does not become evident and cannot be quantified. This early damage can be minimized and the prognosis improved by prompt institution of ART. Further, early-start ART results in a smaller pool of chronically virus infected CD4 cells and lower chances of drug resistance. The SART trial and other observational studies have demonstrated that prompt institution of ART is associated with reduction in risk for serious illness or death to less than half compared to delaying treatment untill CD4 cell count falls to < 350/μL. Transmission of HIV to uninfected sexual partner is also curtailed by early institution of ART.

The availability of more potent, safer and better tolerated newer ARV drugs, including integrase inhibitors, has facilitated early institution of ART to asymptomatic infected subjects. The convenience, lowered cost and lowered pill burden of FDCs of modern ARV drugs has made early start and life-long ART more acceptable to PL-HIV.

The WHO (2016) guideline has recommended that ART should be started in all adults including pregnant and breast-feeding women, adolescents as well as children as soon as possible after diagnosis of HIV infection is confirmed, irrespective of the CD4 cell count or the HIV-RNA load or the clinical stage of the disease. The WHO further recommends life-long continuation of ART in all infected patients regardless of normalization of CD4 count, or undetectable HIV-RNA or absence of opportunistic infections or other comorbidities. With adequate adherence to current ART, the life-expectancy of HIV infected subjects appears to approach that of uninfected subjects, if treatment is instituted early in the course of the disease. The WHO recommendation of immediate-start ART in all HIV positive subjects has been accepted by the Govt. of India, and is being implemented by NACO.

Therapeutic regimens Whenever ART is instituted, it should be aggressive with at least 3 anti-HIV drugs. The optimum response to any regimen is reduction of plasma HIV-RNA to undetectable levels (<50 copies/μL) and restoration of CD4 cell count to near normal within 6 months. The immune status improves and opportunistic infections become less common. There is a sense of well-being, and patients gain weight. Neurological manifestations of AIDS are mitigated and new Kaposi's lesions do not appear. Therapy with 3 drugs is considered optimal. Addition of a fourth drug affords little/no additional benefit, but may be tried in failed patients. Availability of multiple drugs has made it possible to employ a variety of combination regiments, so that choice has to be made on the basis of efficacy, tolerability, durability of effectiveness, convenience, drug interactions, impact on future ART options and cost.

Taking into consideration the above factors and the experience gained so far, the first line regimens universally include 2 NRTIs + 1 NNRTI. Placing emphasis over efficacy and tolerability, the preferred NRTIs are lamivudine, abacavir, tenofovir and emtricitabine. Efavirenz is preferred over nevirapine as the NNRTI, while etravirine is reserved for cases who have not responded to these NNRTIs. Nevirapine should be avoided in patients with hepatic dysfunction and in those receiving rifampin.

The first-line WHO (2016) recommended regimens for adults and adolescents are listed in the box.

First-line antiretroviral regimens for adults and adolescents*

Preferred regimen
1. Tenofovir + Lamivudine + Efavirenz[£]
2. Tenofovir + Emtricitabine + Efavirenz[£]
Alternative regimens
1. Zidovudine + Lamivudine + Efavirenz[£]
2. Zidovudine + Lamivudine + Nevirapine[£]
3. Tenofovir + Lamivudine + Dolutegravir
4. Tenofovir + Emtricitabine + Dolutegravir
5. Tenofovir + Lamivudine + Nevirapine[£]
6. Tenofovir + Emtricitabine + Nevirapine[£]

*Recommended by WHO-2016 guidelines on use of antiretroviral drugs.

[£]For pregnant and breast-feeding women as well.

The other important general points are:

- The 3 drugs in the regimen should belong to at least 2 different classes. Single class regimens are inferior. There is convincing evidence that 3 NRTI regimens are clinically less effective, and are not recommended now.
- For treatment-naive patients, only PI sparing regimens (2 NRTI + NNRTI/Integrase inhibitor) are chosen. They are more convenient with lower pill burden, simpler dosing schedules, more acceptable, better tolerated and produce no less metabolic complications.
- In countries where cost is not a major constraint, the integrase inhibitors raltegravir and dolutegravir are now being used alongwith 2NRTIs as the preferred regimen, because of high efficacy, better tolerability and convenience of dosing. One metaanalysis has found that dolutegravir had superior efficacy in suppressing viral load compared to boosted PIs or efavirenz.
- Discontinuation rates due to adverse effect were lower with dolutegravir compared to boosted PI regimens.
- In patients with metabolic disorders, dolutegravir/raltegravir containing regimens should be preferred over PI containing regimens.
- Abacavir + lamivudine + dolutegravir is a highly active regimen that may be employed in patients with high HIV-RNA load.
- Tenofovir + entricitabine + efavirenz is another highly active combination suitable for large viral load patients.
- The PI containing regimens (2 NRTI + PI or NRTI + NNRTI + PI) are reserved for advanced cases who have failed earlier regimens.
- Low dose ritonavir boosted PIs are preferred over higher dose single PI due to lower pill burden and better tolerability.
- If drug toxicity develops, either the entire regimen should be replaced or the offending drug should be changed. No dose reduction should be tried.
- Treatment is life-long.
- Institution of ART in patients with latent or partially treated opportunistic infection may produce '*immune reconstitution inflammatory*

syndrome' (IRIS) characterized by marked inflammatory reaction against residual organisms and constitutional symptoms due to 'reestablishment' of immune function.

- Pregnancy in women does not contraindicate ART. Drugs considered relatively safe during pregnancy are: zidovudine, lamivudine, tenofovir, emtricitabine, efavirenz, nevirapine and nelfinavir.
- Components of a regimen should not have overlapping toxicities.
- The ARV drug combinations that should not be employed are given in the box.

Antiretroviral drug combinations to be avoided

1. Zidovudine + stavudine:	Pharmacodynamic antagonism
2. Stavudine + didanosine:	Increased toxicity (neuropathy, lactic acidosis)
3. Lamivudine + didanosine:	Clinically not additive
4. Tenofovir + didanosine:	Lower efficacy
5. Lamivudine + emtricitabine:	Similar drugs

Durability of the regimens depends mainly on adherence of the patient to it. Compliance is a major determinant of outcome. Use of combined drug formulations greatly improves convenience and adherence, and are recommended, unless doses have to be individualized for specific reasons. Therapy should not be discontinued during an acute opportunistic infection, except in case of intolerance, interactions or toxicity. Since multiple antiretroviral, anti-*P. jiroveci*, antitoxoplasma, anti-CMV/herpes virus, antitubercular, antifungal or other drugs may have to be used in a patient, careful attention to drug interactions and toxicities has to be paid.

Changing a failing regimen An ART regimen is considered to have failed when:

- Plasma HIV-RNA count is not rendered undetectable (<50 copies/μL) within 6 months therapy.
- Repeated detection of virus in the plasma after initial suppression to undetectable levels despite continuation of the drug regimen.
- Clinical deterioration, fall in CD4 cell count, serious opportunistic infection while continuing drug therapy.

Failure is due to development of resistance to one or more components of the regimen. Treatment failures are to be anticipated and occur invariably after one to few years. The failed regimen should be changed entirely (all 3 drugs changed) to drugs that have not been administered earlier. However, lamivudine, even if administered in the failed regimen, may be continued in the second-line regimen, because it may exert residual antiviral activity and has the potential to reduce viral fitness, as well as improve viral sensitivity to AZT and TDF. A single drug should not be changed or added to a failed regimen, because this may tantamount to virtual monotherapy.

In designing second line regimens, drugs with known overlapping viral resistance should be avoided, e.g. efavirenz should not be replaced by nevirapine, lamivudine should not be replaced by emtricitabine, both are similar in action. Viral resistance testing is recommended for selecting the salvage regimen. A boosted PI is nearly always included in 2nd line regimens. Because an NNRTI is nearly always used in 1st line regimens, and resistance to EFV confers cross resistance to NVP; this class is practically out for 2nd line regimens. The 2nd line regimens suggested by NACO (2013) are listed in the box.

Choice of 2nd line ART regimens (NACO 2013)*

Failed 1st line regimen	*Second-line regimens*	
	NRTI component	*PI component*
1. Zidovudine + Lamivudine + Nevirapine/Efavirenz 2. Tenofovir + Lamivudine + Nevirapine	*Choices* *1st:* Tenofovir + Abacavir *2nd:* Didanosine + Abacavir *3rd:* Tenofovir + Zidovudine ± Lamivudine (continued)	*Choices* *1st:* Atazanavir/r *2nd:* Lopinavir/r *3rd:* Saquinavir/r *4th:* Indinavir/r *5th:* Nelfinavir

* NACO guidelines (2013), naco.gov.in 2013

ART— Antiretroviral therapy; NRTI—Nucleoside reverse transcriptase inhibitor; PI—Protease inhibitor; r—low dose ritonavir boosted

SECTION 12

The WHO (2016) guidelines recommend:

- The 2nd line ART regimens should consist of two NRTIs + one ritonavir boosted PI.
- After failure on tenofovir + lamivudine/emtricitabine based 1st line regimen, use zidovudine + lamivudine as the backbone 2nd line regimen.
- After failure on zidovudine/stavudine + lamivudine based regimen, use tenofovir + lamivudine/emtricitabine in 2nd line regimen.
- The preferred ritonavir boosted PI options for 2nd line regimens are FDCs of atazanavir or lopinavir.
- The FDC of ritonavir boosted darunavir can be used as alternative PI.
- A combination of raltegravir + lopinavir/r can be used as alternative 2nd line regimen.

Prophylaxis of HIV infection

Pre-exposure prophylaxis (PrEP) This serves to protect people at high risk of contacting HIV infection. Many large randomized controlled trials among men who have sex with men, sex workers and other key populations (*see* box) have demonstrated that daily treatment with tenofovir alone or its FDC with emtricitabine substantially reduced the risk of HIV infection (51% risk reduction against placebo in a meta-analysis of 10 trials). Accordingly, the WHO has strongly recommended offering PrEP to people at high risk of contacting HIV infection. Any one assessed to be at high risk, including the key risk groups (listed in box), should be eligible for PrEP.

Pre-exposure prophylaxis of HIV infection*

Drug regimen

Tenofovir 300 mg daily

±

Emtricitabine 200 mg daily

Key risk groups

- Men who have sex with men
- Sex workers
- Injection drug users
- Transgender people
- Uninfected partner of heterosexual serodiscordant couples

*Clinical guidelines: ARV drugs for HIV prevention; WHO (2016)

Post-exposure prophylaxis (PEP) Health care workers and others who get accidentally exposed to the risk of HIV infection by needle-stick or other sharp injury or contact with blood/biological fluid of HIV patients or blood transfusion should be considered for PEP. The type of exposure which warrants PEP, or does not warrant PEP is detailed in the box. The aim of PEP is to suppress local viral replication prior to dissemination, so that the infection is aborted.

Type of exposur warranting post-exposure prophylaxis of HIV

High-risk exposure

- Source symptomatic HIV patient, with high HIV-RNA titre or low CD4 count, not taking ART.
- Exposure through large bore hollow needle-stick, deep puncture, patient's blood visible on needle, or sexual exposure or major splash or large area of contact of longer duration with mucous membrane or abraded skin, of blood, genital secretions, amniotic fluid, CSF, breast milk, etc.

Low-risk exposure

- Source is HIV positive but asymptomatic with low HIV-RNA titre and high CD4 count, or taking ART.
- Exposure through mucous membrane, small area of brief contact or superficial scratch or through thin and solid needle-stick.

No risk exposure

- Source is confirmed to be HIV negative
- Exposure with urine, sweat, non-blood stained saliva, etc.
- Exposure through unbroken skin.

A 4 week regimen of at least 2 ARV drugs (mostly 2 NRTIs) has been found to significantly reduce the risk of HIV infection, if started soon after exposure. The current (2016) WHO guidelines recommend a minimum 2 NRTI-ARV drug regimen, preferably with added 3rd drug of a different class (*see* box).

If the source HIV patient has already received one or more ART regimens, it is likely that he/she be harbouring drug resistant virus. In such a case alternative PEP regimens may be required. If the drugs received by the source person is known, the PEP regimen may be individualized to include at least 2 drugs that the source has not received and is unlikely to

Post-exposure prophylaxis of HIV infection*	
For adults and adolescents	
Preferred 2 NRTI:	Tenofovir (300 mg) + Emtricitabine (200 mg) daily
	±
Preferred PI:	Lopinavir/r (400 + 100 mg) or Atazanavir/r (300 + 100 mg) daily
Alternative 3rd drug:	Darunavir/r (600 + 100 mg BD) or Raltegravir (400 mg BD) or Efavirenz (600 mg daily)
For children ≤ 10 years	
Preferred 2 NRTI:	Zidovudine + Lamivudine
Alternative 2NRTI:	Abacavir + Lamivudine or Tenofovir + Lamivudine/ Emtricitabine
Preferred PI:	Lopinavir/r
Alternative 3rd drug:	Atazanavir/r or Darunavir/r or Efavirenz or Raltegravir
Duration of regimen:	4 weeks

* Adopted from—ARV drugs for HIV prevention, WHO guidelines (2016)

be resistant to. Nevirapine is not recommended for PEP in adults and in children ≥2 years due to its hepatotoxic potential.

When indicated, PEP should be started as soon as possible, preferably within 1–2 hours of exposure. The likelihood of preventing infection declines with the delay; most guidelines do not recommend starting it beyond 72 hours of exposure.

Prophylaxis after sexual exposure The same PEP regimen as for needle-stick may be employed after sexual exposure to HIV. In USA, a 28-day regimen of tenofovir + emtricitabine (as FDC once daily) + raltegravir (400 mg twice daily) is most popular.

Perinatal HIV prophylaxis HIV may be transmitted from the mother to the child either through the placenta, or during delivery, or by breastfeeding. The highest risk (>2/3rd) of transmission is during the birth process. As per current recommendation, all HIV positive women, who are not on ART, should be put on the standard 3 drug ART. This should be continued through delivery and into the post-natal period, and has been shown to prevent vertical transmission of HIV to the neonate, as well as benefit mother's own health. The first line NACO (2013) regimen for pregnant women is:

Tenofovir 300 mg + Lamivudine 300 mg + Efavirenz 600 mg (as FDC tablet) once daily.

In addition the neonate should be given syrup nevirapine for 6 weeks. Delivery by cesarean section is advised if HIV-RNA is > 1000 copies/μL near the time of delivery.

☞ PROBLEM DIRECTED STUDY

60.1 A dental surgeon consults you with the following problem:
During a dental procedure he got exposed to a 26-year-old female patient's blood and saliva through a piercing injury on the finger. A needle had penetrated across his gloves and skin to a depth of 2–3 mm, but was withdrawn immediately and the area washed under running water. On enquiry, the patient revealed that one year back she had tested HIV positive, but was asymptomatic and not taking any anti-HIV medication.
(a) Should the dental surgeon be advised to take post-exposure prophylactic medication for HIV, or no medication is indicated under the circumstances?
(b) If medication is advised, which drug/drugs, doses and duration of use would be appropriate?
(see Appendix-1 for solution)

Chapter 61 Antimalarial Drugs

These are drugs used for prophylaxis, treatment and prevention of relapses of malaria.

Malaria, caused by 4 species of the protozoal parasite *Plasmodium*, is endemic in most parts of India and other tropical countries. It continues to be a major public health problem, mainly due to *P. falciparum (P.f.)* infection and its complications. As per latest WHO estimate.* ~ 216 million cases and ~ 0.445 million deaths occurred globally due to malaria in 2016, out of which 90% cases and deaths were in Africa and 7% in south-east Asia (including India). In India the National Malaria Eradication Programme (NMEP) started in 1958, achieved near complete disappearance of the disease in 1960s (from 75 million cases in 1950s to 0.1 million cases in the 1960s). However, due to the development of insecticide resistance among mosquitoes and other factors, it staged a comeback in the mid 1970s (6.47 million cases in 1976), and continues to prevail in endemic/subendemic proportions, so that 80% indian population lives in malaria risk areas. The NMEP was renamed National Antimalaria Programme (NAMP), which now is 'National vector borne diseases control programme' (NVBDCP) with a wider disease coverage. For the year 2016, the NVBDCP[§] has reported 1.06 million confirmed malaria cases in India, out of which nearly 50% were falciparum malaria with 242 recorded deaths. Though, the actual number of malaria cases, as well as deaths in India is much higher, there is a marked decline in both because of effective use of artemisinin-based combination therapy (ACT) for falciparum malaria.

The bark of *Cinchona* tree, growing in Peru, was introduced in Europe in the early 17th century as a cure for fevers. Later it was realized to be a specific remedy for malaria. *Quinine*, isolated from *Cinchona* bark in 1820, replaced the crude preparation and continued to be the major antimalarial drug till 1942. The world's supply of *Cinchona* bark for producing quinine was met by Java and neighbouring countries. This was cut off from the Germans during World War I and from the Allies during World War II. Due to enormous military importance of malaria and its treatment, intense activity was initiated for the development of antimalarial drugs. *Mepacrine* was produced in Germany in 1926 and extensively field tested by the Allies during World War II. *Chloroquine* was produced in USA soon after as a less toxic alternative to mepacrine. It had already been synthesized and used by Germans in 1934 as 'Resochin'. *Proguanil* was introduced in 1945 by the British as a well tolerated clinical curative.

None of the above drugs were found to be capable of preventing relapses in vivax malaria. *Pamaquine* was the first 8-aminoquinoline to be tested in Germany in the 1920s. However, no attention was paid to it because of its poor schizontocide action. This class of drugs was retested during World War II as radical curative and *Primaquine* emerged as the most desirable drug. *Pyrimethamine* was produced in 1951 under a planned post-war research programme for antimalarial drugs. Subsequently, chloroquine resistance emerged in *P. falciparum* and several drugs were developed to overcome it; the important ones are *Mefloquine, Lumefantrine, Atovaquone, Pyronaridine,* etc. However, the

* WHO: World Malaria Report, Nov. 2017: www.who.int/malaria/publications/world-malaria-report-2017/en

§ NVBDCP: nvbdcp.gov.in

most significant advance is the Chinese herb derived fast acting *Artemisinin* compounds, the latest one of which is a synthetic derivative *Arterolane* developed in India.

OBJECTIVES AND USE OF ANTIMALARIAL DRUGS

The aims of using drugs in relation to malarial infection are:

- To prevent clinical attack of malaria (prophylactic).
- To treat clinical attack of malaria (clinical curative).
- To completely eradicate the parasite from the patient's body (radical curative).
- To cutdown human-to-mosquito transmission (gametocidal).

These objectives are achieved by attacking the parasite at its various stages of life cycle in the human host (*see* Fig. 61.1). Antimalarials that act on erythrocytic schizogony are called *erythrocytic schizontocides,* those that act on pre-erythrocytic as well as exoerythrocytic (*P. vivax)* stages in liver are called *tissue schizontocides,* while those which kill gametocytes in blood are called *gametocides.* Antimalarial drugs exhibit considerable stage selectivity of action (*see* Table 61.1). Antimalarial therapy is given in the following forms.

1. Causal prophylaxis The preerythrocytic phase (in liver), which is the *cause* of malarial infection and clinical attacks, is the target for this purpose.

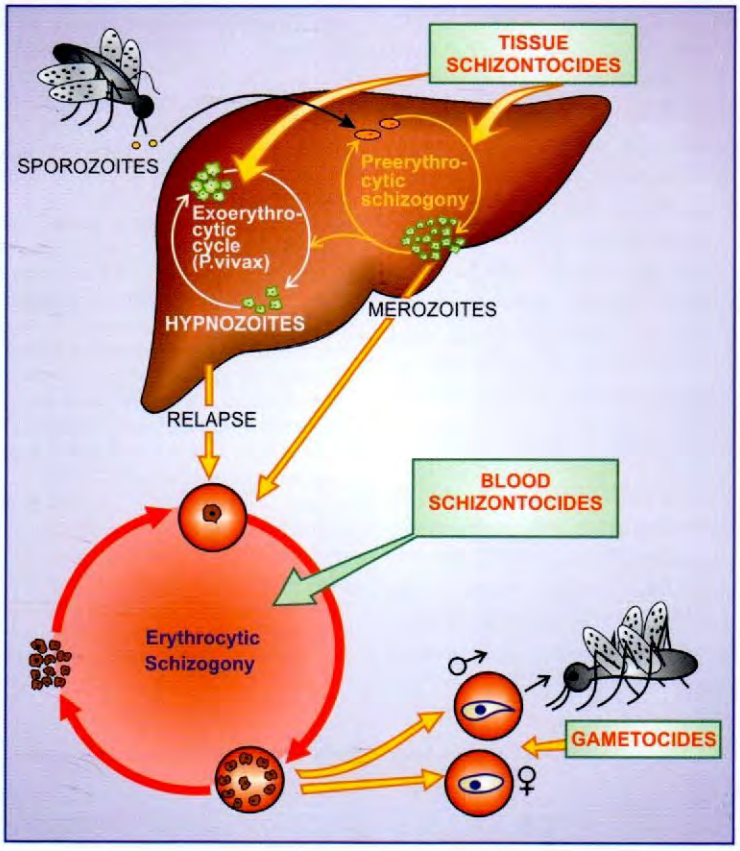
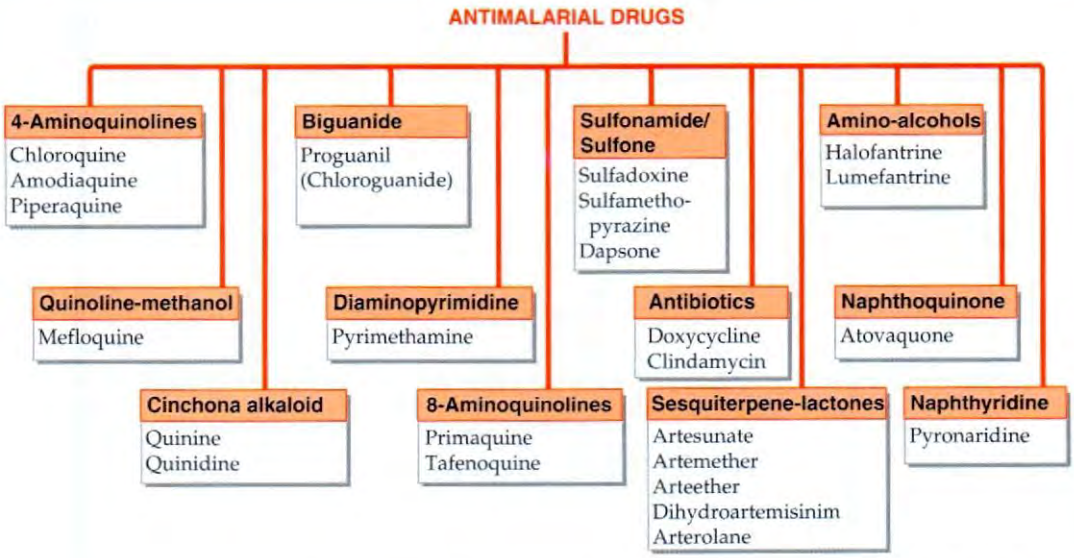


Fig. 61.1: The life cycle of malarial parasite in man. Stages and forms of the parasite at which different types of antimalarial drugs act are indicated.



- Primaquine is a causal prophylactic for all species of malaria, but has not been used in mass programmes, because of its toxic potential.

  Trials in Kenya and Irian Jaya have successfully used primaquine 0.5 mg/kg daily against both *P.f.* and *P.v.* in subjects with normal G-6-PD levels. The CDC (USA) recommends it for short duration travel to *P.vivax* predominant endemic areas, and for subjects who cannot take any other prophylactic drug.
- Proguanil is a causal prophylactic, primarily for *P.f.*, but is not used in India, because of weak activity against liver stages of *P.v.*, and rapid development of resistance when used alone.

A combined formulation of atovaquone (250 mg) + proguanil (100 mg) is commonly used as a prophylactic by Americans and other western travellers visiting malaria endemic areas. Atovaquone also is active against preerythrocytic stage of *P.f.*, but is not approved in India.

2. Suppressive prophylaxis The schizontocides which suppress the erythrocytic phase and thus attack of malarial fever can be used as prophylactics. Though the exoerythrocytic phase in case of vivax and other relapsing malarias continues, clinical disease does not appear.

- Chloroquine (CQ) 300 mg (base*) or 5 mg/kg weekly. In travellers, start one week before with a loading dose of 10 mg/kg and continue till one month after return from endemic area. However, it can be used as a prophylactic only in areas with CQ-sensitive *P.f.* (Mexico, Argentina, etc.). Since CQ-resistant *P.f.* is now widespread in India, and there are no exclusively *P.v.* areas, CQ is no longer employed as prophylactic in India.
- Mefloquine 250 mg started 1–2 weeks before and taken weekly till 4 weeks after return from endemic area, has been used for areas where CQ-resistant *P.f.* is prevalent. In India, use of mefloquine for prophylaxis is not allowed among residents, but may be used by travellers for long term (6 weeks to 1 year) prophylaxis.

  If tolerated, mefloquine is a prophylactic with proven efficacy, but should not be used in subjects with history of neuropsychiatric illness, convulsions or heart disease and for mefloquine-resistant *P.f.* areas (Myanmar, Thailand, Cambodia).
- Doxycycline 100 mg daily starting day before travel and taken till 4 weeks after return from endemic area for CQ-resistant *P.f.*, is suitable for short-term (maximum 6 weeks) visitors. It is contraindicated in pregnant women and children < 8 yr.
- Proguanil 200 mg daily with chloroquine 300 mg weekly affords substantial protection against moderately CQ-resistant *P. falciparum*, but less than that afforded

* All doses expressed in terms of base, e.g. chloroquine phosphate 250 mg = 150 mg base.

Table 61.1: Comparative properties of antimalarial drugs

	Drug	Pre-erythro.		Erythrocytic Phase			Hypnozoite	Gametes	Resistance	Toxicity grading
		Fal.	Viv.	Activity	Onset	Duration				
1.	Chloroquine	–	–	+	Fast	Long	–	–	Slow	+
2.	Mefloquine	–	–	+	Int	Long	–	–	Minor	++
3.	Quinine	–	–	+	Int	Short	–	–	Minor	+++
4.	Proguanil	+	–	+	Int	Short	–	*	Rapid	±
5.	Pyrimethamine	–	–	+	Slow	Long	–	–	Rapid	+
6.	Primaquine	+	+	–	–	–	+	+	Minor	++
7.	Sulfonamides	–	–	±	Slow	Long	–	–	Minor	+±
8.	Tetracyclines	–	–	+	Slow	Short	–	–	Nil	+
9.	Clindamycin	–	–	+	Slow	Short	–	–	Nil	+
10	Artemisinin	–	–	+	Fastest	Short	–	±	Nil	+
11	Lumefantrine	–	–	+	Int	Long	–	–	Nil	+

*Does not kill gametes but may inhibit their development in mosquito.
Pre-erythro. — Preerythrocytic stage;
Fal. — *P. falciparum;* Viv. — *P. vivax;* Int — Intermediate

by mefloquine. It is suitable for long term use, even over 5 years, and has been successfully utilized in Africa, but found ineffective and not employed in India.

Chemoprophylaxis of malaria should be limited to short-term use in special risk groups, such as — nonimmune travellers, nonimmune persons living in endemic areas for fixed periods (army units, labour forces), infants, children and pregnant women (falciparum malaria has serious consequences in the pregnant).

Intermittent preventive treatment in pregnancy (IPTp): In the form of one dose pyrimethamine (75 mg) + sulfadoxine (1500 mg) each in 2nd and 3rd trimester (gap not < 1 month) is recommended by WHO for areas with high *P.f.* endemicity (*P.f.* >30%) to protect pregnant women.

3. Clinical cure The erythrocytic schizontocides are used to terminate an episode of malarial fever. The available drugs can be divided into:

(a) *High-efficacy drugs*: Artemisinin, CQ, amodiaquine, quinine, mefloquine, halofantrine, lumefantrine and atovaquone. These drugs can be used singly to treat attacks of malarial fever, but are now generally combined.

(b) *Low-efficacy drugs*: Proguanil, pyrimethamine, sulfonamides, tetracyclines and clindamycin. These drugs are used only in combination for clinical cure.

The faster acting drugs are preferred, particularly in falciparum malaria where delay in treatment may result in death even if the parasites are cleared from blood by the drug. The exoerythrocytic phase (hypnozoites) of *vivax* and *ovale* persists which can cause *relapses* subsequently without reinfection. Thus, the erythrocytic schizontocides are radical curatives for falciparum, but not for vivax or ovale malaria. However, *recrudescences* occur in falciparum infection if the blood is not totally cleared of the parasites by the drug.

The drugs and regimens used for uncomplicated falciparum and vivax malaria are given in the box (p. 877). Only oral drugs are used for uncomplicated malaria.

Relapses of vivax/ovale malaria are treated in the same way as the primary attack because the parasite remains sensitive to the drug. Recrudescence in falciparum (or vivax) malaria indicates resistant infection, which should be treated with an alternative ACT or with quinine +

Treatment of uncomplicated malaria

A. Vivax (also ovale, malariae) malaria

1. Chloroquine 600 mg (10 mg/kg) followed by 300 mg (5 mg/kg) after 8 hours and then for next 2 days (total 25 mg/kg over 3 days) + Primaquine 15 mg (0.25 mg/kg) daily × 14 days

In occasional case of chloroquine resistance

2. Quinine 600 mg (10 mg/kg) 8 hourly × 7 days + Doxycycline 100 mg daily × 7 days or Clindamycin 600 mg 12 hourly × 7 days
   + Primaquine (as above)
   or
   Artemisinin-based combination therapy (except sulfa-pyrimethamine based ACT)
   + Primaquine (as above)

B. Chloroquine-sensitive falciparum malaria[£]

1. Chloroquine (as above) + Primaquine 45 mg (0.75 mg/kg) single dose (as gametocidal) on day 2, is an option

C. Chloroquine-resistant falciparum malaria

1. Artesunate 100 mg BD (4 mg/kg/day) × 3 days +
   Mefloquine 750 mg (15 mg/kg) on 2nd day and 500 mg (10 mg/kg) on 3rd day.
   or
2. Artemether 80 mg + Lumefantrine 480 mg twice daily × 3 days (child 25–35 kg BW ¾ dose; 15–25 kg BW ½ dose; 5–15 kg BW ¼ dose)
   or
3.* Artesunate 100 mg BD (4 mg/kg/day) × 3 days +
   Sulfadoxine 1500 mg (25 mg/kg) + Pyrimethamine 75 mg (1.25 mg/kg) single dose
   or
4. Arterolane (as maleate) 150 mg + Piperaquine 750 mg once daily × 3 days
   or
5.[$] Quinine 600 mg (10 mg/kg) 8 hourly × 7 days
   + Doxycycline 100 mg daily × 7 days or Clindamycin 600 12 hourly × 7 days

*First line ACT under NVBDCP, except in Northeastern states where FDC of artemether-lumefantrine is used.
[£]In India (including under NVBDCP) all P.f. cases, irrespective of CQ-resistance status, are treated with artemisinin-based combination therapy (ACT) + Primaquine (0.75 mg/kg) single dose on the 2nd day (as gametocidal).
[$]Falciparum malaria during 1st trimester of pregnancy should be treated with a 7 day course of quinine + clindamycin.

doxycycline/clindamycin. However, recrudescences and failures with ACT are infrequent, except with sulfa-pyrimethamine ACT in some areas.

Mixed *P. falciparum* and *P. vivax* infection: This is to be treated as falciparum malaria with ACT other than artesunate + sulfa-pyrimethamine, because sulfa-pyrimethamine is not effective against *P. vivax*. Antirelapse treatment with 14-day course of primaquine may be started concurrently.

Falciparum malaria during pregnancy An attack of falciparum malaria during pregnancy has serious implications both for the mother as well as the foetus. It must be treated promptly and aggressively. Drugs recommended are:

1. Quinine 600 mg TDS × 7 days + clindamycin 300 mg TDS/QID (20 mg/kg/day) for 7 days; can be used during all trimesters, and is a safer option during 1st trimester.
2. Artemisinin-based combination therapy (ACT; *see* box) is a better tolerated 3 day regimen, which may be used during the 2nd and 3rd trimester in preference to 7 day quinine + clindamycin therapy. Safety of ACT during 1st trimester is unproven.

Vivax malaria during pregnancy It can be treated with chloroquine as in non-pregnant, but radical cure with primaquine should be postponed till after delivery.

Severe and complicated falciparum malaria This includes *P. falciparum* infection attended by any one or more of—hyperparasitaemia, hyperpyrexia, fluid and electrolyte imbalance, acidosis, hypoglycaemia (blood glucose < 40 mg/dl), prostration, cardiovascular collapse, jaundice, severe anaemia, spontaneous bleeding, acute respiratory distress, pulmonary edema,

Treatment of severe and complicated falciparum malaria*

1. *Artesunate*: 2.4 mg/kg i.v. or i.m., followed by 2.4 mg/kg after 12 and 24 hours, and then once daily for 7 days. Switchover to 3 day oral ACT inbetween whenever the patient can take and tolerate oral medication.

or

2. *Artemether*: 3.2 mg/kg i.m. on the 1st day, followed by 1.6 mg/kg daily for 7 days. Switchover to 3 day oral ACT inbetween whenever the patient is able to take oral medication.

or

3. α/β Arteether:[$] 150 mg i.m. daily for 3 days (5 days as per WHO) in adults only (not for children). Switchover to 3 day oral ACT inbetween whenever the patient is able to take oral medication.

or

4. *Quinine diHCl*: 20 mg/kg (loading dose) diluted in 10 ml/kg 5% dextrose or dextrose-saline and infused i.v. over 4 hours, followed by 10 mg/kg (maintenance dose) i.v. infusion over 4 hours (in adults) or 2 hours (in children) every 8 hours, untill patient can swallow. Switchover to oral quinine 10 mg/kg 8 hourly to complete the 7 day course.

[$]Arteether (i.m.) is slower acting than artesunate (i.v.), and appears to be less efficacious. It is used only in India.

1. Volume of fluid for i.v. infusion of quinine should be reduced in patients with volume overload/pulmonary edema.
2. If i.v. quinine is to be continued beyond 48 hours, its dose should be reduced to 7 mg/kg 8 hourly.
3. If possible, oral quinine should be substituted by 3 day oral ACT, or doxycycline 100 mg daily should be combined with it.
4. Mefloquine-ACT should not be used in cerebral malaria cases, due to its neuropsychiatric adverse effects.
5. For children weighing <20 kg, WHO (2015) has revised the dose of artesunate to 3 mg/kg (in place of 2.4 mg/kg).
6. Chloroquine HCl i.v. to be used only if none of the above is available and only in adults.

*Adopted from Guidelines for treatment of malaria, 3rd edition; WHO (2015).

haemoglobinuria, black water fever, renal failure and cerebral malaria (impaired consciousness/convulsions/coma). Severe malaria is a medical emergency; parenteral antimalarial (preferably i.v.) drugs have to be used; oral drugs may be substituted when the condition improves. Drugs and regimens employed are detailed in the box.

4. Radical cure About 8–30% P.v. cases relapse due to persistance of exoerythrocytic stage. Drugs which attack this stage (hypnozoites) given together with a clinical curative achieve total eradication of the parasite from the patient's body. A radical curative is needed in relapsing malaria, while in falciparum malaria adequate treatment of clinical attack leaves no parasite in the body (there is no secondary exoerythrocytic tissue phase).

Drug of choice for radical cure of vivax and ovale malaria is:

- Primaquine 15 mg daily for 14 days given concurrently with or immediately after chloroquine/other schizontocide markedly reduces the relapse rate. However, it should be given only to individuals who test negative for G-6-PD deficiency. In G-6-PD deficient patients, primaquine 0.75 mg/kg once a week for 8 weeks may be used cautiously.
- Tafenoquine, a new long-acting 8-aminoquinoline exoerythrocytic schizontocide, has been developed as a single dose antirelapse drug for vivax malaria which is awaiting approval.

5. Gametocidal This refers to elimination of the male and female gametes of *Plasmodia* formed in the patient's blood. Gametocidal action is of no benefit to the patient being treated, but will reduce transmission to mosquito.

Primaquine is gametocidal to all species of *Plasmodia*, while artemisinins have weak lethal action on early-stage but not mature gametes. Gametes exposesd to proguanil may fail to carry on the life cyle normally in the mosquito. Adequate control of clinical attacks will reduce formation of gametes.

- A single dose of primaquine is employed immediately after clinical cure of falciparum malaria to kill the gametes and cut down transmission to mosquito. In India, the dose of primaquine for this purpose recommended by NBVDCP is 45 mg (0.75 mg/kg), while WHO (2015) recommends 15 mg (0.25 mg/

kg), which is considered safer for mass use, and sufficient to interfere with transmissibility to mosquito. This should be given even when an artemisinin is used for clinical cure because artemisinins do not kill all the gametes. Primaquine used for radical cure of vivax malaria eliminates *P.vivax* gametes as well.

Chloroquine (CQ)

It is a rapidly acting erythrocytic schizontocide against all species of plasmodia (except CQ-resistant *P. falciparum*); controls most clinical attacks in 1–2 days with disappearance of parasites from peripheral blood in 1–3 days. Therapeutic plasma concentrations are in the range of 15–30 ng/ml. However, it has no effect on primary and secondary hepatic stages of the parasite—does not prevent relapses in vivax and ovale malaria. CQ has no clinically useful gametocidal activity.

The mechanism of action of CQ is not exactly known. Plasmodia derive nutrition by digesting haemoglobin in their acidic vacuoles. CQ is actively concentrated by sensitive intraerythrocytic plasmodia; higher concentration is found in infected RBCs than in noninfected ones. By accumulating in the acidic vecuoles of the parasite and because of its weakly basic nature, it raises the vacuolar pH and thereby interferes with degradation of haemoglobin by parasitic lysosomes. Polymerization of toxic haeme generated from digestion of haemoglobin to nontoxic parasite pigment haemozoin is inhibited by the formation of CQ-haeme complex. Haeme itself or its complex with CQ then damages the plasmodial membranes. Clumping of pigment and changes in parasite membranes follow. Other related antimalarials like quinine, mefloquine, lumefantrine, pyronaridine appear to act in an analogous manner.

Chloroquine-resistance among *P.vivax* has been slow in developing, but *P. falciparum* has acquired significant resistance, and resistant strains have become prevalent in India (especially the east and north east), South East Asia, China, Africa and South America. Some of these have also acquired resistance to sulfa-pyrimethamine (S/P), proguanil and may be mefloquine, quinine, etc. (multidrug resistant strains). Because *P. falciparum* produces the more severe forms of malaria with considerable mortality, emergence of such strains is the biggest threat to the antimalaria programmes, and is the focus of attention for current research efforts.

Chloroquine-resistance among *P. falciparum* is now widespread in India, and no entirely sensitive areas can be indentified. The largest number of CQ failures are reported from the Northeastern part of India where 24–83% *P. falciparum* cases are resistant to CQ, and some of these (particularly in areas bordering Myanmar) are multidrug resistant. Due to spread of CQ-resistant *P.f.* to most parts of India, with Northeast, Odisha, Karnataka, etc. reporting high rates of resistance, the NVBDCP has switched over to ACT as the first line treatment of *P.f.* cases counrtywide. Resistance in *P. falciparum* is associated with a decreased ability of the parasite to accumulate CQ.

An efflux transporter encoded by the *pfcrt* (P.f. chloroquine-resistance transporter) gene, has been identified in the membranes of the acidic vacuoles of CQ-resistant *P.f.* It serves to pumpout CQ from the vacuoles and thus protects the haeme detoxifying mechanism of the resistant parasite. This appears to be the most important mechanism of CQ-reistance. The *pfmdr* gene encoded P-glycoprotein is an energy-dependent ABC transporter which confers resistance to many antimalarials like quinine, mefloquine, and halofantrine. This transporter is also involved in certain cases of *P.f.* resistance to CQ.

Chloroquine-resistance among *P. vivax* was first reported from Papua New Guinea in 1989. It has now been confirmed from Indonesia, Myanmar, Peru, Columbia, Ethiopia and detected in India, but is focal and sporadic, reported from Chennai, Mathura, tribal areas of Madhya Pradesh, Mumbai and Bihar. It manifests as recrudescence within 1–3 weeks of treating vivax malaria with standard dose of chloroquine. Such cases can be treated by quinine given along with doxycycline/clindamycin or by ACT (other than AS-S/P), followed by primaquine to effect radical cure (*see* box on p. 877). However, CQ continues to be the

standard treatment of vivax malaria in India, because prevalence of CQ resistant *P. vivax* is still low.

Other actions Chloroquine is active against *Entamoeba histolytica* and *Giardia lamblia* as well.

It has antiinflammatory, local irritant and local anaesthetic (on injection), weak smooth muscle relaxant, antihistaminic and antiarrhythmic properties.

Pharmacokinetics Oral absorption of CQ is excellent. About 50% gets bound in the plasma. It has high affinity for melanin and nuclear chromatin: gets tightly bound to these tissue constituents and is concentrated in liver, spleen, kidney, lungs (several hundred-fold), skin, leucocytes and some other tissues. Its selective accumulation in retina is responsible for the ocular toxicity seen with prolonged use.

Chloroquine is partly metabolized by liver and slowly excreted in urine. The early plasma t½ varies from 3–10 days. Because of tight tissue binding, small amounts persist in the body with a terminal t½ of 1–2 months.

Adverse effects Toxicity of CQ is low, but side effects like nausea, vomiting, anorexia, uncontrollable itching, epigastric pain, uneasiness, difficulty in accommodation and headache are frequent and quite unpleasant. Weekly suppressive doses have been safely given for 3 years.

- Prolonged use of high doses (as needed for rheumatoid arthritis, DLE, etc.) may cause loss of vision due to retinal damage. Corneal deposits may also occur and affect vision, but are reversible on discontinuation.
- Loss of hearing, rashes, photoallergy, mental disturbances, myopathy and graying of hair can occur on long-term use.

CQ can be used for treatment of malaria during pregnancy: no abortifacient or teratogenic effects have been reported.

Caution is to be exercised in the presence of liver damage, severe g.i., neurological, retinal and haematological diseases. Attacks of seizures, porphyria and psoriasis may be precipitated.

CQ should not be coadministered with mefloquine, amiodarone and other antiarrhythmics.

Preparations and administration

Chloroquine phosphate: (250 mg = 150 mg base) bitter, tablet should not be chewed. RESOCHIN, CLOQUIN, LARIAGO, NIVAQUIN-P 250 mg tab, 500 mg forte tab, 100 mg (base) per 10 ml oral susp.

Uses

1. Oral CQ causes rapid fever clearance and disappearance of parasitaemia in patients of malaria caused by all *P.ovale* and *P.malariae*, most *P.vivax* and some *P.falciparum* that are still sensitive. In India, it is the drug of choice for clinical cure of vivax, ovale and malariae malaria, but not for *P.f.* CQ is no longer used as a suppressive prophylactic in India, and such use is made only in vivax predominant countries or in those which have CQ-sensitive *P.f.* Combined with proguanil, it has been used as a prophylactic in Africa, but not in India.
2. Extraintestinal amoebiasis (Ch. 62).
3. Rheumatoid arthritis (Ch. 15).
4. Discoid lupus erythematosus—very effective; less valuable in systemic LE.
5. Lepra reaction (*see* p. 837).
6. Photogenic reactions.
7. Infectious mononucleosis: affords symptomatic relief.

Amodiaquine (AQ) It is almost identical to CQ in properties and is less bitter. Studies in Africa have found amodiaquine to be somewhat faster acting than CQ.

Experience in Africa over the past > 3 decades supports use of AQ to treat uncomplicated falciparum malaria, but it is not recommended for prophylaxis due to risk of hepatotoxicity and agranulocytosis on prolonged use. There is evidence now that AQ is effective even in areas with CQ-resistant *P. falciparum*. Coformulated with artesunate (AS/AQ) the combined amodiaquine-artesunate tablet has become 1st line treatment of falciparum malaria in many African countries. On the basis of successful clinical trials in India, the combined formulation of this ACT has been recently approved for use in falciparum malaria, irrespective of CQ-resistance status.

Side effects of AQ are similar to that of CQ; itching may be less common, though still the most common complaint. Neutropenia has been associated with AQ when it is used in children and in HIV patient receiving antiretroviral therapy.

Dose: for treatment of acute attack of malaria: 25–35 mg/kg over 3 days; CAMOQUIN 200 mg (as HCl = 150 mg base) tab; BASOQUIN 150 mg (base) per 5 ml susp.

Piperaquine (*see* under ACT, p. 891)

Mefloquine

This quinoline drug was originally tested during World War II, but introduced for use only in 1963 when it was reinvestigated and found effective against CQ-resistant *P.f.* Mefloquine (MQ) is intrinsically fast acting erythrocytic schizontocide, but slower than CQ or quinine due to very slow and variable rate of absorption after oral ingestion. It is effective against CQ-sensitive as well as resistant plasmodia. A single dose (15 mg/kg) controls fever and eliminates circulating parasites in infections caused by *P. falciparum* or *P. vivax* in partially immune as well as nonimmune individuals. However, it neither has gametocidal activity, nor kills vivax hypnozoites. Like CQ relapses occur subsequently in vivax malaria. It is also an efficacious suppressive prophylactic for multi-resistant *P. falciparum* and other types of malaria. Due to extensive use as monotherapy, MQ-resistance among *P. falciparum* has become common in Thailand, Cambodia and Myanmar, but is sporadic in Africa, South America and Middleeast. Since it has not been widely used in India, MQ-resistance is not a problem, but due to its long t½ chances of selection of resistant strains are high; MQ-resistant *P. falciparum* isolates have been reported from Northeast, Gujarat and Andhra Pradesh. Resistance to MQ confers cross resistance to quinine and halofantrine.

The mechanism of action of MQ is not known, but the morphological changes produced in the intraerythrocytic parasite resemble quinine and CQ induced changes. Like CQ it accumulates in infected RBCs (including those with CQ-resistant *P.f.*), binds to haeme and this complex may be damaging the parasite membranes. However, recent evidence suggests that the site of action of MQ is in the parasitic cytosol rather than in the acidic vacuole. The major mechanism by which *P.f.* develops MQ-resistance is by enhanced translation of *pfmdr1* gene, though *Pfcrt* mutation may also be involved.

Pharmacokinetics Oral absorption of MQ is good but peak concentrations are reached 5–15 hours. It is highly plasma protein bound and concentrated in many organs including liver, lung and intestines. Extensive metabolism occurs in liver and it is primarily secreted in bile. Considerable enterohepatic circulation of MQ and its tissue binding accounts for the long t½ which is 2–3 weeks.

Adverse effects MQ is bitter in taste; common reaction is dizziness, nausea, vomiting, diarrhoea, abdominal pain, sinus bradycardia and Q-T prolongation. These are usually mild and largely dose related, but may be severe in some. Major concern has been a variety of neuropsychiatric reactions (disturbed sense of balance, ataxia, errors in operating machinery, strange dreams, anxiety, hallucinations, rarely convulsions) occurring in some recipients. These are dose related and subside over 1–3 weeks on discontinuation. Patients recovering from cerebral malaria are more prone to develop convulsions. Rare events are haematological, hepatic and cutaneous toxicity. MQ appears to be safe during pregnancy, but should be avoided in 1st trimester unless absolutely essential. MQ is contraindicated in patients with anxiety, depression, psychosis, and in those with cardiac conduction defects.

Interactions Halofantrine or quinidine/quinine or CQ given to patients who have received MQ cause QTc lengthening—cardiac arrests are reported. These drugs should not be administered if MQ has been given < 12 hours earlier.

Use Mefloquine is an effective drug for multi-resistant *P. falciparum*. To check the spread of

MQ-resistance, current recommendation is to use it only in combination with artesunate as ACT for uncomplicated falciparum malaria, including CQ-resistant and CQ + sulfa-pyrimethamine (S/P) resistant cases. However, due to adverse effect potential of MQ, this ACT is not favoured now. MQ cannot be given parenterally and is not used in complicated/severe malaria.

For prophylaxis of malaria among travellers to areas with multidrug resistance; 250 mg (5 mg/kg in children) per week is started preferably 1–2 weeks before travel to assess side effects in the individual. It is not recommended for prophylaxis in residents of the endemic area.

MEFQUE, CONFAL, FACITAL 250 mg tab; to be taken with plenty of water after meals.

Mepacrine (Quinacrine, Atabrine) It is an acridine derivative erythrocytic schizontocide, more toxic and less effective than chloroquine. It is obsolete as an antimalarial, but is also active against giardia and tapeworms.

Quinine

Quinine is the levo rotatory alkaloid obtained from cinchona bark, and the oldest antimalarial still in use. Its *d*-isomer quinidine is used as an antiarrhythmic (and for malaria as well in some countries).

Quinine is an erythrocytic schizontocide for all species of plasmodia, but less effective and more toxic than CQ. Resurgence of interest in quinine is due to the fact that most CQ and multidrug-resistant strains of *P. falciparum* still respond to it. However, resistance even to quinine has been described in certain parts of Southeast Asia and in Brazil where quinine + tetracycline has been the standard treatment of complicated malaria. Quinine-resistance has been encountered sporadically in India, particularly along Myanmar border. There is partial cross resistance between quinine and MQ, but many MQ-resistant cases respond to quinine. Though effective in terminating an acute attack of falciparum malaria, quinine may not prevent recrudescence—indicating incomplete clearance of the parasites. Doxycycline or clindamycin is mostly added to it for complete parasite clearance.

Quinine has no effect on preerythrocytic stage and on hypnozoites of relapsing malaria, but kills *vivax, ovale* and *malariae* gametes. Like CQ it is a weak base, and acts in an analogous manner to inhibit polymerization of haeme to hemozoin; free haeme or haeme-quinine complex damages parasite membranes and kills it. However, the exact mechanism of action is not known.

Resistance to quinine in *P.f.* appears to involve both enhanced translation as well as mutation of *Pfmdr* gene among different strains.

Quinine has many other actions:

1. *Local irritant and anaesthetic* Quinine is intensely bitter and irritant. Orally it causes nausea, vomiting, epigastric discomfort. Injections can cause pain and local necrosis in the muscle and thrombosis in the vein. Local inflammation may be followed by fibrosis.

2. *Systemic actions* Gastric secretion is increased. Quinine is a weak analgesic and antipyretic; affects hearing and vision at higher doses. Cardiodepressant, antiarrhythmic and hypotensive actions are similar to quinidine (*see* Ch. 39). Rapid i.v. injection can produce marked fall in BP and cardiovascular collapse.

Quinine directly decreases contractile power of skeletal muscle fibre (*see* Ch. 25). It stimulates the myometrium and can cause abortion in early pregnancy. However, it is not a dependable abortifacient. Blood sugar is slightly lowered due to release of insulin from the pancreas. Rapid i.v. injection of quinine has caused hypoglycaemia.

Pharmacokinetics Quinine is rapidly and completely absorbed orally. It is 70% bound to plasma proteins, especially α_1 acid glycoprotein, which increases during acute malarial infection. CSF concentrations are low. A large fraction of the dose is metabolized in the liver by CYP3A4 and excreted in urine with a t½ of 10–12 hours. Quinine is noncumulative.

Adverse effects Toxicity of quinine is high and dose related; 8–10 g taken in a single dose may be fatal.

Cinchonism A large single dose or higher therapeutic doses taken for a few days produce a syndrome called 'cinchonism'. It consists of ringing in ears, nausea, vomiting (due to both gastric irritation and CTZ stimulation), headache, mental confusion, vertigo, difficulty in hearing and visual defects (due to direct neurotoxicity as well as constriction of retinal and auditory

vessels). Diarrhoea, flushing and marked perspiration may also appear. The syndrome subsides completely if the drug is stopped.

Poisoning with still higher doses results in the above symptoms in an exaggerated form. In addition, delirium, fever, tachypnoea followed by respiratory depression, pulmonary edema, hypoglycaemia, marked weakness and prostration can occur. Hypotension, cardiac arrhythmias develop only on rapid i.v. injection — the patient may die. Watch Q-T prolongation during i.v. infusion of quinine; stop if it exceeds 25%.

Few individuals are idiosyncratic/hypersensitive to quinine; cinchonism may appear after a single therapeutic dose. Purpura, rashes, itching, angioedema of face and bronchoconstriction may develop.

Quinine occasionally causes haemolysis, especially in pregnant women and in patients of falciparum malaria, resulting in haemoglobinuria (black water fever) and kidney damage.

During pregnancy it should be used only for serious falciparum malaria, with special care to prevent hypoglycaemia.

Uses

1. *Malaria* Quinine is used orally for uncomplicated CQ-resistant malaria, and i.v. for complicated/cerebral malaria.

(a) *Uncomplicated resistant falciparum malaria:* Quinine may be used orally as an alternative to ACT in uncomplicated CQ-resistant falciparum malaria. Because of narrow therapeutic index, frequent side effects and a 7 day course, quinine is used for resistant malaria only when none of the ACT is available or suitable. However, it is the drug of choice during 1st trimester of pregnancy.

(b) *Complicated and severe malaria including cerebral malaria:* Quinine (i.v.) has been the drug of choice for cerebral malaria (falciparum malaria with impaired consciousness) and other forms of complicated malaria. However, clinical trials have established that parenteral artemisinins are faster acting, more effective, better tolerated and more conveniently administered. Therefore, artesunate (i.v./i.m.) or artemether (i.m.) or arteether (i.m.) are now preferred over quinine for severe malaria. The dosage and schedule for i.v. infusion of quinine for severe malaria is given in the box on p. 878. Hypoglycaemia due to hyperinsulinemia is the most important side effect which can be prevented by infusing quinine in 5% dextrose.

Supportive treatment needed in cerebral malaria is cooling for fever, i.v. diazepam for convulsions, correction of fluid and electrolyte balance and acidosis. Corticosteroids are useless, may be harmful—avoid them.

2. Nocturnal muscle cramps: a single tablet of quinine (300 mg) at bed time may benefit some, but not all cases, and risks may not justify use. Quinine is also effective in myotonia congenita.

REZOQUIN, QUININE, QUINARSOL 300, 600 mg tab, 600 mg/2 ml inj.

Proguanil (Chloroguanide)

It is a relatively slow-acting erythrocytic schizontocide for both *P.f.* and *P.v.* In addition, it inhibits the preerythrocytic stage of *P.f.* Gametocytes exposed to proguanil are not killed but may fail to develop properly in the mosquito. Proguanil is cyclized in the body to a triazine derivative (cycloguanil) which inhibits plasmodial DHFRase-thymidylate synthase in preference to the mammalian DHFRase. Resistance to proguanil develops rapidly due to mutational changes in the plasmodial DHFRase-thymidylate synthase enzyme. There is partial cross-resistance between proguanil and pyrimethamine, which is a directly acting plasmodial DHFRase inhibitor.

Absorption of oral proguanil is slow, but almost complete. It is partly metabolized and excreted in urine; t½ is 16–20 hr; noncumulative. It is very well tolerated; side effects are less compared to CQ. Mild abdominal symptoms, vomiting, occasional stomatitis, haematuria, rashes and transient loss of hair are reported.

In the late 1940s and early 1950s proguanil was extensively used as a clinical curative for vivax malaria, especially in endemic areas with partially immune population. However, such use is now obsolete, because proguanil alone cannot be relied upon in nonimmune patients, particularly those with falciparum malaria, due to slow response and chances of rapid resistance. Currently in India, proguanil has little role either in prophylaxis or in clinical cure of malaria. Its combination with atovaquone (*see* p. 889) is commonly used in Thailand, USA and many other countries as a fast-acting erythrocytic schizontocide for treatment of multidrug resistant falciparum malaria. Proguanil potentiates the schizontocidal action of atovaquone by a DHFRase unrelated action. Moreover, *P.f.* does not easily develop resistance to this combination.

Atovaquone-proguanil (MALARONE) is also used by western travellers as a causal prophylactic while visiting CQ-resistant/multidrug-resistant *P.f.* endemic areas. In Africa proguanil combined with CQ has been used as a suppressive prophylactic in moderately CQ-resistant *P.f.* areas.

PROGUMAL 100 mg tab.

Pyrimethamine

It is a directly acting inhibitor of plasmodial DHFRase (does not require conversion to a cyclic triazine, as is the case with proguanil). Selective antimalarial action of pyrimethamine depends on high affinity for plasmodial enzyme (~2000 times greater than for the mammalian enzyme). In contrast to trimethoprim, it has very poor action on bacterial DHFRase. Under the influence of pyrimethamine, schizogony of malarial parasite in blood gradually stops. At high doses, it inhibits *Toxoplasma gondii*.

Pyrimethamine is more potent than proguanil, and a slowly acting erythrocytic schizontocide, but does not eliminate the preerythrocytic phase of *P. falciparum* or the exoerythrocytic phase of *P.vivax*. If used alone, resistance develops rather rapidly by mutation in the DHFRase enzyme of the parasite with reduced affinity. Pyrimethamine resistant plasmodia exhibit cross resistance to proguanil.

Pharmacokinetics Absorption of pyrimethamine from g.i.t. is good but slow. Certain organs like liver, spleen, kidney and lungs concentrate pyrimethamine. It is metabolized and excreted in urine with a t½ of 4 days. Prophylactic concentrations remain in blood for 2 weeks.

Adverse effects Pyrimethamine is relatively safe. The only side effects are occasional nausea and rashes. Folate deficiency is rare; megaloblastic anaemia and granulocytopenia may occur with higher doses, especially in those with marginal folate stores. This can be treated by folinic acid.

Use Pyrimethamine is used only in combination with a sulfonamide as sulfa-pyrimethamine (S/P) or dapsone (*see* below) for treatment of falciparum malaria.

Sulfonamide-pyrimethamine (S/P)

Sulfonamides/dapsone are not particularly effective antimalarial drugs in their own right; have some inhibitory influence on the erythrocytic phase, especially of *P. falciparum*. However, they form supra-additive synergistic combination with pyrimethamine due to sequential block (as in case of cotrimoxazole: *see* p. 757). Though, both components are slow acting, the combination acts faster, so that it can be employed as a clinical curative for *P. falciparum*. Efficacy against *P. vivax* is low; it should not be used for vivax malaria or for mixed *P. falciparum-P. vivax* infection. By the addition of sulfonamide, development of resistance to pyrimethamine is retarded. There is no cross-resistance with other groups of antimalarial drugs.

The popular combinations are:

Sulfadoxine 500 mg + pyrimethamine 25 mg tab: RIMODAR, FANCIDAR, LARIDOX, MALOCIDE; REZIZ 500 mg + 25 mg tab and per 10 ml susp; REZIZ FORTE 750 mg + 37.5 mg tab.

Sulfamethopyrazine 500 mg + pyrimethamine 25 mg tab: MALADEX.

As clinical curative: Sulfadoxine 1500 mg + pyrimethamine 75 mg (3 tab) single dose (children 9–14 yr 2 tab, 5–8 yr 1½ tab, 1–4 yr 1 tab).

Sulfadoxine and sulfamethopyrazine are ultra-long acting sulfonamides (*see* p. 756). They attain low blood concentrations, but are able to synergise with pyrimethamine which also has long t½. The combination has the potential to cause serious adverse effects (exfoliative dermatitis, Stevens-Johnson syndrome, etc.) due to the sulfonamide. Therefore, use is restricted to single dose treatment of uncomplicated CQ-resistant falciparum malaria. Prophylactic use is limited to 2–3 doses given in 2nd and 3rd trimester for intermittent preventive treatment in pregnancy (IPTp) *see* p. 876. It is contraindicated in infants and in individuals allergic to sulfonamide. There is no evidence that single dose of the combination used for treating malaria harms the foetus during pregnancy, but should be given with folate supplementation.

The major importance of sulfa-pyrimethamine combination is due to its efficacy against CQ-resistant *P. falciparum*. Compliance is good due to single dose therapy and few acute side effects. Resistance to S/P among *P. falciparum* was first noted in 1980, and has spread globally now.

It is high in South East Asia, South America and Southern Africa, so much that it is no longer employed in these countries. In India, S/P resistance appears to be sporadic, except in the North east, particularly in areas bordering Myanmar from where 35–44% S/P failures were recorded. As such, NVBDCP does not use artesunate-S/P ACT in North-east India. To contain further spread of S/P resistance in India, the National drug policy mandates compulsory use of artesunate along with S/P for treatment of falciparum malaria.

S/P is the first choice treatment for toxoplasmosis, which mainly occurs in immunocompromised patients.

Primaquine

Unlike other antimalarial drugs, primaquine is a poor erythrocytic schizontocide. It has weak action on *P. vivax*, but blood forms of *P. falciparum* are totally insensitive. On the other hand, it is more active against the preerythrocytic stage of *P. falciparum*. Primaquine differs from all other available antimalarials in having a marked effect on primary as well as secondary hepatic phases of the malarial parasite. It is highly active against gametocytes and hypnozoites.

The mechanism of action of primaquine is not precisely known, but the reactive intermediate metabolites of primaquine are beleved to generate intraparasitic toxic oxidative species which disrupt the electron transport in plasmodial mitochondria. Acquired resistance to hypnozontocidal and gametocytocidal action of primaquine has not been observed.

Pharmacokinetics Primaquine is readily absorbed after oral ingestion. It is oxidized in liver with a plasma t½ of 6–8 hrs and excreted in urine within 24 hours. It is not a cumulative drug.

Adverse effects The usual doses of primaquine produce only abdominal pain, g.i. upset, weakness or uneasiness in chest as side effect. These effects can be minimized by taking the drug with meals. CNS and cardiovascular symptoms are infrequent. Leucopenia occurs rarely with larger doses.

The most important toxic potential is dose related haemolysis, methaemoglobinaemia, tachypnoea and cyanosis. These effects are due to the oxidant property of primaquine. Its metabolites are more potent in this regard. However, in normal individuals doses < 60 mg (base) produce little haemolysis. Those with G-6-PD deficiency are highly susceptible, and haemolytic anaemia can occur with 15–30 mg/day. There are several variants of G-6-PD deficiency, and the defect is graded. Massive haemolysis is associated only with the 'Mediterranean' and few other variants. The incidence of G-6-PD deficiency is low among Indians, except in some tribal people of Jharkhand, Andhra Pradesh, Madhya Pradesh and Assam. Incidence is high among black races and Mediterranean people. Spot tests are available for detecting G-6-PD deficiency. Passage of dark urine is an indication of haemolysis, and primaquine should be promptly stopped if it occurs. The risk of haemolysis and leucopenia is increased in patients of rheumatoid arthritis, SLE and in those acutely ill.

Primaquine should not be given during pregnancy, because the foetus is G-6-PD deficient.

Use

Vivax malaria: The primary indication of primaquine is for radical cure of relapsing (vivax, ovale) malaria. A dose of 15 mg/day (children 0.25 mg/kg/day) for 2 weeks is given along with full curative dose of CQ or another blood schizontocide to simultaneously eliminate both exoerythrocytic as well as erythrocytic phases of the parasite. The G-6-PD status of the patient should be tested before giving 14 day primaquine course. Primaquine should be taken with food to reduce g.i. side effects.

Falciparum malaria: A single 45 mg dose of primaquine is given with the curative dose of ACT or CQ to kill the gametes and cut down transmission to mosquito. However, the recent (2015) WHO guideline has advised a lower 15 mg (0.25 mg/kg) single dose for this purpose.

MALIRID, EVAQUIN, LEOPRIME (as phosphate 26 mg = 15 mg base) 2.5, 7.5, 15, 45 mg tab.

Primaquine 15 mg/day given with clindamycin 600 mg TDS is an alternative drug for *Pneumocystis jiroveci* pneumonia in AIDS patients.

Tafenoquine

This new 8-aminoquinoline is being developed as a single dose antirelapse drug for vivax malaria. The need for 14 daily doses of primaquine for effective relapse prevention is the biggest hurdle in implementing antirelapse therapy. Tafenoquine has a long plasma t½ of 14–19 days (t½ of primaquine is 6–8 hours). Thus, it continues to act for weeks after a single dose. In phase 3 clinical trials 800 mg over 1-3 days (along with CQ) has achieved upto 100% relapse prevention.

Tafenoquine is highly active against vivax hypnozoites. It has also shown some activity against asexual erythrocytic stages of *P.v.* and *P.f.* (including CQ-resistant strains), but clearance of fever and parasitaemia were slow. Therefore, it must be accompanied by CQ or another rapidly acting erythrocytic schizontocide for vivax malaria. Tafenoquine shares with primaquine the potential to cause haemolysis in G-6-PD deficient individuals and the g.i. side effects. Incidents of anaemia, haemolysis and methaemoglobinemia are reported, but overall tolerability appears to be good.

Tafenoquine has undergone phase-3 dose titration trial in India and some other countries (along with the standard 3 day CQ) for relapse prevention in vivax malaria, and a new drug application for approval has been submitted to US-FDA in Nov. 2017. It is likely to emerge as a single dose radical curative.

Doxycycline

This antibiotic has slowly acting and weak erythrocytic schizontocidal action against all plasmodial species including *P. falciparum* resistant to CQ, MQ and S/P. The progeny schizonts of doxycycline exposed plasmodia die slowly. However, no clinically useful action is exerted on the preerythrocytic stage. Gametocytes and vivax hypnozoites are also not killed. Doxycycline is never used alone to treat malaria, but only in combination with quinine for the treatment of CQ-resistant malaria (falciparum or vivax) as described on p. 877.

Doxycycline 200 mg/day has also been combined with artesunate to treat mefloquine/chloroquine/S/P-resistant falciparum malaria in Thailand.

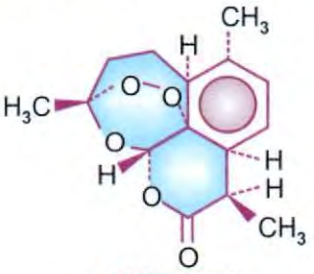
Doxycycline 100 mg/day is used as a 2nd line prophylactic for short-term travellers to CQ-resistant *P. falciparum* areas. It is not to be given to children and pregnant women.

Clindamycin (*see* p. 806)

This is another bacteriostatic antibiotic that has slow acting erythrocytic schizontocidal property against all species of plasmodia including multidrug resistant strains of *P. falciparum*. Liver stages and gametocytes are not affected. It markedly potentiates the antimalarial activity of quinine and artemisinin, and is always used in combination with one of these. Clindamycin is a second choice drug to doxycycline for adding to quinine or to artesunate for the treatment of multidrug resistant falciparum malaria, or CQ-resistant vivax malaria. In contrast to doxycycline, it can be used in children and pregnant women. However, clindamycin is not used for prophylaxis of malaria, because of thrice daily dosing and risk of adverse effects.

ARTEMISININ DERIVATIVES

Artemisinin is the active principle of the plant *Artemisia annua* used in Chinese traditional medicine as 'Quinghaosu'. It is a sesquiterpene lactone endoperoxide active against *P. falciparum* resistant to all other antimalarial drugs as well as sensitive strains and other malarial species. Potent and rapid blood schizontocide action is exerted eliciting quicker defervescence and parasitaemia clearance (in 24–48 hr) than CQ or any other drug. In the erythrocytic schizogony cycle, artemisinins exert action on a wide range of stages—from ring forms to early schizonts; thus have the broadest time window of antimalarial action.



ARTEMISININ

Artemisinin is poorly soluble in water as well as in oil. Several derivatives have been produced for clinical use. *Artemether* is soluble in oil, while *Artesunate* (sod.) is water soluble. Both can be given orally as well as i.m., but artesunate sod. can also be given i.v. Their active metabolite generated in the body *Dihydroartemisinin* (DHA) is also used orally. An injectable compound *Arteether* (i.m. in oil) was produced in India in the 1990s, and lately a totally synthetic oral compound *Arterolane* has been developed here. All these drugs are collectively referred to as '*Artemisinins*'.

In addition to their potent schizontocidal action, these drugs are lethal to early stage malarial gametes but not mature ones. By decreasing the population of gametes, they reduce but do not totally interrupt disease transmission. Artemisinins do not kill primary liver forms or vivax hypnozoites.

The duration of action is short and recrudescence rate is high when artemisinins are used alone in short courses. Recrudescence depends upon the dose and duration of therapy as well as on severity of disease. Resistance among *P.f.* to artemisinins is not a clinical problem yet, but in some areas (Cambodia, Thailand, Myanmar) delayed parasitaemia clearance has been noted which is indicative of decreased responsiveness. This reemphasizes the need to use artemisinins only in combination (as ACT) with a long acting drug which acts by a different mechanism. No cross resistance with any other class of antimalarial drugs occurs.

Because artemisinins are short acting drugs, monotherapy needs to be extended beyond the disappearance of the parasites to prevent recrudescence. After 5 days treatment recrudescence rate is ~10%, while with a 3 day course it is ~50%. Recrudescence can be totally prevented by combining 3 day artemisinin with a long-acting drug (*see* ACT later).

Mechanism of action of artemisinin is not definitely known. The endoperoxide bridge in its molecule appears to interact with haeme in the parasite. Ferrous iron-mediated cleavage of the bridge releases a highly reactive free-radical species that binds to membrane proteins, causes lipid peroxidation, damages endoplasmic reticulum, and ultimately results in lysis of the parasite. Another line of evidence has shown that the artemisinin free-radicals specifically inactivate a plasmodial sarcoplasmic-endoplasmic calcium ATPase labelled 'Pf ATP6'.

Artesunate The sodium salt of artesunate is water-soluble and is administered by oral, i.m. or i.v. routes. After oral ingestion, absorption is incomplete but fast, reaching peak in <60 min. It is rapidly converted to the active metabolite dihydroartemisinin (DHA) with a t½ of 30–60 min. The t½ of DHA is 1–2 hours. After repeated dosing, artesunate causes autoinduction of its own metabolism by CYP2B6 and CYP3A4. Intravenous artesunate is the 1st choice drug for severe malaria. Orally, it is used as ACT with 3 different partner drugs for uncomplicated falciparum malaria.

FALCIGO, FALCYNATE, ARTINATE 50 mg tab, 60 mg/vial inj; LARINATE, ARNATE 50 mg tab.

Artemether It is lipid-soluble and is administered orally or i.m., but not i.v. Absorption after oral as well as i.m. dosing is slower and rather unpredictable taking 2–6 hours. It undergoes substantial first pass metabolism and is converted to DHA. Extensive metabolism by CYP3A4 yields a t½ of 5–8 hours. For severe malaria, it is a 2nd choice option when i.v. artesunate is not available or cannot be used. Oral artemether is used in combination with lumefantrine (*see* p. 889–90).

PALUTHER, LARITHER, 80 mg inj (in 1 ml arachis oil), MALITHER 40 mg cap, 80 mg/ml inj.

α/β Arteether This compound developed in India is available for i.m. administration only to adults for complicated malaria. Because of its longer elimination t½ (23 hours), it is recommended in a 3 day schedule, but is considered less dependable in severe/complicated malaria. The WHO recommends a 5 day course (*see* box p. 878).

Dose: 150 mg i.m. daily for 3 days in adults.

E-MAL, FALCY, RAPITHER-AB; LEOTHER 150 mg/2 ml amp (box of 3 amp).

Dihydroartemisinin (DHA) and Arterolane These are available for oral use only in combination, and are considered with ACT (*see* p. 891).

Adverse effects Data from >10000 monitored patients shows that artesunate and artemether produce few adverse effects; most are mild: nausea, vomiting, abdominal pain, itching, drug fever, delayed haemolysis and other hypersensitivity reactions. Headache, tinnitus, dizziness, bleeding, dark urine, transient reticulopenia and leucopenia are rare and subside when the patient improves or the drug is stopped. Millions of patients have been treated so far without any serious neurological or other toxicity, but close monitoring of the patient is advocated. Intravenous artesunate is much safer than i.v. quinine.

Interactions Concurrent administration of artemisinins with drugs prolonging Q-T, like antiarrhythmics, tricyclic antidepressants and phenothiazines may increase the risk of cardiac conduction defects. However, no interference with any ACT partner drugs has been noted.

Use

Uncomplicated falciparum malaria Oral artemisinins are indicated for the treatment of all cases of uncomplicated falciparum malaria (CQ-resistant as well as sensitive) as ACT. Even when used alone, they are almost 100% effective, but because of short duration of action recrudescence rates are high. In order to preserve their powerful antimalarial activity and to reduce recrudescence rates, they must be used in combination with a long-acting schizontocide which acts by a different mechanism. Monotherapy with oral artemisinin derivative is prohibited in India. Fixed-dose drug combination (FDC) formulations of ACT are being encouraged, and 5 such FDCs are now available (*see* box on p. 890).

For *vivax* malaria, artemisinins (as ACT) are indicated only in case of CQ-resistant infection and when quinine + doxycycline/clindamycin also cannot be used. Use of artemisinins for prophylaxis of malaria is not allowed because wide spread prophylactic use will foster resistance. Moreover, they have a short duration of action and higher potential toxicity. Their cidal action on early stage gametes reduces transmission of resistant *P.f.* infection, but does not totally interrupt it. Single dose primaquine is recommended after ACT to kill all circulating gametes.

Severe and complicated falciparum malaria Parenteral artemisinins are highly effective and are the drugs of choice irrespective of CQ-resistance status. Quinine infused i.v. had been the drug of choice for severe and complicated malaria, including cerebral malaria, but now i.v./i.m. artemisinins are preferred, while quinine is used only as an alternative when artemisinins cannot be used. Quinine (i.v.) continues to be the drug used for severe falciparum malaria during 1st trimester of pregnancy, because safety of artemisinins is not yet proven. Artesunate (i.v.) offers several advantages:

- It causes faster parasite clearance than i.v. quinine.
- It is safer and better tolerated than i.v. quinine.
- Its dosing schedule is simpler.
- Evidence from clinical trial indicates higher efficacy and lower mortality.*

Because i.v. injection achieves more rapid peak concentration, and only artesunate sod. can be given i.v., the NVBDCP uses only i.v. artesunate for severe malaria.

Halofantrine It is a phenanthrene methanol blood schizontocide having activity comparable to mefloquine with which it exhibits cross resistance. It is effective against *P. falciparum* resistant to CQ and S/P, as well as against *P. vivax*. It is not active against gametocytes or hepatic stages of the malarial parasite.

Oral absorption of halofantrine is low and erratic, and side effects are relatively common. Prolongation of QTc interval is seen even at therapeutic doses and few cases of serious ventricular arrhythmia (some fatal) are on record.

* Artesunate versus quinine for treatment of severe falciparum malaria: a randomized trial. *Lancet*, **2005;** *366*: 717-25. (Trial conducted in India, Bangladesh, Myanmar and Indonesia).

Halofantrine is not approved in India, but in other countries it has been used for multiresistant falciparum malaria when no other effective alternative is available.

Lumefantrine (*see* below under ACT)

Pyronaridine (*see* below under ACT)

Atovaquone This synthetic naphthaquinone is a rapidly acting erythrocytic schizontocide as well as active against preerythrocytic stage of *P. falciparum* and other plasmodia. *Pneumocystis jiroveci* and *Toxoplasma gondii* are also susceptible to atovaquone. It collapses plasmodial mitochondrial membranes and interferes with ATP production. Proguanil potentiates its antimalarial action and prevents emergence of resistance. A fixed dose oral combination of the two drugs (MALARONE), UK is used for 3 day treatment of uncomplicated CQ-resistant *P. falciparum* as well as *P. vivax* malaria in USA, UK and some other countries, but not in India.Taken once daily with food, this combination is also used as a prophylactic by nonimmune travellers visiting endemic areas.

Atovaquone is also employed as a second line drug for opportunistic infections with *P. jiroveci* and *T. gondii* in AIDS patients. It produces few side effects—diarrhoea, vomiting, headache, rashes, fever, and is contraindicated during pregnancy.

ARTEMISININ-BASED COMBINATION THERAPY (ACT)

Noting that use of antimalarial drugs singly has failed to curtail the prevalence of malaria globally, particularly due to emergence of CQ-resistant, followed by multidrug-resistant *P. falciparum,* the WHO has recommended that all cases of acute uncomplicated falciparum malaria should be treated only by combining one of the artemisinin compounds with another effective erythrocytic schizontocide. In choosing the companion drug, the most important consideration is its elimination t½ (governing stay of the drug in the body), because effective concentrations in blood must be maintained for at least 3–4 asexual cycles of the parasite, i.e. 6–8 days, to exhaust the parasite burden. Therefore, short t½ drugs have to be given for 7 days, while longer acting drugs can be given for 1–3 days. However, long t½ drugs allow subinhibitory concentrations to persist in the blood facilitating selection of resistant mutants. Combining a short t½ drug with a long t½ drug in the conventional 3 day regimen runs the risk of *de facto* monotherapy after the short t½ drug is eliminated. This risk is minimized by choosing a short t½ drug that reduces the parasite load rapidly and drastically. Artemisinin compounds fulfil this requirement, as they rapidly kill > 95% plasmodia. They leave only a small biomass of the parasites to be eliminated by the long t½ drug, reducing the chances of selecting resistant mutants. Advantages of ACT over other antimalarials are:

- Rapid clinical and parasitological cure.
- High cure rates (>95%) and low recrudescence rate.
- Absence of parasite resistance (the components prevent development of resistance to each other).
- Good tolerability profile.

The ACT regimens for oral treatment of uncomplicated falciparum malaria that are already in use in India, or are WHO approved, are given in the box on p. 890. Oral ACTs are not to be used in severe or complicated malaria, for which parenteral drugs are needed.

1. Artemether-lumefantrine Lumefantrine is an orally active, high efficacy, long-acting erythrocytic schizontocide, related chemically and in mechanism of action to halofantrine and MQ. Like the other schizontocides, vivax hypnozoites are not affected. Lumefantrine is highly lipophilic; absorption starts after 2 hours of ingestion and peaks at 6–8 hours. Antimalarial action is slower than CQ. Plasma protein binding is 99%, and it is metabolized predominantly by CYP3A4. Terminal t½ is 2–3 days, which is prolonged to 4–6 days in malaria patients.

Lumefantrine is used only in combination with artemether, as FDC tablets. The two components protect each other from plasmodial resistance. As such, no clinically relevant resistance has developed so far. Clinical efficacy is high achieving 95–99% cure rate. Artemether-lumefantrine is active even in multidrug resistant *P.f.* areas including MQ-resistant. It has been extensively employed in Southeast Asia and Africa and is now popular in India. The NVBDCP uses this ACT for falciparum malaria in the northeastern

ACT regimens for uncomplicated falciparum malaria*

1. *Artemether-lumefantrine (1:6)*[£, $]
   Artemether (80 mg BD) + lumefantrine (480 mg BD) × 3 days
   COARTEM, COMBITHER, LUMETHER (artemether 20 mg + lumefantrine 120 mg tab.) to be taken with fatty meal.
   Adult and child >35 kg 4 tab BD; child 25–35 kg 3 tab BD; 15–25 kg 2 tab BD; 5–15 kg 1 tab BD, all for 3 days.
   FALCIMAX PLUS, ARTE PLUS (artemether 80 mg + lumefantrine 480 mg tab) 1 tab BD × 3 days for adults.
2. *Artesunate-mefloquine (AS/MQ)*[£, $]
   Artesunate 100 mg BD (4 mg/kg/day) × 3 days + mefloquine 750 mg (15 mg/kg) on 2nd day and 500 mg (10 mg/kg) on 3rd day (total 25 mg/kg).
   MEFLIAM PLUS: Artesunate 100 mg + mefloquine 200 mg pack of 6 FDC tabs; LARINATE-MF Kit: Artesunate 200 mg (3 tabs) + mefloquine 250 mg (6 tabs) kit; FALCIGO PLUS kit (Artesunate 50 mg tab + Mefloquine 250 mg tab kit)
3. *Artesunate-amodiaquine (AS/AQ)*[$]
   Artesunate 200 mg (4 mg/kg) + amodiaquine 600 mg (10 mg/kg) per day × 3 days
   Artesunate 25 mg/50 mg/100 mg +Amodiaquine 67.5 mg/135 mg/270 mg fixed dose combination tablets; ASAQ, FALCINIL-Aq: 25 + 67.5 mg, 50 + 135 mg, 100 + 270 mg FDC tabs.
4. *Artesunate-sulfadoxine + pyrimethamine (AS-S/P)*[£, $]
   Artesunate 100 mg BD (4 mg/kg/day) × 3 days + sulfadoxine 1500 mg (25 mg/kg) and pyrimethamine 75 mg (1.25 mg/kg) single dose.
   ZESUNATE kit, MASUNATE kit, FALCIART kit (Artesunate 100 mg × 6 tab + sulfadoxine 500 mg/pyrimethamine 25 mg × 3 tab kit)
5. *Dihydroartemisinin-piperaquine (DHA/PPQ 1:8)*[£, $]
   DHA 120 mg (2 mg/kg) + piperaquine 960 mg (16 mg/kg) daily × 3 days; for children < 25 kg body weight, DHA not less than 2.5 mg/kg + piperaquine 20 mg/kg daily × 3 days.
   PALUDOSE PLUS: Dihydroartemisinin 40 mg + piperaquine 320 mg tab.; DYSURE: DHA 80 mg + piperaquine 640 mg per 5 ml suspension.
6. *Arterolane-piperaquine*
   Arterolane (as maleate) 150 mg + piperaquine 750 mg daily × 3 days (approved only for adults).
   SYNRIAM (arterolane 150 mg + piperaquine 750 mg) cap, 1 cap OD × 3 days

* All drugs are administered orally
[£]WHO approved ACTs; [$] Approved in India

region. While artemether quickly reduces parasite biomass and resolves symptoms, lumefantrine prevents recrudescence. Gametocyte population is reduced, checking transmission.

Artemether-lumefantrine must be administered with fatty food or milk, which markedly enhances lumefantrine (and to some extent artemether) absorption, and ensures adequate blood levels. Failure to take it with fat rich food limits absorption and may result in recrudescence. This ACT is generally well tolerated; side effects are—headache, dizziness, sleep disturbances, abdominal pain, arthralgia, myalgia, pruritus and rash. Comparative studies indicate that it is better tolerated than AS/MQ. Artemether-lumefantrine should not be given with drugs metabolized by CYP2D6 (metoprolol, neuroleptics, tricyclic antidepressants, etc.), because lumefantrine inhibits the isoenzyme CYP2D6. Lumefantrine causes minimal prolongation of QTc. Since artemether can also prolong Q-Tc to some extent, artemether-lumefantrine ACT should not be given to patients receiving Q-Tc prolonging drugs. It is to be avoided in first trimester of pregnancy and during breastfeeding.

2. Artesunate-mefloquine (AS/MQ) This was the most extensively used ACT in Thailand, Myanmar and other Southeast Asian countries as well as in South-America and Africa; and was found highly effective in uncomplicated falciparum malaria. However, many areas in far-East already have MQ-resistant *P.f.*, but

by combining with AS, further spread of MQ resistance was checked. Nevertheless, some of the far-East countries have switched over to alternative ACTs. The adverse effect potential of AS/MQ is less favourable than other ACTs. Therefore, it is less popular now. In India AS/MQ has been used to a limited extent, but small studies have shown ~ 100% efficacy. A kit with separate AS and MQ tablets as well as a FDC formulation is now available (*see* box on p. 890). Side effects of MQ are more troublesome, and need to be watched for.

3. Artesunate-amodiaquine (AS/AQ) Amodiaquine (AQ; *see* p. 880) has long been used parallel to CQ. While AQ itself has a short t½ due to rapid metabolism, its metabolite, an equally potent antimalarial has long t½ of 10–18 days. Because of close structural resemblance of AQ to CQ, it was apprehended that AQ may not be an effective antimalarial in areas with CQ-resistant *P.f.* However, trials in Africa showed that AQ produced satisfactory response in such areas. Addition of artesunate further improved the cure rate. Trials were conducted in Africa with AS/AQ coformulated as FDC tablets, which produced high cure rates, and now this ACT has become the first-line therapy of uncomplicated falciparum malaria in many African countries. Recent trial in India also yielded ~ 97% cure of falciparum malaria. This ACT has now been marketed in India as FDC tablets in 3 strengths for different age groups (*see* box on p. 890), to be taken twice daily for 3 day treatment of uncomplicated falciparum malaria.

4. Artesunate-sulfadoxine + pyrimethamine (AS-S/P) This ACT has been adopted as the first line treatment for uncomplicated falciparum malaria in India, except in the north-eastern states bordering Myanmar, from where S/P resistance has been reported. This does not imply that AS-S/P is the best ACT, because it is not effective against multidrug-resistant strains which are nonresponsive to S/P. However, in rest of India so far this ACT appears to be working satisfactorily with >96% success rate. As such, NVBDCP continues to use AS-S/P ACT as the firstline therapy, including that during 2nd and 3rd trimester of pregnancy. This ACT appears to produce fewer side effects than artesunate/mefloquine. Private clinics, however, are using alternative ACTs. Some other malaria endemic countries have found AS-S/P ACT to be inferior.

5. Dihydroartemisinin (DHA)-piperaquine Piperaquine is a bisquinoline congener of CQ developed in China as a high efficacy long-acting (t½ 3–4 weeks) erythrocytic schizontocide with a slower onset of action because of larger volume of distribution. The mechanism of action is similar to CQ. It is more active against CQ-resistant *P. falciparum* and retains equal activity against CQ sensitive organisms. The efflux transporters of the resistant parasite are believed to be unable to pump out the bulky molecule of piperaquine. In 1978, piperaquine replaced CQ in China, where it has been extensively used for mass prophylaxis as well as treatment of malaria.

Piperaquine is coformulated with DHA in a dose ratio of 8:1 and extensively evaluated in multidrug resistant *P.f.* areas of Cambodia, Thailand, Vietnam, etc. with high success rate. In clinical trials, efficacy of DHA-piperaquine FDC has been found comparable to artemether-lumefantrine. Safety profile of DHA-piperaquine is good and it is well tolerated even by children. However, dizziness, vomiting and other g.i. symptoms are common; rashes are rare. The DHA-piperaquine FDC has achieved >98% response rate in clinical trials on uncomplicated falciparum malaria patients in India, and has been approved. WHO (2015) has recommended a higher per kg dose for children weighing < 25 kg.

6. Arterolane-piperaquine Arterolane is a novel orally active synthetic trioxolane congener of artemisinin that has been developed in India and marketed in combination with piperaquine. Arterolane acts rapidly at all stages of asexual schizogony of malarial parasite including

multidrug resistant *P.f.*, but has no effect on the hepatic stages. It accumulates in the food vacuole of the parasite, and thus differs from artemisinins which do not accumulate at this site. It also has moderate gametocidal activity similar to that of artemether-lumefantrine.

Both arterolane and piperaquine are well absorbed orally, and absorption is unaffected by food. Peak plasma arterolane concentration is reached in 3–5 hours and it has a large volume of distribution. The major metabolic pathway is oxidation, mainly by CYP3A4, which is also the primary isoenzyme responsible for piperaquine metabolism. Arterolane is short acting and its plasma t½ varies between 1–3 hours.

Arterolane-piperaquine FDC has undergone multicentric clinical trials in India, Bangladesh and Thailand. In uncomplicated falciparum malaria this ACT has produced ≥ 95% cure rate with a fever and parasitaemia clearance time of 24–48 hours. In a comparative trial its efficacy and tolerability was found equivalent to artemether-lumefantrine. Side effects are generally mild headache, postural dizziness, vomiting, abdominal pain and diarrhoea. Thus, arterolane-piperaquine appears to be an effective and well tolerated alternative ACT.

7. Artesunate-pyronaridine Pyronaridine is a water-soluble Mannich base resembling structurally to amodiaquine. It is an erythrocytic schizontocide with high efficacy and mechanism of action similar to CQ. It has been used in China for ~ 40 years, and is active against both CQ-sensitive and CQ-resistant *P. falciparum*. Other malarial species are also sensitive. The onset of action is slower and duration long. It is concentrated in RBCs and metabolized with a terminal t½ of 7 days. Weak analgesic-antipyretic action is produced at higher doses.

Clinical efficacy of artesunate-pyronaridine FDC (dose ratio 1:3) has been tested in falciparum malaria in China, Thailand and Africa with >95% success. Multidrug-resistant *P. falciparum* and *P. vivax* also respond. Clinical trials have been completed in India with > 95% cure rate. However, this ACT has not yet been approved for use in India.

PROBLEM DIRECTED STUDY

61.1 A 20-year-old girl reported to the district hospital OPD with irregular episodes of high fever for the past 3 days. The fever is preceded by chills and shivering and attended by headache, body ache, pain in abdomen, nausea and weakness. The fever lasts 4–6 hours and subsides after sweating. On enquiry she informed that she belongs to a village in the tribal area of Madhya Pradesh. About a month back she had returned from her home after a 3 weeks vacation and she works as a house maid in the city. Blood smear examination showed presence of intraerythrocytic *P. vivax* parasites. She was treated with the standard 1.5 g chloroquine (base) course over 3 days, and was given primaquine 15 mg tab to be taken once daily for 14 days, after she tested negative for G-6PD deficiency. She was afebrile on the 4th day, but returned back 7 days later with similar episode of chills and fever. Finger prick blood smear was positive for *P. vivax*. She confirmed continuing to take daily primaquine medication.

(a) What is the most likely cause of recurrence of fever and parasitaemia?
(b) How should the 2nd episode of fever be treated?
(c) Should primaquine medication be continued or stopped?
(see Appendix-1 for solution)

Chapter 62 Antiamoebic and Other Antiprotozoal Drugs

ANTIAMOEB IC DRUGS

These are drugs useful in infection caused by the anaerobic protozoa *Entamoeba histolytica.*

Amoebiasis has a worldwide distribution (over 50 million people suffer invasive disease, but many more harbour it). It is endemic in most parts of India (about 15% people are infected) and other developing countries. Poor environmental sanitation and low socio-economic status are important factors in the spread of the disease, which occurs by faecal contamination of food and water. Amoebic cysts reaching the intestine transform into trophozoites which either live on the surface of colonic mucosa as commensals—form cysts that pass into the stools (luminal cycle) and serve to propagate the disease, or invade the mucosa—form amoebic ulcers (Fig. 62.1) and cause acute dysentery (with blood and mucus in stools) or chronic intestinal amoebiasis (with vague abdominal symptoms, amoeboma).

Occasionally the trophozoites pass into the bloodstream, reach the liver *via* portal vein and cause amoebic liver abscess. Other organs like lung, spleen, kidney and brain are rarely

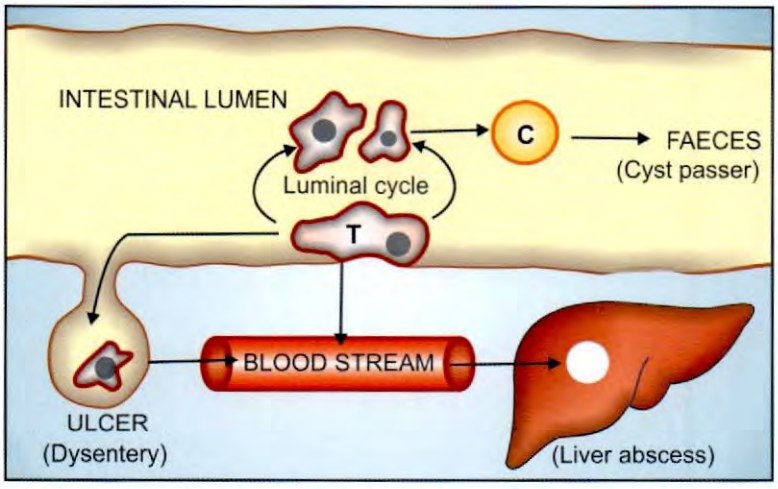
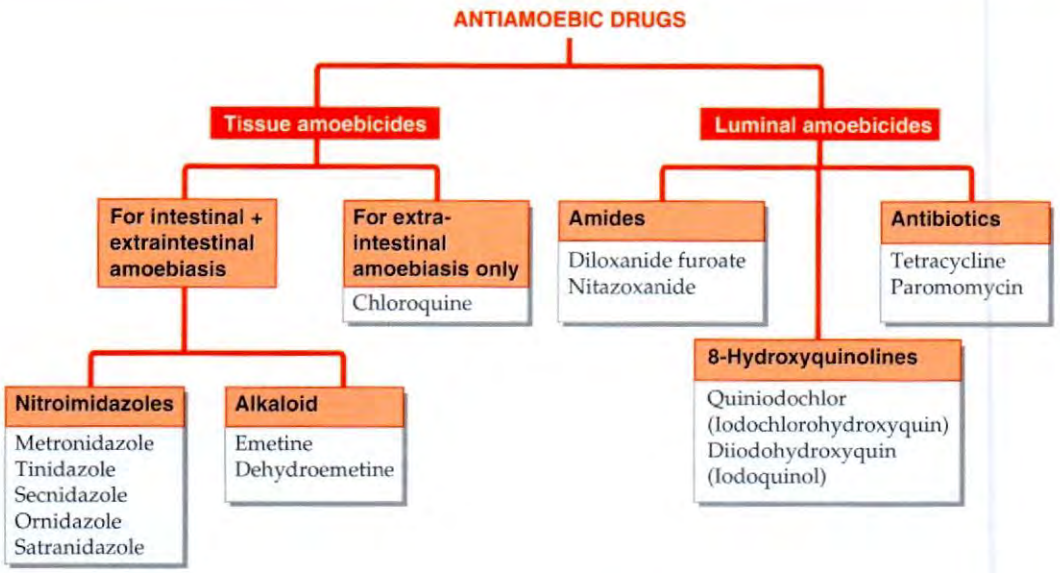


Fig. 62.1: The luminal cycle and invasive forms of amoebiasis. T—trophozoite; C—cyst



involved in extraintestinal amoebiasis. In the tissues, only trophozoites are present; cyst formation does not occur. Tissue phase is always secondary to intestinal amoebiasis, which may be asymptomatic. In fact, most chronic cyst passers are asymptomatic. In the colonic lumen, the *Entamoebae* live in symbiotic relationship with bacteria, and a reduction in colonic bacteria reduces the amoebic population.

The 'Brazil root' or *Cephaelis ipecacuanha* was used for the treatment of dysentery in the 17th century. The pure alkaloid emetine obtained from it was found to be a potent antiamoebic in 1912. Emetine remained the most efficacious and commonly used drug for amoebiasis till 1960. Many 8-*hydroxyquinolines* (quiniodochlor, etc.) became very popular drugs for diarrhoea and amoebic dysentery, but have come under a cloud since they were held responsible for causing epidemics of 'Subacute myelo-optic neuropathy' (SMON) in Japan in 1970s.

Soon after its triumph as an antimalarial in 1948, *chloroquine* was found to be an effective and safe drug for hepatic amoebiasis. Diloxanide furoate was a useful addition in 1960, covering mainly chronic intestinal forms of the disease. However, the most remarkable development was the demonstration of antiamoebic property of *metronidazole* in the early 1960s. This drug had been introduced a few years back as a well tolerated, orally effective agent for trichomonas vaginitis. Of the many congeners of metronidazole that were tested, tinidazole has emerged in the 1970s as a good alternative, and others have been added subsequently.

NITROIMIDAZOLES

Metronidazole

It is the prototype nitroimidazole introduced in 1959 for trichomoniasis and later found to be a highly active amoebicide. It has broad-spectrum cidal activity against anaerobic protozoa, including *Giardia lamblia* in addition to the above two. Many anaerobic and microaerophilic bacteria, such as *Bact. fragilis, Fusobacterium, Clostridium perfringens, Cl. difficile, Helicobacter pylori, Campylobacter,* peptococci, spirochetes and anaerobic *Streptococci* are sensitive. Metronidazole does not affect aerobic bacteria. Clinically significant resistance has not developed among *E. histolytica,* but decreased responsiveness of *T. vaginalis* has been observed in some areas. Anaerobic bacteria and *G. lamblia* also can develop metronidazole resistance, but this is a clinical problem only in the case of *H. pylori.*

Metronidazole is selectively toxic to anaerobic and microaerophilic microorganisms. After entering the cell by diffusion, its nitro group is reduced by certain redox proteins operative only in anaerobic microbes to a highly reactive nitro radical which exerts cytotoxicity. The nitro radical

of metronidazole acts as an electron sink which competes with the biological electron acceptors of the anaerobic organism for the electrons generated by the pyruvate : ferredoxin oxidoreductase (PFOR) enzyme pathway of pyruvate oxidation. The energy metabolism of anaerobes that have no mitochondria is thus, disrupted. Aerobic environment attenuates cytotoxicity of metronidazole by inhibiting its reductive activation. Moreover, O_2 competes with the nitro radical of metronidazole for the free electrons generated during energy metabolism of anaerobes. Anaerobes which develop metronidazole resistance become deficient in the mechanism that generates the reactive nitro radical from it or have lower levels of PFOR.

Metronidazole, in addition, has been found to inhibit cell mediated immunity, to induce mutagenesis and to cause radiosensitization.

Pharmacokinetics Metronidazole is almost completely absorbed from the small intestines; little unabsorbed drug reaches the colon. It is widely distributed in the body, attaining therapeutic concentration in vaginal secretion, semen, saliva and CSF. Metabolism occurs in liver primarily by oxidation and glucuronide conjugation followed by renal excretion. Plasma t½ is 8 hrs.

Adverse effects Side effects of metronidazole are relatively frequent and unpleasant, but mostly nonserious.

- Anorexia, nausea, metallic taste and abdominal cramps are the most common. Looseness of stool is occasional.
- Less frequent side effects are—headache, glossitis, dryness of mouth and impairment of concentration.
- Urticaria, flushing, heat, itching, rashes and fixed drug eruption occur in allergic subjects, warrant discontinuation of the drug and preclude future use of nitroimidazoles.
- Prolonged administration may cause peripheral neuropathy and CNS effects. Seizures have followed very high doses. Leucopenia is likely with repeated courses.
- Thrombophlebitis of the injected vein occurs if the solution is not well diluted.

Contraindications Metronidazole is contraindicated in neurological disease, blood dyscrasias, first trimester of pregnancy (though no teratogenic effect has yet been demonstrated, its mutagenic potential warrants caution). Cautious use in chronic alcoholics.

Interactions A disulfiram-like intolerance to alcohol occurs in some patients taking metronidazole.

Alcohol-metronidazole interaction occurs only in some individuals, while majority of those taking it can consume alcohol without any reaction.

Enzyme inducers (phenobarbitone, rifampin) may reduce its therapeutic effect. Cimetidine can reduce metronidazole metabolism: its dose may need to be decreased.

Metronidazole enhances warfarin action by inhibiting its metabolism. It can decrease renal elimination of lithium and precipitate toxicity. FLAGYL, METROGYL, METRON, ARISTOGYL 200, 400 mg tab, 200 mg/5 ml susp. (as benzoyl metronidazole: tasteless); 500 mg/100 ml i.v. infusion; UNIMEZOL 200, 400 mg tabs, 200 mg/5 ml susp. METROGYL GEL, LUPIGYL GEL: 1% gel for vaginal/topical use.

Uses

1. *Amoebiasis*: Metronidazole is a first line drug for all forms of amoebic infection. Many dosage regimens have been tried; the current recommendations are:

For invasive dysentery and liver abscess—800 mg TDS (children 30–50 mg/kg/day) for 7–10 days. In severe cases of amoebic dysentery or liver abscess 500 mg (children 10–15 mg/kg) may be infused i.v. slowly every 6–8 hours for 7–10 days or till oral therapy can be instituted.

For mild intestinal disease—400 mg TDS for 5–7 days. Metronidazole is less effective than many luminal amoebicides in eradicating amoebic cysts from the colon, because it is nearly completely absorbed from the upper bowel.

2. *Giardiasis* It is highly effective in a dose of 400 mg TDS for 7 days. A shorter course of 3 days with 2 g/day is equally effective.

3. *Trichomonas vaginitis* It is the drug of choice; 2.0 g single dose is preferred.

Alternatively 400 mg BD–TDS may be used for 7 days. Additional intravaginal treatment is needed only in refractory cases. Repeated courses may be necessary in some patients, but should be given with gaps of 4–6 weeks. The male partner should be treated concurrently in cases of recurrent infections.

Nonspecific bacterial vaginosis also responds.

4. ***Anaerobic bacterial infections*** Anaerobic bacterial infections occur mostly after colorectal or pelvic surgery, appendicectomy, etc. Brain abscesses and endocarditis may be caused by anaerobic organisms.

Metronidazole is an effective drug for these and is generally used in combination with gentamicin or cephalosporins (because many are mixed infections). For serious cases i.v. administration is recommended: 15 mg/kg infused over 1 hr followed by 7.5 mg/kg every 6 hrs till oral therapy can be instituted with 400–800 mg TDS. *Prophylactic use* in high risk situations (colorectal/biliary surgery) is recommended.

Other drugs effective in anaerobic infections are clindamycin and chloramphenicol.

5. ***Pseudomembranous enterocolitis*** caused by *Cl. difficile* is generally associated with use of antibiotics. Oral metronidazole 400–800 mg BD–TDS for 10–14 days is more effective, more convenient, less toxic, and therefore preferred over vancomycin which may be used in nonresponsive cases, or when the infection recurs.

6. ***Acute necrotizing ulcerative gingivitis (ANUG)*** Metronidazole/tinidazole are the drugs of choice for ANUG (also called 'trench mouth') which is caused by mixed flora of anaerobes like fusobacteria, spirochetes and bacteroides. Metronidazole 200–400 mg TDS (15–30 mg/kg/day) is often combined with amoxicillin, tetracycline or erythromycin. The response is rapid with disappearance of the spirochete-fusobacterium complex from the lesions and resolution of pain, bleeding, ulceration and bad breath within 2–3 days; but treatment must be continued for at least 5 days.

7. ***Helicobacter pylori gastritis/peptic ulcer*** (*see* p. 705–06) Metronidazole 400 mg TDS or tinidazole 500 mg BD are combined with amoxicillin/clarithromycin and a proton pump inhibitor in triple drug regimens to eradicate *H. pylori*.

Tinidazole It is an equally efficacious congener of metronidazole, similar to it in every way except:

- Metabolism is slower; t½ is ~12 hr; duration of action is longer; dosage schedules are simpler. Thus, it is more suited for single dose or once daily therapy.
- Some comparative trials in amoebiasis have reported higher cure rates.
- Generally better tolerated; the incidence of side effects is lower: metallic taste (2%), nausea (1%), rash (0.2%).

TINIBA 300, 500, 1000 mg tabs; 800 mg/400 ml i.v. infusion; TRIDAZOLE 300, 500 mg tab; FASIGYN 0.5 g and 1 g tab., TINI 0.3 g, 0.5 g, 1.0 g tabs, 75 mg/5 ml and 150 mg/5 ml oral susp.

Recommended schedules are—

Intestinal amoebiasis: 2 g OD oral for 3–6 days (children 30–50 mg/kg/day), or 0.6 g BD for 5–10 days.

Amoebic liver abscess: The 2 g oral daily dose may be continued for 3–6 days. In case oral therapy is not possible, tinidazole 800 mg in 400 ml may be infused i.v. over 40–60 min daily until oral treatment can be instituted.

Trichomoniasis and giardiasis: 2 g single oral dose or 0.6 g OD for 7 days.

Anaerobic bacterial infections:

prophylactic—2 g single oral dose before colorectal/biliary surgery;

therapeutic—2 g followed by 0.5 g BD oral for 5 days. In severe cases, i.v. tinidazole may be used as described above.

H. pylori: 500 mg BD oral for 1–2 weeks in triple combination.

Secnidazole A congener of metronidazole with the same spectrum of activity and

potency. Absorption after oral administration is rapid and complete, but metabolism is slower resulting in a plasma t½ of 17–29 hours. After 48 hr of a single 2 g dose, plasma secnidazole concentration may still remain within the range of MIC values against sensitive organisms. In intestinal amoebiasis a single 2 g dose has been found to yield high cure rates. Side effect profile is similar to metronidazole and reported incidence is 2–10%.

Dose: 2 g single dose (children 30 mg/kg) for mild intestinal amoebiasis, giardiasis, trichomonas vaginitis and nonspecific bacterial vaginosis. For acute amoebic dysentery 0.5 g TDS for 5 days is recommended.

SECNIL, SECZOL 0.5, 1.0 g tabs; NOAMEBA-DS 1.0 g tab.

Ornidazole It has activity similar to metronidazole, but it is slowly metabolized—has longer t½ (12–14 hr). Dose and duration of regimens for amoebiasis, giardiasis, trichomoniasis, anaerobic infections and bacterial vaginosis resemble those for tinidazole. In chronic intestinal amoebiasis and asymptomatic cyst passers 0.5 twice daily for 5 to 7 days has also been used. Side effect profile is similar to tinidazole.

DAZOLIC 500 mg tab, 500 mg/100 ml vial for i.v. infusion.
ORNIDA 500 mg tab, 125 mg/5 ml susp.

Satranidazole Another nitroimidazole having longer t½ (14 hr). Advantages claimed are: better tolerability—minimal nausea, vomiting or metallic taste, absence of neurological and disulfiram-like reactions and that it does not produce the acetamide metabolite which is a weak carcinogen.

Dose: Amoebiasis 300 mg BD for 3–5 days, giardiasis and trichomoniasis 600 mg single dose.

SATROGYL 300 mg tab.

Emetine

It is an alkaloid from *Cephaelis ipecacuanha*. Emetine is a potent and directly acting amoebicide—kills trophozoites but has no effect on cysts. It acts by inhibiting protein synthesis in amoebae by arresting intraribosomal translocation of tRNA-amino acid complex.

In acute dysentery the stool is rapidly cleared of the trophozoites and symptomatic relief occurs in 1–3 days (even faster than metronidazole), but it is not curative in the sense that the patient continues to pass cysts in the stool. It is highly efficacious in amoebic liver abscess also.

Emetine cannot be given orally because it will be vomited out. It is administered by s.c. or i.m. injection: 60 mg OD. It is a local irrirant and has high systemic toxicity, *viz*, nausea, vomiting (due to CTZ stimulation and gastric irritation), abdominal cramps, diarrhoea, weakness, stiffness of muscles, myositis, hypotension, ECG changes and myocarditis.

Use Emetine is now rarely used for acute amoebic dysentery or for amoebic liver abscess, only in patients not tolerating metronidazole. A luminal amoebicide must always follow emetine to eradicate the cyst forming trophozoites.

It is also effective in liver fluke infestation.

EMETINE HCl: 60 mg /2 ml inj; for not more than 10 days to avoid cumulative toxicity.

Dehydroemetine It is equally effective bu less cumulative and less toxic to the heart Thus, it is usually preferred over emetine.

Dose: 60–100 mg s.c./i.m.OD for not more than 10 days.

DEHYDROEMETINE HCl: 30 mg/ml inj, 1 and 2 ml amps.

Chloroquine The pharmacology of chloroquine is described in Ch. 61. It kills trophozoites of *E. histolytica* and is highly concentrated in liver. Therefore, it is used in hepatic amoebiasis only. Because it is completely absorbed from the upper intestine and not so highly concentrated in the intestinal wall—it is neither effective in invasive dysentery nor in controlling the luminal cycle (cyst passers).

Efficacy of chloroquine in amoebic liver abscess approaches that of emetine, but duration of treatment is longer and relapses are relatively more frequent, but amoebae do not develop resistance to chloroquine. A luminal amoebicide must always be given with or after chloroquine to abolish the luminal cycle.

Dose for amoebic liver abscess: 600 mg (base) for two days followed by 300 mg daily for 2–3 weeks. Though chloroquine is relatively safe, side effects are frequent. The 2–3 week course is poorly tolerated. In amoebic liver abscess, chloroquine is generally employed following a course of emetine or as an alternative to it. In case of bigger abscess, it may also be used after a course of metronidazole.

Diloxanide furoate

It is a highly effective luminal amoebicide which directly kills trophozoites responsible for production of cysts. The furoate ester is hydrolysed in intestine and the released diloxanide is largely absorbed. Diloxanide as such is a weaker amoebicide than its furoate ester. No systemic antiamoebic activity is evident despite its absorption. It is primarily metabolized by glucuronidation and is excreted in urine.

Diloxanide furoate exerts no antibacterial action. It is less effective in invasive amoebic dysentery, because of poor tissue amoebicidal action. However, a single course produces

high (80–90%) cure rate in mild intestinal amoebiasis and in asymptomatic cyst passers.
Dose: 500 mg TDS for 5–10 days; children 20 mg/kg/day.
FURAMIDE, AMICLINE 0.5 g tab; in TINIBA-DF diloxanide furoate 250 mg + 150 mg tinidazole and TINIBA-DF FORTE 500 mg + 300 mg tabs; in ENTAMIZOLE 250 mg + 200 mg metronidazole and ENTAMIZOLE FORTE 500 mg + 400 mg tabs.

Diloxanide furoate is very well tolerated; the only side effects are flatulence, occasional nausea, itching and rarely urticaria. It is a preferred drug for mild intestinal and asymptomatic amoebiasis, and is given after or along with any tissue amoebicide to eradicate cysts. Combined use with metronidazole or tinidazole is quite popular. Some chronic cases require repeat courses for eradication.

Nitazoxanide This salicylamide congener of the anthelmintic niclosamide, introduced for the treatment of giardiasis and cryptosporidiosis is also active against many other protozoa including *E. histolytica, T. vaginalis,* and helminths—*Ascaris, H. nana,* etc. It is a prodrug which on absorption is converted to the active form *tizoxanide,* an inhibitor of PFOR enzyme that is an essential pathway of electron transport energy metabolism in anaerobic organisms. Activity against metronidazole-resistant *Giardia* has also been demonstrated. Tizoxanide generated from nitazoxanide is glucuronide conjugated and excreted in urine as well as bile.

Nitazoxanide is the most effective drug for *Cryptosporidium parvum* infection (upto 88% cure), which causes diarrhoea, especially in children and in AIDS patients. It is also indicated in giardiasis, and may be used as an alternative luminal amoebicide in amoebic dysentery. Abdominal pain, vomiting and headache are mild and infrequent side effects.
Dose: 500 mg (children 7.5 mg/kg) BD × 3 days
NITACURE, NITCOL, NITARID 200 mg, 500 mg tabs, 100 mg/5 ml dry syrup.

8-HYDROXYQUINOLINES

Several 8-hydroxyquinolines including *Quiniodochlor* and *Iodoquinol* were widely employed in the past. They are active against *Entamoeba, Giardia, Trichomonas,* some fungi (dermatophytes, *Candida*) and some bacteria. They kill the cyst forming amoebic trophozoites in the intestine, but do not have tissue amoebicidal action. Like diloxanide furoate, they are not very effective in acute amoebic dysentery but afford relief in chronic intestinal amoebiasis. Their efficacy to eradicate cysts from asymptomatic carriers is rated lower than that of diloxanide furoate. They are totally valueless in extraintestinal amoebiasis.

Absorption of 8-hydroxyquinolines from the intestine is variable. The absorbed fraction is conjugated in liver with glucuronic acid and sulfate and excreted in urine; t½ is ~12 hours. Therapeutic concentrations are not attained in the intestinal wall or in liver. The unabsorbed part reaches lower bowel and acts on luminal cycle of amoebae.

Being inexpensive, these drugs were widely and injudiciously used for the prophylaxis and treatment of nonspecific diarrhoeas, traveller's diarrhoea, dietary indiscretion, etc., but are infrequently prescribed now, except in some poor localities.

8-Hydroxyquinolines produce few side effects—nausea, transient loose and green stools, pruritus, etc. but carry toxic potential if improperly used.

Iodism (furunculosis, inflammation of mucous membranes) and goiter may develop on prolonged intake. Individuals sensitive to iodine may experience acute reaction with chills, fever, angioedema and cutaneous haemorrhages.

Prolonged/repeated use of relatively high doses of quiniodochlor caused a neuropathic syndrome called 'subacute myelo-optic neuropathy' (SMON) in Japan in an epidemic form, affecting several thousand people in 1970. Other 8-hydroxyquinolines have also produced neuropathy and visual impairment. However, despite widespread use in the past, only sporadic and unconfirmed cases have been reported from India. The 8-hydroxyquinolines have been banned in Japan and few other countries, but in India they are prohibited only for pediatric patients, because their use for chronic diarrhoeas in children has caused blindness.

8-Hydroxyquinolines are cheap and have good patient acceptability. They may be employed in intestinal amoebiasis as alternative to diloxanide furoate.

Other uses are—giardiasis; local treatment of monilial and trichomonas vaginitis, fungal and bacterial skin infections.

Quniodochlor (Iodochlorohydroxyquin, Clioquinol): 250–500 mg TDS; (not to exceed 1.5 g/day for 14 days).

ENTEROQUINOL, QUINOFORM, DEQUINOL 250 mg tab.

Diiodohydroxyquin (Iodoquinol): 650 mg TDS; (not to exceed 2.0 g/day for 14 days).

DIODOQUIN 650 mg tab, 210 mg/5 ml susp.

Tetracyclines

Tetracyclines have modest direct inhibitory action on *Entamoeba*. The older tetracyclines are incompletely absorbed in the small intestine, reach the colon in large amounts and inhibit the bacterial flora with which *Entamoebae* live symbiotically. Thus, they indirectly reduce proliferation of entamoebae in the colon and are especially valuable in chronic cases who have only the luminal cycle with little mucosal invasion. Tetracyclines have an adjuvant role in conjunction with a more efficacious luminal amoebicide. They may be added as the third drug along with a nitroimidazole + a luminal amoebicide.

Paromomycin

It is an aminoglycoside antibiotic which closely resembles neomycin and is described in Ch. 54. Distinctively, paromomycin is active against many protozoa like *Emtamoeba, Giardia, Cryptosporidium, Trichomonas, Leishmania* and some tape worms, in addition to having antibacterial spectrum like neomycin. In the 1960s an oral formulation of paromomycin was introduced as a luminal amoebicide and was briefly marketed in India as well. However, it was soon overshadowed by metronidazole, became commercially unviable and was discontinued. It has gained popularity again and is being frequently used in USA and some other countries. In India and Africa, parenteral (i.m.) paromomycin is being used in resistant Kalaazar (*see* p. 904).

Orally administered paromomycin acts only in the gut lumen. It is neither absorbed nor degraded in the intestines, and is eliminated unchanged in the faeces. Thus, it is largely free from systemic toxicity. Its effect on gut flora resembles that of neomycin.

Paromomycin is an efficacious luminal amoebicide, achieving similar or even better clearing of cysts from stools compared to diloxanide furoate in asymptomatic cyst passers. Good symptomatic relief and cyst clearance is obtained in chronic amoebic colitis. Paromomycin is an alternative drug for giardiasis, especially during 1st trimester of pregnancy when metronidazole and other drugs are contraindicated.

Dose: Oral: 500 mg (children 10 mg/kg) TDS, for 7 days for amoebiasis/giardiasis/cryptosporidiosis.

Side effects are limited to the g.i.t.; nausea, vomiting, abdominal cramps, diarrhoea; rarely rashes, renal impairment on prolonged use.

NOTES ON THE TREATMENT OF AMOEBIASIS

1. Acute amoebic dysentery Most cases of amoebic dysentery respond to a single adequate course of treatment. Metronidazole/tinidazole are the drugs of choice; afford quick symptomatic relief and kill the trophozoites in 5–10 days. Secnidazole, ornidazole, are the alternatives. Adjuvant measures for diarrhoea and abdominal pain may be needed. Dehydroemetine is rarely used in the most severe cases or when metronidazole produces severe allergic reaction or neurotoxicity. Dehydroemetine should be discontinued as soon as acute symptoms are controlled (2–3 days) and metronidazole started, except in case of metronidazole intolerance.

The above treatment should be followed by a course of luminal amoebicide to ensure eradication of *E. histolytica* from the colon and to prevent carrier (cyst passing) state. A tetracycline, added as the third drug, may have adjuvant value.

2. Mild intestinal amoebiasis/asymptomatic cyst passers Nitroimidazoles afford rapid symptomatic relief in mildly symptomatic intestinal amoebiasis and are the first line drugs. However, they mostly fail to clear cysts. Therefore, the standard practice is to give diloxanide furoate or another luminal amoebicide, either concurrently or immediately after. Luminal amoebicides alone are generally slower in action, but avoid side effects of metronidazole. Asymptomatic cyst passers are mostly treated wtih only luminal amoebicide. Chronic cases may require 2–3 repeated courses in which drugs may be alternated. A tetracycline may be given concurrently with the luminal amoebicide in cases which fail to clear completely.

Treatment of different forms of amoebic infection

Drugs of Choice	Alternative Drugs
Acute Amoebic Dysentery	
• Metronidazole 800 mg oral TDS × 7–10 days (in severe cases 500 mg slow i.v. 6 hourly till oral therapy can be instituted) or • Tinidazole 2.0 g oral daily × 3–6 days + *Luminal amoebicide* • Diloxanide furoate 500 mg TDS × 5–10 days	• Ornidazole 2.0 g oral daily × 3 days or • Secnidazole 0.5 g oral TDS × 5 days *Alternative luminal amoebicides* • Quiniodochlor 250–500 mg oral TDS × 7–14 days or • Iodoquinol 650 mg oral TDS × 7–14 days or • Paromomycin 500 mg oral TDS × 7–10 days ± • Tetracycline 250 mg TDS × 7–10 days (adjuvant)
Mild intestinal amoebiasis/Asymptomatic cyst passers*	
• Metronidazole 400 mg oral TDS × 5–7 days or • Tinidazole 2.0 g oral OD × 2–3 days + *Luminal amoebicide* (as above)	• Ornidazole 0.5 g oral BD × 5–7 days or • Secnidazole 2.0 g oral single dose *Alternative luminal amoebicides* (as above) ± • Tetracycline 250 mg TDS × 7–10 days (adjuvant)
Amoebic liver abscess	
• Metronidazole 800 mg oral TDS × 10 days (in serious cases 500 mg slow i.v. infusion 6 hourly × 10 days) or • Tinidazole 2.0 g oral daily × 3–6 days (severe cases: 800 mg i.v. daily × 6 days or till oral can be given) + *Luminal amoebicide* (as above)	• Emetine/Dehydroemetine 60 mg i.m./s.c. × 8–10 days followed by or alternatively • Chloroquine 600 mg (base) oral daily × 2 days, followed by 300 mg daily for 2–3 weeks. *Alternative luminal amoebicides* (as above, but no role of tetracycline)

*In asymptomatic cases, a luminal amoebicide alone may be used (the nitroimidazole may be omitted). Repeat courses after a gap of 2–3 weeks may be needed with the same or alternative drugs to eradicate the chronic luminal cycle.

3. Amoebic liver abscess It is a serious disease; complete eradication of trophozoites from the liver is essential to avoid relapses. Metronidazole and tinidazole are the first choice drugs effective in > 95% cases. Critically ill patients may be treated with i.v. metronidazole for the entire course, or at least initially, followed by oral dosing. Dehydroemetine is to be used only if metronidazole cannot be given for one reason or the other, and in patients not cured by metronidazole. Large abscesses usually take months to resolve, even if all trophozoites are killed. If a big abscess has formed, it may be aspirated.

A luminal amoebicide must be given later to finish the intestinal reservoir of infection. A course of chloroquine may be administered after that of metronidazole/dehydroemetine in those with incomplete response or to ensure that no motile forms survive in the liver.

DRUGS FOR GIARDIASIS

Giardia lamblia is a flagellate protozoon which infects children and adults by oro-faecal contamination and mostly lives as a commensal in the intestine. It sometimes invades the mucosa and causes acute watery short duration

diarrhoea with foul smellling stools, gas and abdominal cramps. If untreated, it may pass on to chronic diarrhoea with greasy or frothy stools but no blood or mucus. Many drugs useful in amoebiasis are also effective in giardiasis.

1. *Metronidazole* 400 mg TDS (children 15 mg/kg/day) for 5–7 days or 2 g daily for 3 days, Or

tinidazole 0.6 g daily for 7 days or 2 g single dose, Or

secnidazole 2 g single dose

These may be considered as the drugs of choice, but ~ 10% patients may not be cured, and a second course or alternative drug may be needed.

2. *Nitazoxanide* (*see p. 898*) This prodrug of the PFOR enzyme inhibitor tizoxanide has become available for the treatment of diarrhoea and dysentery caused by *Cryptosporidium parvum, Giardia lamblia* and *E. histolytica.* The dosage schedule is convenient—500 mg (children 7.5 mg/kg) twice daily for 3 days. Efficacy (~80% cure) approaches that of metronidazole.

3. *Quiniodochlor* 250 mg TDS for 7 days is a somewhat less effective alternative.

4. *Furazolidone* It is a nitrofuran compound active against many gram-negative bacilli including *Salmonella* and *Shigella*, also *Giardia* and *Trichomonas*. For giardiasis 100 mg TDS for 5–7 days has been used, but is inferior to metronidazole or tinidazole. It has also been used in bacterial enteritis, but is not a first line treatment.

Furazolidone is partly absorbed from intestines and excreted in urine which turns orange—patients should be told about it. Side effects are mild and infrequent—nausea, headache, dizziness.

FUROXONE 100 mg tab, 25 mg/5 ml susp.

DRUGS FOR TRICHOMONIASIS

Trichomonas vaginalis is another microaerophilic flagellate protozoon which causes vulvovaginitis. It is a common sexually transmitted disease affecting ~ 10% sexually active women. Several drugs are partly effective by vaginal application, but may not entirely clear the infection; recurrences are frequent; repeat courses are required.

1. Drugs used orally

Metronidazole 400 mg TDS for 7 days or 2 g single dose, or *Tinidazole* 600 mg daily for 7 days or 2 g single dose or *Secnidazole* 2 g single dose, are the drugs of choice. They produce upto 90% cure. However, vaginitis due to nitroimidazole resistant *T. vaginalis* is being reported. Some resistant cases respond to higher doses, particularly of tinidazole. Additional intravaginal treatment is required only in refractory cases. A hard core of recurrent cases may remain. A repeat course can be given after 6 weeks. In some cases recurrences are due to reinfection from the male partner who harbours the parasite in the seminal vesicles but remains asymptomatic. In such cases, both partners should be treated concurrently to prevent cross infection of each other.

2. Drugs used intravaginally

1. *Diiodohydroxyquin* 200 mg inserted intravaginally at bed time for 1–2 weeks;
   FLORAQUIN 100 mg vaginal pessaries.
2. *Quiniodochlor* 200 mg inserted in the vagina every night for 1–3 weeks;
   GYNOSAN 200 mg vaginal tab.
3. *Povidone-iodine* 400 mg inserted in the vagina daily at night for 2 weeks;
   BETADINE VAGINAL 200 mg pessaries.

DRUGS FOR LEISHMANIASIS

Visceral leishmaniasis (VL; kala-azar) caused by *Leishmania donovani* (and other Leishmania species) occurs in several tropical and subtropical regions of the world. Though prevalence of the disease globally, including India, is continuously declining over the past decade, still according to WHO estimate made in 2015, about 0.3 million cases of VL occur annually worldwide with > 20,000 deaths each year. About 90% of the cases occur in India, Brazil, Ethiopia, Kenya, Somalia and Sudan, but the disease is also present in other countries of East Africa, South America, Mediterranean basin and central Asia. In india, leishmaniasis is prevalent in Bihar, West Bengal, Jharkhand and eastern UP; the worst affected being Bihar which contributes 50% cases that occur world over. In treating VL, the geographical location is important, because the species of *Leishmania* causing VL and its responsiveness to different drugs differs between different regions. The

disease is highly concentrated in North Bihar and the parasite is resistant to sodium stibogluconate (SSG), the first line drug in many other countries.

Leishmaniasis is transmitted by the bite of the female sandfly phlebotomus. In the fly the parasite exists in the flagellate extracellular (*promastigote*) form, while in man it is found only intracellularly within macrophages in the nonflagellate (*amastigote*) form. Mucocutaneous and dermal leishmaniasis are caused respectively by *L. braziliensis* and *L. tropica* (also other species). Visceral leishmaniasis (VL) is fatal unless treated.

The currently used drugs for treatment of VL are:

1. Sodium stibogluconate (SSG)
   (or Meglumine antimonate—in French speaking countries of Latin and south America)
2. Amphotericin B (AMB)
3. Miltefosine
4. Paromomycin.

Pentamidine was used in resistant kala-azar till 15 years back but not now. *Ketoconazole* and *Allopurinol* have weak antileishmania action, but are not used now.

Kala-azar is primarily a disease of the economically poor class, and the areas affected are underdeveloped. India launched the 'Kala-azar Control Programme' in 1990, which was upgraded in the year 2000 to aim at elimination of the disease. The programme is implemented under the NVBDCP, which has laid down its own treatment guidelines, and provides free treatment. Under the programme over 33,000 cases of VL were treated in 2011 with 90 deaths. The number of cases declined by 33% in 2013 and only 20 died. However, the actual number of cases is much greater. Only confirmed cases (by 'rapid diagnostic test' or splenic aspirate examination) are to be treated with antileishmania drugs.

The choice of drugs, doses and regimens as currently recommended by WHO and NVBDCP are summarized in the box (p. 903).

Cure is indicated by clinical improvement and absence of relapse within 6 months. This can be confirmed by absence of leishmania in splenic aspirate smear examination.

1. Sodium stibogluconate (SSG) It has been the standard first line drug for VL in most parts of the world achieving > 90% cure rate, and is still used in East Africa, Central Asia, Mediterranean basin and South America, but is no longer effective in India and Nepal because of extensive resistance. Over 60% cases in Bihar are unresponsive. Therefore, SSG is no longer used in India. It is a water soluble pentavalent antimonial, the supplied solution contains 10% (100 mg/ml) antimony, and doses are expressed in terms of elemental Sb. The mechanism of action and the basis of selective toxicity to the leishmania amastigotes is unclear. It was believed that -SH dependent enzymes are inhibited by antimony and bioenergetics of the parasite is interfered with. This occurs due to blocking of glycolytic and fatty acid oxidation pathways. However, recent evidence indicates that a specific reductase enzyme present in leishmania amastigots reduces pentavalent-Sb of SSG to the toxic trivalent form, which then promotes efflux of glutathione and other reduced thiols from the parasite residing within macrophages, exposing them to oxidative damage. Resistance to SSG may involve reduced capacity of the parasite to convert it to the trivalent form, and/or alteration in thiol metabolism of the parasite.

Sod. stibogluconate is rapidly absorbed from the site of i.m. injection and excreted unchanged in urine within 6–12 hrs. A small fraction enters tissues and remains stored for long periods. Repeated doses are cumulative. Accumulation of SSG within macrophages accounts for its prolonged inhibitory effect on leishmania residing there. SSG is administered by deep i.m. injection (into buttocks) or by slow i.v. injection daily or on alternate days.

Adverse effects Though, antimonials are toxic drugs, but the pentavalent compounds (particularly SSG) are better tolerated. Nausea, vomiting, metallic taste, cough, pain abdomen, pain and stiffness of injected muscle, sterile abscesses, and mental symptoms may occur. Q-T prolongation may herald arrhythmias. Few cases of shock and death are on record.

Used alone or in combination with paromomycin, SSG is still a 1st line drug in East Africa, Central Asia and South America.

2. Amphotericin B (AMB) (*see* Ch. 58) This antifungal antibiotic is available in two types of preparations. The older and less expensive one is formulated with deoxycholate (AMB-DOC), while in the newer one it is incorporated in liposomes (L-AMB), and is expensive. Like fungi, leishmania has high percentage of ergosterol and is susceptible to this antibiotic which has high affinity for ergosterol and acts by binding to it. Presently, AMB is the most effective drug with highest cure rate in kala-azar: up to 99% clinical and parasitological cure has been reported from India in SSG resistant

*** Recommended treatment regimens for visceral leishmaniasis (Kala-azar) caused by *L. donovani* in the Indian subcontinent**

£1. Amphotericin B deoxycholate (AMB-DOC): 0.75–1.0 mg/kg i.v. infusion over 4 hours daily or on alternate days till 15 mg/kg total dose.
¥2. Liposomal amphotericin B (L-AMB): 3–5 mg/kg i.v. infusion daily for 3–5 days (total dose 15 mg/kg)
or
L-AMB 10 mg/kg single dose i.v. infusion
$3. Miltefosine (all doses given orally with meals for 28 days)
Adults (>12 years) weighing > 25 kg: 100 mg/day (50 mg cap twice daily)€
Adults (>12 years) weighing < 25 kg: 50 mg/day (50 mg cap once daily)
Children (2–11 years): 2.5 mg/kg/day (as 10 mg caps)
4. Paromomycin sulfate: 15 mg (11 mg base) per kg/day i.m. for 21 days
5. Sodium stibogluconate (SSG): 20 mg (Sb^{5+})/kg i.m. or slow i.v. daily for 30 days (only in areas where the *Leishmania* is still sensitive to SSG).

COMBINATIONS (co-administered drugs)
1. L-AMB (5 mg/kg i.v. infusion single dose) + Miltefosine (as above) for 7 days.
2. L-AMB (5 mg/kg i.v. infusion single dose) + Paromomycin (as above) for 10 days.
3. Miltefosine (as above) daily for 10 days + Paromomycin (as above) daily for 10 days.

RESCUE TREATMENT (of failure/non-responsive cases)
1. AMB-DOC or L-AMB at higher doses.

*Adopted from Report of meeting of the WHO Expert Committee on control of leishmaniasis, March 22–26, 2010; WHO Technical Report Series No. 949 (2010)
$ Used as 1st line treatment under NVBDCP
£ Used as 2nd line treatment by NVBDCP.
¥ 1st preference regimen recommended by WHO.
€ The WHO in additon recommends miltefosine dose to be 150 mg/day for adults weighing > 50 kg, while NVBDCP treats all adults above 25 kg with 100 mg/day

cases, and it is treated as the 'reference drug' while comparing the efficacy of other drugs. However, high toxicity and need for prolonged hospitalization, monitoring and repeated slow i.v. infusions limit its application. Therefore, it is the 2nd line treatment of VL under NVBDCP, though the WHO recommends it as the drug of choice and accords it higher preference over miltefosine. Because miltefosine is teratogenic, AMB is the drug of choice in pregnant women and breast feeding mothers.

Liposomal AMB is particularly suited for kala-azar because it delivers the drug inside the reticuloendothelial cells in spleen and liver where the amastigotes live, but high cost is prohibitive. As such, use of L-AMB in India is limited. Using L-AMB, the total dose of 15 mg/kg can be administered over 3–5 days with ~ 98% cure, and WHO has accorded it the highest preference. Even a single dose treatment has been tried, reporting 90% cure at 5 mg/kg, and 98% cure at 10 mg/kg.

AMB is also useful in mucocutaneous and dermal leishmaniasis.

3. Miltefosine It is a derivative of alkyl phosphocholine with potent antileishmania activity that has been tested in India since the 1980s, but was approved only in 2002 as the first orally active drug for kala-azar. Due to spread of SSG resistance in Bihar and neighbouring areas, NVBDCP is now using miltefosine as the 1st line treatment of VL in India. A 4 week course of miltefosine has achieved >95% cure rate in India and 90% in Ethiopia. Cutaneous leishmaniasis can also be cured by 4 week thrapy. Miltefosine is available in India only through NVBDCP. It is also available in few other countries of the Indian region, in South America and has been recently US-FDA approved.

The mechanism of antileishmania action of miltefosine is not known. However, studies suggest that it may be interfering with lipid metabolism of the parasite or prevent synthesis

of some critical cell surface anchor molecules, or alter signal transduction. Leishmania can develop resistance to miltefosine and this may be due to mutation limiting transport of the drug into the parasite cell.* Recently, decreased responsiveness has been suspected in India. To prevent development of resistance to this useful drug, combination therapy with paromomycin or AMB is being promoted.

Miltefosine is rapidly absorbed after oral medication, and widely distributed in the body. It is a long acting drug with biphasic elimination. In the early phase, t½ is ~7 days while the terminal t½ is ~ 4 weeks. Anorexia, vomiting and diarrhoea are the commonest side effects occurring in over 50% patients. However, these are generally brief and resolve with continued use. Skin allergy and rise in hepatic transaminases occurs in some recipients indicating hepatic derangement, but this is usually mild and reverses on stopping the drug. Reversible kidney dysfunction with rise in serum creatinine has also been noted. Miltefosine is teratogenic. It is contraindicated in pregnant women. When miltefosine is given, it should be ensured that female patients do not get pregnant during and till 3 months after miltefosine course.

4. Paromomycin This aminoglycoside antibiotic is described in Ch. 54 and with antiamoebic drugs on p.899. For intestinal protozoal infections, it is used by the oral route and remains confined to the gut. In 2006 it was approved in India for use in VL by the i.m. route. Over the past 2 decades paromomycin has been tried in India and Africa for kala-azar and found to be effective in SSG-resistant cases. The WHO recommends 21 day paromomycin treatment as an alternative to miltefosine, but is considered to have lower efficacy, particularly in Africa.

In a phase III trial on 667 kala-azar patients in Bihar,[$] paromomycin 11 mg/kg/day × 21 days has yielded 95% cure rate, which was statistically not inferior to 99% cure rate obtained with AMB 1 mg/kg × 15 injections over 30 days. Mortality was <1% with both the drugs. Several other trials have confirmed the efficacy of paromomycin in VL.

Though paromomycin produces ototoxicity (in 2% recipients), reversible elevation of serum transaminase and injection site pain, but renal toxicity is rare. Paromomycin is a less expensive and easier to use, but some what less effective alternative to AMB in kala-azar.

Topical paromomycin is effective in dermal leishmaniasis.

Combination therapy

Like in the case of TB, leprosy, HIV and malaria, combination therapy with 2 effective drugs has several advantages in the treatment of VL. These are:

- Limiting risk of development of drug resistance, thereby prolonging the effective life-time of available medicines.
- Attaining higher efficacy and cure rate.
- Shortening of duration of therapeutic regimen; better compliance and convenience.
- Reduction of overall dose; lower toxicity and cost.

Clinical studies in India have testified to the high efficacy of drug combinations, and have shown that duration of treatment can be reduced by half or more. The 3 combinations tested were:

- L-AMB (5 mg/kg i.v. single dose) + Miltefosine (oral) daily × 7 days
- L-AMB (5 mg/kg i.v. single dose) + Paromomycin (i.m.) daily × 10 days
- Miltefosine (oral) daily × 10 days + Paromomycin (i.m.) daily × 10 days.

Each of these combinations yielded 98–99% cure rate. As such, these combinations are recommended with high preference by WHO. However, cost of L-AMB (even single dose) is high.

HIV and Leishmania coinfection

HIV and leishmania infections worsen each other. In endemic areas, HIV positive subjects

*Sundar S, Chakravarty J. Leishmaniasis: an update of current pharmacotherapy. *Expert Opin Pharmacother;*. **16,** 237-52, 2015.

[$]Sundar S, *et al:* Injectable paromomycin for visceral leishmaniasis in India. *N Engl J Med.* **2007;***356*: 2571-2581.

are more likely to develop VL, harbour higher and disseminated leishmania load, and have poorer prognosis. Similarly, occurrence of VL in a HIV positive subject is regarded to be a sign of AIDS and warrants intensive therapy. Coinfected patients have a poorer response to antileishmania as well as anti-HIV drugs. Therapy of such patients is difficult and mortality is high.

Drugs used locally for dermal leishmaniasis (oriental sore)

Dermal leishmaniasis is not a life-threatening condition; many cases are treated by local application of drugs.

1. *Sodium stibogluconate*: Infiltrate 2 ml of the solution (100 mg antimony/ml) around the sore.
2. *Paromomycin* (15%) *ointment:* applied topically on the sore, twice daily for 20 days.

Small and mild lesion may heal by itself in a few months. Multiple sores and severe cases should be treated by systemic drugs as for kala-azar.

Antibiotics may be needed for secondary infection of the sore.

☞ PROBLEM DIRECTED STUDY

62.1 A 50-year-old gardener weighing 58 kg was admitted to the hospital with fever for 4 days, severe pain in right upper part of abdomen, loss of appetite, vomiting and marked weakness. He was not well for the past 2–3 weeks and had lost weight. There was no history of chronic diarrhoea. Palpation of abdomen revealed soft tender enlargement of liver 2 cm below costal margin. Marked tenderness was noted in the lower right intercostal region. Ultrasound showed a solitary 2.5 cm diameter abscess with sharp margins in the right lobe of liver. Stool examination was negative for any kind of ova and cysts. A clinical diagnosis of amoebic liver abscess was made and he was treated with:

Injection Metronidazole 500 mg i.v. over 1 hour every 8 hours for 5 days along with infusion of glucose-saline and vitamins. The fever and vomiting subsided and he started eating food. The injections were substituted by oral metronidazole 800 mg 3 times a day for another 5 days, and the patient became well, except weakness and mild tenderness in the right lower chest. Repeat ultrasound showed abscess cavity size to decrease to 1.5 cm. The patient was discharged with advise for vitamins and food.

(a) Was the choice of medication and route correct, or a better drug/route of administration is available?

(b) Should metronidazole therapy be extended or a repeat course given?

(c) Should the patient be given any other antiamoebic medication in addition to or following metronidazole?

(*see* Appendix-1 for solution)

Chapter 63 Anthelmintic Drugs

Anthelmintics are drugs that either kill (vermicide) or expel (vermifuge) infesting helminths.

Helminthiasis is prevalent globally (1/3rd of world's population harbours them), but is more common in developing countries with poorer personal and environmental hygiene. Multiple infestations in the same individual are not infrequent. In the human body, g.i.t. is the abode of many helminths, but some worms also live in tissues, or their larvae migrate into tissues. They harm the host by depriving him of food, causing blood loss, injury to organs, intestinal or lymphatic obstruction and by secreting toxins. Helminthiasis is rarely fatal, but is a major cause of ill health.

The choice of drug for each worm infestation is based not only on efficacy, but also on lack of side effects/toxicity, ease of administration (preferably single dose) and low cost. Development of resistance has not been a problem in the clinical use of anthelmintics. A therapeutic grouping of the anthelmintics is presented in the chart, and the current choice of drugs for worm infestations common in the Indian subcontinent is given in Table 63.1.

Mebendazole

It is a benzimidazole introduced in 1972. This congener of thiabendazole became very popular because it retained the broad-spectrum

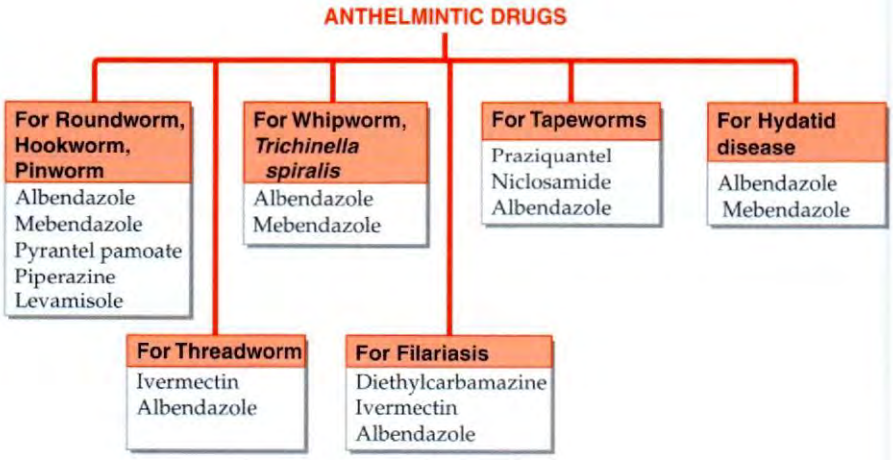


Table 63.1: Choice of drugs for helminthiasis

Worm	First choice drugs	Alternative drugs
1. ROUNDWORM		
Ascaris lumbricoides	Mebendazole, Albendazole, Pyrantel	Piperazine, Levamisole Ivermectin
2. HOOKWORM		
Ancylostoma duodenale	Pyrantel, Mebendazole, Albendazole	Levamisole
Necator americanus	Mebendazole, Albendazole	Pyrantel
3. PIN WORM		
Enterobius (Oxyuris) vermicularis	Pyrantel, Mebendazole, Albendazole	Piperazine
4. THREAD WORM		
Strongyloides stercoralis	Ivermectin	Albendazole
5. WHIPWORM		
Trichuris trichiura	Mebendazole	Albendazole
6. Trichinella spiralis	Albendazole	Mebendazole
7. FILARIA		
Wuchereria bancrofti, Brugia malayi	Diethyl carbamazine, Ivermectin	Albendazole
8. CUTANEOUS LARVA MIGRANS		
Ancylostoma caninum	Albendazole	Ivermectin
9. TAPEWORMS		
Taenia saginata	Praziquantel	Niclosamide, Albendazole
Taenia solium	Praziquantel	Niclosamide, Albendazole
Hymenolepis nana	Praziquantel	Niclosamide, Nitazoxanide
Neurocysticercosis	Albendazole	Praziquantel
10. HYDATID DISEASE		
Echinococcus granulosus,	Albendazole	Mebendazole
E. multilocularis	Albendazole	

anthelmintic activity but not the toxicity of its predecessor. Mebendazole has produced nearly 100% cure rate/reduction in egg count in roundworm, hook worm (both species), *Enterobius* and *Trichuris* infestations, but is much less active on *Strongyloides*. Upto 75% cure has been reported in tapeworms, but *H. nana* is relatively insensitive. It expels *Trichinella spiralis* from intestines, but efficacy in killing larvae that have migrated to muscles is uncertain. Prolonged treatment has been shown to cause regression of hydatid cysts in the liver. Treatment after resection of the cyst may prevent its regrowth.

The immobilizing and lethal action of mebendazole on worms is rather slow: takes 2–3 days to develop. The major site of action of mebendazole appears to be the microtubular protein 'β-tubulin' of the parasite. It binds to β-tubulin of susceptible worms with high affinity and inhibits its polymerization. Intracellular microtubules in the cells of the worm are gradually lost. In addition, it blocks glucose uptake in the parasite, inhibits some mitochondrial enzymes and depletes its glycogen stores. Hatching of nematode eggs and their larvae are also inhibited. Ascaris ova are killed.

Pharmacokinetics Absorption of mebendazole from intestines is minimal; 75–90% of an oral dose is passed in the faeces. The fraction absorbed is excreted mainly as inactive metabolites in urine/faeces.

Adverse effects Mebendazole is well tolerated even by patients in poor health. Diarrhoea, nausea and abdominal pain have attended its use in heavy infestation. Incidents of expulsion of *Ascaris* from mouth or nose have occurred, probably due to starvation of the parasite and their slow death. Allergic reactions, loss of hair and granulocytopenia have been reported with high doses.

Safety of mebendazole during pregnancy is not known, but it is contraindicated on the basis of animal data.

Uses and administration Mebendazole is available as: MEBEX, WORMIN 100 mg chewable tab and 100 mg/5 ml suspension. MEBAZOLE 100 mg tab. The dose and duration of treatment is the same for children above 2 years as for adults; ½ dose for 1–2 yr age.

Roundworm, Hookworm, Whipworm: 100 mg twice a day for 3 consecutive days. No fasting, purging or any other preparation of the patients is needed.

Upto 7 day treatment may be needed in heavy trichuriasis, and cure rates are lower, than in ascariasis.

Pin worm *(Enterobius)* 100 mg single dose, repeated after 2–3 weeks (to kill the ova that have developed later). Strict hygienic measures and simultaneous treatment of all children in the family or class is advocated to cut down autoinfection and person to person infection. This holds true of enterobiasis, irrespective of drug used.

Trichinosis: 200 mg BD for 4 days; less effective than albendazole.

Hydatid disease: 200–400 mg BD or TDS for 3–4 weeks; less effective than albendazole.

Mebendazole is one of the preferred drugs for treatment of multiple infestations and is more effective than albendazole in trichuriasis. It has also been used for mass treatment, but need for multiple doses is a drawback.

Albendazole

It is a subsequently introduced congener of mebendazole: retains the broad-spectrum activity and excellent tolerability of its predecessor, and has the advantage of single dose administration in many infestations. One dose treatment has produced cure rates in ascariasis, hookworm (both species) and enterobiasis which are comparable to 3 day treatment with mebendazole. Results in trichuriasis have been inferior to mebendazole. In strongyloidosis, it is more effective than mebendazole. A 3 day course has achieved nearly 50% cure, and a second course repeated after 3 weeks cured practically all patients. Three day treatment has been found necessary for tapeworms including *H. nana*. Results in hydatid disease and hookworm have been superior to mebendazole. Albendazole has weak microfilaricidal action, kills cysticerci, hydatid larvae, ova of ascaris/hookworm and is also effective in cutaneous larva migrans. The mechanism of action of albendazole is similar to that of mebendazole.

Pharmacokinetics Absorption of albendazole after oral administration is significant, but inconsistent. Absorption is enhanced when the drug is taken with fatty meal (this may help in treating neurocysticercosis and hydatid disease). The fraction absorbed is converted by first pass metabolism to its sulfoxide metabolite which has potent anthelmintic action. In contrast, the metabolites of mebendazole and thiabendazole are inactive. Albendazole sulfoxide is widely distributed in the body, enters brain and is excreted in urine with a t½ of 8.5 hours. Thus, albendazole is able to exert antihelmintic activity in tissues as well.

Side effects Albendazole is well tolerated; only gastrointestinal side effects have been noted. Few patients have felt dizziness. Prolonged use, as in hydatid or in cysticercosis, has caused headache, fever, alopecia, jaundice and neutropenia.

ZENTEL, ALMINTH, ALBEZOLE, COMBANTRIN-A 400 mg tab, 200 mg/5 ml suspension.

Uses No preparation or postdrug fasting/purging is required. For intestinal worms it should be given on empty stomach, while for cysticercosis, hydatid and cutaneous larva migrans it should be given with a fatty meal.

- *Ascaris,* hookworm, *Enterobius* and *Trichuris:* a single dose of 400 mg (for adults and children above 2 yrs; 200 mg for 1–2 yr age) is sufficient. Three day treatment may be needed in heavy trichuriasis.
- Tapeworms and *Strongyloides*: 400 mg twice daily for 3 consecutive days. It is a second choice drug to praziquantel and niclosamide for tapeworm infestation. Efficacy in strongyloidosis is low, and it is the 2nd choice drug to ivermectin.
- Trichinosis: Three day treatment with 400 mg twice daily expels the adult worm from intestine, but has limited effect on larvae that have migrated to muscles, for which there is not effective specific treatment. Larvae are not killed but symptomatic relief occurs. Corticosteroids and analgesics are added if systemic manifestations are severe.
- Neurocysticercosis: Albendazole is the anthelmintic of choice for the treatment of neurocysticercosis (*see* p. 913). Usually 8–15 days course of 400 mg BD (15 mg/kg/day) is employed. Cysticercosis of other tissues (muscles, subcutaneous area) also responds, but no drug should be given for ocular cysticercosis, because blindness can occur due to the reaction to dead cysticerci.
- Cutaneous larva migrans: Albendazole 400 mg daily for 3–5 days is the drug of choice; kills larvae and relieves symptoms. Albendazole 400 mg twice daily for 5 days is the most effective therapy for visceral larva migrans as well.
- Hydatid disease: 400 mg BD for 4 weeks, repeat after 2 weeks (if required), up to 3 courses. It is the preferred treatment given before and after surgery as well as for inoperable cases.
- Filariasis: Added to diethylcarbamazine (DEC) or ivermectin, albendazole has adjuvant value in treating lymphatic filariasis. A single dose of its combination with either DEC or ivermectin given yearly has been used in mass programmes to suppress microfilaraemia and disease transmission.

Yearly mass treatment of children with 400 mg albendazole has been shown to lower worm burden, particularly in developing countries, and has been recommended by WHO.

Because albendazole has exhibited embryotoxicity in animals, use in pregnant women is contraindicated. It should be given with caution to patients with hepatic or renal disease.

Pyrantel pamoate

It was introduced in 1969 for pin worm infestation in children; use soon extended to roundworm and hookworm as well. Efficacy against *Ascaris, Enterobius* and *Ancylostoma* is high and comparable to that of mebendazole. Lower cure rates (about 60%) have been obtained in case of *Necator* infestation. It is less active against *Strongyloides* and inactive against *Trichuris* and other worms.

Pyrantel activates nicotinic cholinergic receptors in the worms resulting in persistent depolarization, giving rise to slowly developing contracture and spastic paralysis. Worms are then expelled. An anticholinesterase action has also been demonstrated. Because piperazine causes hyperpolarization and flaccid paralysis, it antagonizes the action of pyrantel. Cholinergic receptors in mammalian skeletal muscle have very low affinity for pyrantel.

Only 10–15% of an oral dose of pyrantel pamoate is absorbed: this is partly metabolized and excreted in urine.

Adverse effects Pyrantel pamoate is remarkably free of side effects: occasional g.i. symptoms, headache and dizziness are reported. Other advantages are—it is tasteless, non-irritant and does not provoke abnormal migration of worms. Safety of pyrantel pamoate in pregnant women and in children below 2 years has not been established.

Use and administration For *Ascaris, Ancylostoma* and *Enterobius*: a single dose of 11 mg/kg is recommended. A 3 day course for *Necator* and for *Strongyloides* is needed.

No fasting, purging or other preparation of the patient is required.

NEMOCID, ANTIMINTH, EXPENT 250 mg tab, 50 mg/ml suspension (10 ml bottle).

Piperazine

Introduced in 1950, it is a highly active drug against *Ascaris* and *Enterobius*; achieves ~90% cure rates. However, because of availability of more convenient and better tolerated albendazole/mebendazole it is now infrequently used. Piperazine causes hyperpolarization of *Ascaris* muscle by a GABA agonistic action. Opening of Cl^- channels causes relaxation and depresses responsiveness to contractile action of ACh. Flaccid paralysis occurs and worms are expelled alive. They recover if placed in piperazine free medium. Therefore, often a purgative (senna) is given with it, but is not mandatory. No fasting or patient preparation is required. Piperazine does not excite *Ascaris* to abnormal migration. It does not affect neuromuscular transmission in man.

A considerable fraction of the oral dose of piperazine is absorbed; partly metabolized in liver and excreted in urine. Piperazine is safe, but nausea, vomiting, abdominal discomfort and urticaria may be felt. Dizziness and excitement occur at high doses; toxic doses produce convulsions; death is due to respiratory failure. It is contraindicated in renal insufficiency and in epileptics, but is safe in the pregnant.

Dose: For roundworm infestation 4 g once a day for 2 consecutive days; children 0.75 g/year of age (max. 4 g) is considered curative. Because of its ability to relax ascarids, it is of particular value in intestinal obstruction due to roundworms. It can be used during pregnancy while safety of other drugs is not established.

Pin worm: 50 mg/kg (max. 2 g) once a day for 7 days or 75 mg/kg (max. 4 g) single dose, repeated after 3 weeks.
PIPERAZINE CITRATE 0.75 g/5 ml elixir in 30 ml, 115 ml bottle; 0.5 g (as phosphate) tablets;
Combination of any other anthelmintic (except piperazine) with a purgative in the same formulation is banned in India.

Levamisole, Tetramisole

Tetramisole was developed in the late 1960s. It is racemic; its levo isomer (levamisole) was found to be more active and preferable. Both are active against many nematodes, but use is restricted to ascariasis and ancylostomiasis as a second line drug. The ganglia in worms are stimulated causing tonic paralysis and expulsion of live worms. Interference with carbohydrate metabolism (inhibition of fumarate reductase) may also be contributing.

Dose: Ascariasis—Single dose 150 for adults, 100 mg for children 20–39 kg body weight, 50 mg for 10–19 kg.
Ancylostomiasis—Two doses at 12 hour intervals. It is less effective against *Neccator*.

Levamisole: DEWORMIS, VERMISOL 50, 150 mg tab, 50 mg/5 ml syr.

Levamisole is an immunomodulator as well: restores depressed T cell function. It was used as a disease modifying drug in rheumatoid arthritis and as an adjunct in malignancies, aphthous ulcers and recurrent herpes, but repeated doses produce severe reactions; not used now.

Adverse effects One or two doses used in helminthiasis are well tolerated. Incidence of side effects—nausea, abdominal pain, giddiness, fatigue, drowsiness or insomnia is low.

Diethylcarbamazine citrate (DEC)

Developed in 1948, it is the first drug for filariasis caused by the nematodes *Wuchereria bancrofti* (90% cases) and *Brugia malayi*. DEC is absorbed after oral ingestion, distributed all over the body (V = 3–5 L/kg), metabolized in liver and excreted in urine. Excretion is faster in acidic urine. Plasma t½ of usual clinical doses is 4–12 hours, depending on urinary pH.

Diethylcarbamazine is microfilaricidal. It has a highly selective effect on microfilariae (Mf). A dose of 2 mg/kg TDS clears Mf of *W. bancrofti* and *B. malayi* from peripheral blood in 7 days. However, Mf present in nodules and transudates (hydrocoele) are not killed. The most important action of DEC appears to be alteration of organelle membranes of the Mf promoting cell death. It is also suggested that muscular activity of Mf and adult worms is affected so that they are dislodged. Prolonged treatment may kill adult *B. malayi* and probably *W. bancrofti* worms also. Thus, DEC is slow acting macrofilaricidal.

DEC is active against Mf of *Loa loa* and *Onchocerca volvulus* as well. The adult worm of *L. loa* but not *O. volvulus* is killed. DEC reduces worm burden in ascariasis, but efficacy is low.

Uses

1. *Filariasis*: DEC 2 mg/kg TDS is the first line drug: produces rapid symptomatic relief; Mf disappear from blood and patient becomes noninfective to mosquitoes in 7 days. However, the adult worm survives in lymphatics and gives rise to intermittent microfilaraemia and symptoms. Prolonged treatment with different schedules has been found to achieve radical

SECTION 12

cure in most patients. A total dose of 72–126 mg/kg spread over 12 days to 3 weeks has been found satisfactory, but more than one course may be needed with a gap of 3–4 weeks. Elephantiasis due to chronic lymphatic obstruction is not affected by DEC, because fibrosis of lymphatics is irreversible. Yearly treatment with a combination of DEC (6 mg/kg) and albendazole (400 mg) single dose on mass scale has brought down transmission of filariasis by reducing microfilaraemia.

2. *Tropical pulmonary eosinophilia*: DEC (2–4 mg/kg TDS) for 2–3 weeks produces dramatic improvement in the signs and symptoms of eosinophilic lung or tropical eosinophilia. The benefit probably reflects anti-microfilarial action: the symptoms of the disease being presumably due to reaction to the Mf.

The associated cough may respond to inhaled corticosteroids.

HETRAZAN, BANOCIDE 50, 100 mg tab, 120 mg/5 ml syr; 50 mg/ 5 ml pediatric syr; to be taken after meals.

Loa loa and *O. volvulus* infections can also be treated with DEC, but the risk of life-threatening reaction to dying Mf is high. DEC is better avoided initially, or a small (25–50 mg) test dose is given first which is unlikely to produce severe reaction. Ivermectin does not produce such severe reactions and is preferred for initial treatment, but is less effective against adult worms than DEC.

Adverse effects Side effects are common but generally not serious. Nausea, loss of appetite, headache, weakness and dizziness are the usual complaints.

A febrile reaction with rash, pruritus, enlargement of lymph nodes, bronchospasm and fall in BP may occur due to mass destruction of Mf and adult worms. This is usually mild, but may be severe. The reaction can be minimized by starting with a low dose (0.5 mg/kg) and escalation to full dose over the next 4 days. When the reaction occurs, DEC should be temporarily withheld and antihistaminics and/or corticosteroids given. Subsequent administration of DEC does not cause such reaction. Leukocytosis and mild albuminuria are also noted.

Ivermectin It is an extremely potent semisynthetic derivative of the antinematodal principle obtained from *Streptomyces avermitilis*. Ivermectin is the drug of choice for single dose treatment of onchocerciasis and strongyloidosis, and is comparable to DEC for bancroftian and brugian filaria. It is microfilaricidal but not macrofilaricidal. Ivermectin (0.2 mg/kg single dose) is also highly effective in cutaneous larva migrans and ascariasis, while efficacy against *Enterobius* and *Trichuris* is moderate. It has been used as add-on drug to albendazole/mebendazole in heavy trichuriasis. Certain insects, notably scabies and head lice are killed by ivermectin.

Nematodes develop tonic paralysis when exposed to ivermectin. It acts through a special type of glutamate gated Cl^- channel found only in invertebrates. Such channels are not involved in the motor control of flukes and tapeworms which are unaffected by ivermectin. Potentiation of GABAergic transmission in the worm has also been observed. The lack of GABA-related actions in man could be due to its low affinity for mammalian GABA receptors and its exclusion from the brain by P-glycoprotein mediated efflux at the blood-brain barrier.

A single 10–15 mg (0.2 mg/kg) oral dose of ivermectin, preferably with 400 mg albendazole, given annually for 5–6 years has been used for filariasis. Single 0.15–0.2 mg/kg dose has yielded highest cure rate in strongyloidosis, but repeat dose may be given if stool remains positive. For *Strongyloides* hyper-infection syndrome occurring in immunocompromised patients, daily treatment till the syndrome subisdes and larvae are eradicated is needed. Ivermectin reduces burden of other intestinal nematodes as well.

Ivermectin has replaced DEC for onchocerciasis and has been used in the 'river blindness' control programme of WHO in Africa and Latin America. One dose of ivermectin is given at 6–12 month intervals—produces long lasting reduction of Mf counts in eye and skin, without affecting the adult worm. Though it does not cure *O. volvulus* infection, ocular inflammation/damage as well as lymphadenopathy are suppressed with only mild ocular or systemic reactions.

Ivermectin is the only drug effective orally in scabies and pediculosis. Single 0.2 mg/kg dose cures most patients.

IVERMECTOL, IVERMEC, VERMIN 3, 6 mg tabs; to be taken on empty stomach.

Ivermectin is well absorbed orally, widely distributed in the body, but does not enter CNS, sequestrated in liver and fat, and has a long terminal t½ of 48–60 hours. It is metabolized by CYP3A4, but no drug interactions related to this isoenzyme are known. Side effects have been mild—pruritus, giddiness, nausea, abdominal pain, constipation, lethargy and transient ECG changes, but more important are the reactions due to degeneration products of the Mf, which are fever, urticaria, myalgia, edema and tender lymph nodes. Safety of ivermectin in pregnant women and young children is not established.

Doxycycline In a recent innovative approach, doxycycline (100–200 mg/day for 4–6 weeks) has been used to treat filariasis. It acts indirectly by killing *Wolbachia* which are obligate symbiotic gram negative bacteria that are essential for adult *W.bancrofti* and *O. volvulus* worms.

Niclosamide

Niclosamide is a highly effective drug against cestodes infesting man—*Taenia saginata*, *T. solium*, *Diphyllobothrium latum* and *Hymenolepis nana*, as well as pin worm *(Enterobius)*, but is infrequently used now due to availability of praziquantel. The drug appears to act by inhibiting oxidative phosphorylation in mitochondria and interfering with anaerobic generation of ATP by the tapeworm. Injured by niclosamide, the tapeworms are partly digested in the intestine. In cases of *T. solium*, digestion of the dead segments can be hazardous, because the ova released from them may develop into larvae in the intestine, penetrate its wall and cause visceral cysticercosis. Though, the magnitude of such risk is uncertain, many experts do not use niclosamide now for *T. solium* infestation.

Regimen for tapeworm Niclosamide is available as 0.5 g tab (NICLOSAN). After a light breakfast, 2 tablets are to be chewed and swallowed with water, followed by another 2 tablets after 1 hr (total 2 g); total dose for children 2–6 years is 1 g. A saline purge is given 2 hours after the later dose to wash off the worm. The scolex should be searched in the stools to be sure that the worm will not grow again. Cure rate of 85–95% has been obtained by one day treatment. A thorough purge is essential in the cases of *T. solium* so that all segments are passed out and cysticercosis does not occur. Because praziquantel does not lead to digestion of the worm and kills encysted larvae as well, it is the drug of choice for *T. solium*.

For *H. nana*, the 2 g dose is repeated daily for 5 days. This is needed because cysticerci of *H. nana* (which are not affected by niclosamide) develop in the jejunal villi of the same host and worms appear in the intestinal lumen after 4 days. However, no purgative is required. In some cases treatment may have to be repeated after 10 days. Praziquantel is now preferred due to single dose treatment.

Adverse effects Niclosamide is tasteless and nonirritating. It is minimally absorbed from g.i.t.—no systemic toxicity occurs. It is well tolerated; minor abdominal symptoms are produced occasionally. Malaise, pruritus and light headedness are rare. Niclosamide is safe during pregnancy and in poor health patients.

Praziquantel

This anthelmintic has wide ranging activity against *Schistosomes*, other trematodes, cestodes and their larval forms but not nematodes. It is rapidly taken up by susceptible worms and appears to act by causing leakage of intracellular calcium from the membranes producing contracture and paralysis of the worms. Selectivity of action of praziquantel on tapeworms and flukes may be dependent on the presence of a specific variant of Ca^{2+} channel sensitive to praziquantel in these worms. The tapeworms lose grip of the intestinal mucosa and are expelled. Flukes and schistosomes are also dislodged in tissues and veins. Praziquantel is active against adult as well as juvenile and larval stages of tapeworms.

At relatively higher concentrations, it causes vacuolization of the tegument and release of the contents of tapeworms and flukes followed by their destruction by immune mechanisms of the host. This action appears to be more important in cases of schistosomes and flukes.

Pharmacokinetics Praziquantel is rapidly absorbed from intestines; absorption is enhanced if it is ingested with food. High first pass metabolism in liver limits its systemic bioavailability. Phenytoin, carbamazepine and dexamethasone induce praziquantel metabolism and further

decrease its bioavailability. Patients of neurocysticercosis are mostly receiving these drugs which may contribute to therapeutic failure of praziquantel. It crosses blood-brain barrier and attains therapeutic concentrations in the brain and CSF. The plasma t½ is short (1.5 hours). Metabolites are excreted chiefly in urine.

Adverse effects Despite systemic absorption, praziquantel has exhibited no systemic toxicity. It tastes bitter: can produce nausea and abdominal pain. Other side effects are headache, dizziness and malaise. When used for schistosomes and visceral flukes, symptoms like itching, urticaria, rashes, fever and bodyache occur as a reaction to the destroyed parasites. Destruction of cysticerci in the brain may produce neurological complications (*see* below).

No interaction with food, alcohol or tobacco has been noted.

Uses

1. *Tapeworms*: Praziquantel administered as a single dose has achieved 90–100% cure rate in all human tapeworms. This level of efficacy is similar to or better than that of niclosamide, particularly in case of *H. nana*.

T. saginata, T. solium: 10 mg/kg single dose in the morning. It is especially valuable in case of *T. solium*, because it kills the tapeworm larvae within the cysts and there are no chances of systemic cysticercosis developing.

H. nana, D. latum: 15–25 mg/kg single dose in the morning. This is much simpler compared to 5 day treatment needed with niclosamide for eradication of *H. nana*. In case of heavy infestation, retreatment after one week is desirable.

2. *Neurocysticercosis*: The role of anthelmintics in this condition is controversial; only selected cases should be treated with them. Praziquantel was the first drug found to be effective in neurocysticercosis: 50 mg/kg daily in 3 divided doses for 15–30 days kills the larvae lodged in brain and other tissues. However, it is now the 2nd choice drug to albendazole (*see* below).

Praziquantel or albendazole are contraindicated in ocular cysticercosis because reaction to the dead cysticerci may lead to blindness.

3. *Schistosomes*: All 3 species can be treated with 40–75 mg/kg given once or in instalments over one day.

4. *Other flukes*: Praziquantel is the drug of choice for all schistosome and fluke infestations except *Fasciola hepatica*. The flukes respond to 75 mg/kg single day treatment in most cases, and on two occasions in the remaining.

CYSTICIDE 500 mg tab, DISTOCIDE 600 mg tab.

Anthelmintic treatment of neurocysticercosis

Cysticercosis of various organs, including brain, occurs in *T. solium* infestation due to migration of the larvae from the gut to various tissues *via* bloodstream. Anthelmintic treatment of neurocysticercosis may or may not be appropriate, because the cysts do not cause any problem unless the larva dies and its products induce an intense focal reaction. The anthelmintic kills the larvae and precipitates the reaction, resulting in meningeal irritation, rise in intracranial pressure, seizures and other neurological phenomena. However, it prevents future episodes due to spontaneous death of the cysticerci. The decision whether or not to give the anthelmintic may be taken depending on the number, location and viability of the cysts. Active cysts, multiple parenchymal cysts, or intraventricular cysts likely to enlarge and cause hydrocephalus are better treated. Inactive and calcified cysts may be left alone.

Out of the two anthelmintics effective in killing cysticerci, albendazole is now preferred over praziquantel for the following reasons:

- The course of treatment is shorter (8–15 day) compared to praziquantel (15–30 days).
- Cure rates in terms of resolution of symptoms and disappearance of cysts are higher (75–85% with albendazole) than praziquantel (50–60%).
- Corticosteroids (which have to be given concurrently) enhance the absorption of

albendazole, but lower the blood levels of praziquantel. Phenytoin and carbamazepine also lower praziquantel levels.

- Albendazole is cheaper.

Whichever anthelmintic is used, corticosteroids (prednisolone 40–60 mg/day or dexamethasone 8–12 mg/day) must be started 2 days before and continued till 2 weeks after completing the anthelmintic course. This is necessary to suppress the inflammatory reaction to the products of killed larvae. Absorption of both albendazole and praziquantel is enhanced by ingesting them with food, particularly fatty food. For patients with seizures (as most of them are), adequate anticonvulsant treatment should be given beforehand and the fits controlled. Phenytoin and carbamazepine are the most commonly used drugs. These drugs induce the metabolism of praziquantel, which may necessitate use of higher doses. The anticonvulsant must be continued through the course of anthelmintic medication and for an indefinite period (mostly 1–6 months) after it. While parenchymal cysts respond to albendazole in 8–15 days, intraventricular and subarachnoid cysts may require treatment for a month or longer. It is very important to kill and expel the adult worm from the gut to eliminate the source of future cysticerci.

☞ PROBLEM DIRECTED STUDY

63.1 A 40-year-old male weighing 60 kg presented with history of 2 episodes of sudden onset fits over the past 3 days. There is no past history of fits or any nervous disorder. The patient has been having headache for the last one month or so which responds to paracetamol. His wife who witnessed the fits gave a description which fitted tonic-clonic seizures. The wife also informed of noticing some behavioural changes for the last 2 months. The fits were followed by confused behaviour and drowsiness for 2–3 hours. There is no family history of fits or mental illness. MRI scan of the brain revealed 4 active cortical parenchymal cysticerci. A diagnosis of neurocysticercosis was made.

(a) Should this patient be treated with specific anthelmintic drug, or only symptomatic treatment of seizures is indicated?

(b) If anthelmintic therapy is to be given, should antiseizure drug also be given? If both are to be given, should they be given concurrently or one after the other or in overlapping manner starting with one first? What should be the sequence?

(c) If anthelmintic is to be given, which drug, dose and duration of treatment would be appropriate and why?

(d) Whether any other medication needs to be given? If so which, when, how long and why?

(*see* Appendix-1 for solution)

SECTION 13

CHEMOTHERAPY OF NEOPLASTIC DISEASES

Chapter 64 Anticancer Drugs

The anticancer drugs either kill cancer cells or modify their growth. However, selectivity of majority of drugs is limited and they are one of the most toxic drugs used in therapy.

Treatment of malignant diseases with drugs is a rather recent development—started after 1940 when nitrogen mustard was used, but progress has been rapid, both in revealing pathobiology of the diseases and in discovery of new drugs. The latest innovations target growth factors, specific signaling pathways, angiogenesis, tumour antigens, immune therapies, etc. to introduce a different spectrum of drugs. In addition, attempts have been made to define optimal combinations, treatment strategies and patient support measures. Cancer chemotherapy is now of established value and a highly specialized field to be handled by oncology specialists supported by a multidisciplinary team. Only the general principles and an outline will be presented here.

In addition to their prominent role in leukaemias and lymphomas, drugs are used in conjunction with surgery, radiotherapy and immunotherapy in the *combined modality approach* for many solid tumours, especially metastatic. In malignant diseases, drugs are used with the aim of:

1. *Cure or prolonged remission* Chemotherapy is the primary treatment modality that can achieve cure or prolonged remission in:

Acute leukemias	in children	Choriocarcinoma
Wilm's tumour		Hodgkin's disease
Ewing's sarcoma		Lymphosarcoma
Retinoblastoma		Burkitt's lymphoma
Rhabdomyosarcoma		Testicular teratomas
		Seminoma
		Mycosis fungoides

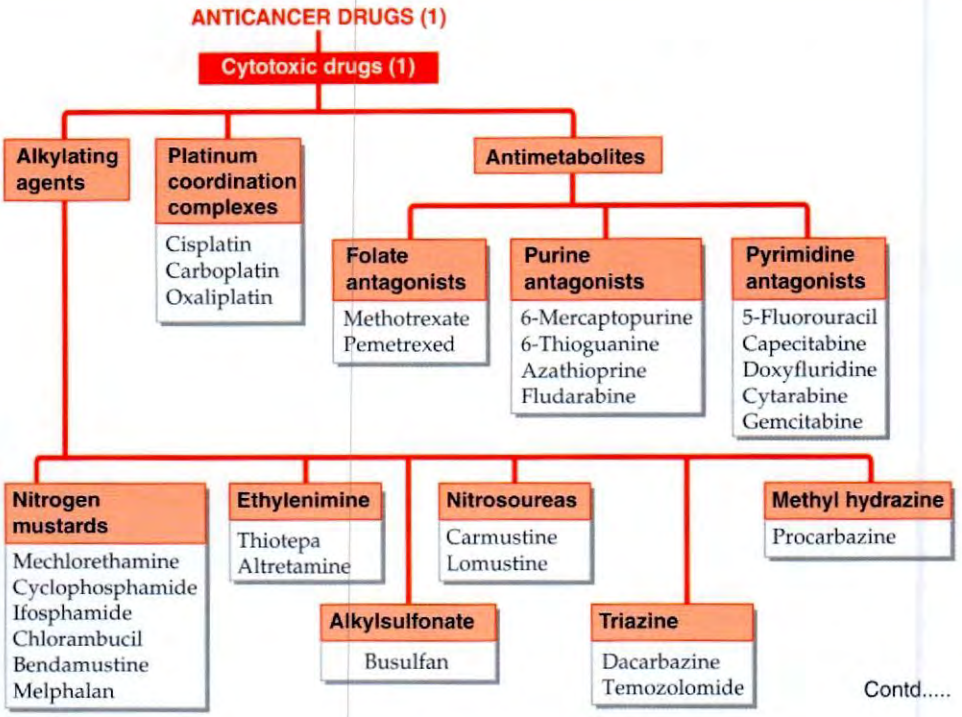
2. *Palliation* Gratifying results are obtained (shrinkage of evident tumour, alleviation of symptoms) and life is prolonged by chemotherapy in:

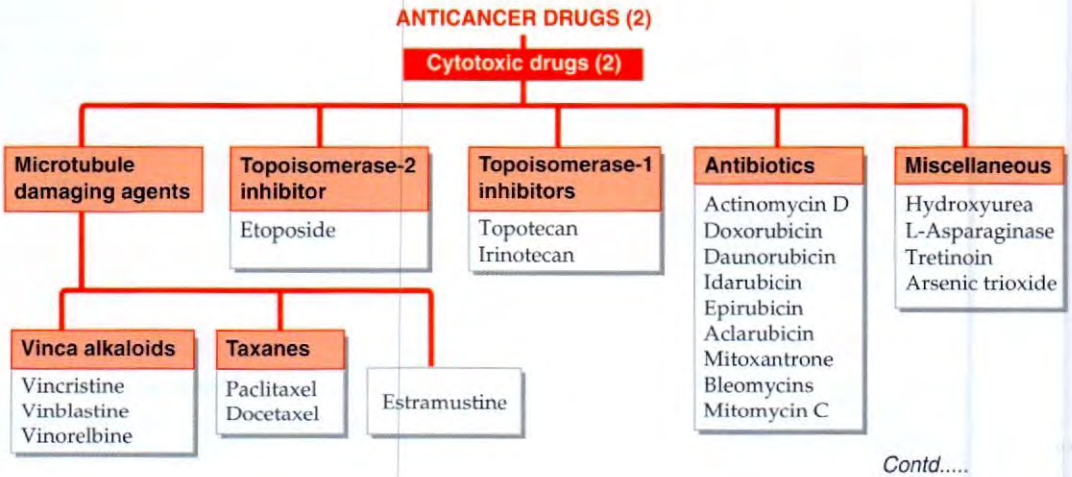
Breast cancer	Chronic lymphatic leukemia
Ovarian carcinoma	Chronic myeloid leukemia
Endometrial carcinoma	Non-Hodgkin lymphomas
Myeloma	Head and neck cancers
Prostatic carcinoma	Lung (small cell) cancer

Many other malignant tumours are less sensitive to drugs—life may or may not be prolonged by chemotherapy. Tumours that are largely refractory to presently available drugs are:

Colorectal carcinoma	Malignant melanomas
Carcinoma pancreas	Bronchogenic carcinoma
Carcinoma stomach	(non-small cell)
Carcinoma esophagus	Hepatoma
Renal carcinoma	Sarcoma

3. *Adjuvant chemotherapy* Drugs are used to mop up any residual malignant cells (micrometastases) after surgery or radiotherapy. This is routinely employed now and may achieve

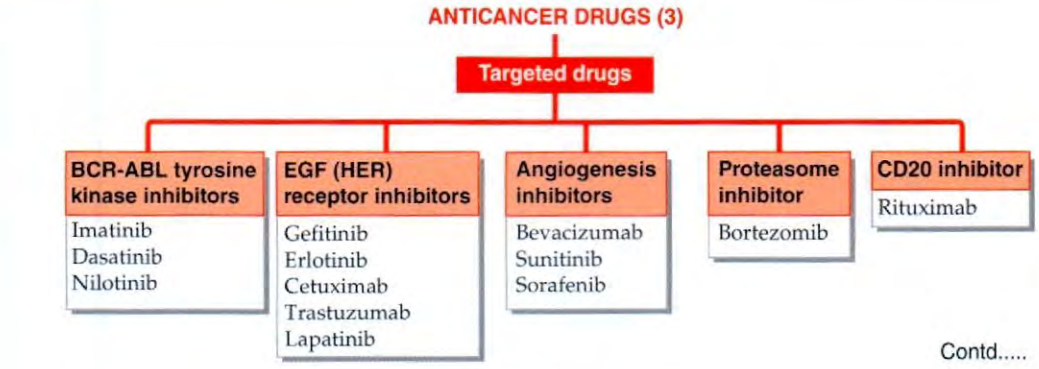




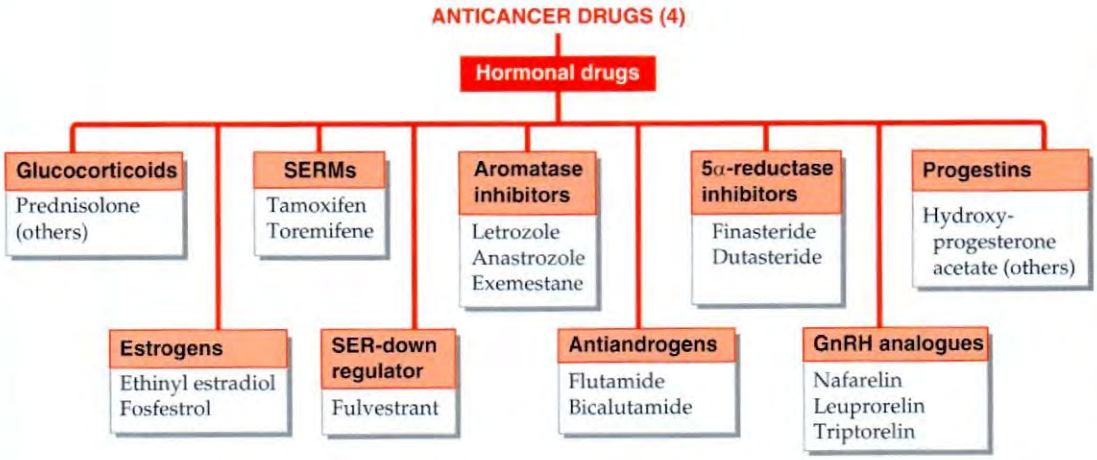
apparent cure, especially in early breast, lung and colonic cancers.

GENERAL TOXICITY OF CYTOTOXIC DRUGS

Majority of the cytotoxic drugs have more profound effect on rapidly multiplying cells, because the most important target of action are the nucleic acids and their precursors, and rapid nucleic acid synthesis occurs during cell division. Many cancers (especially large solid tumours) have a lower growth fraction (lower percentage of cells are in division) than normal bone marrow, epithelial linings,



Contd.....



reticuloendothelial (RE) system and gonads. These tissues are particularly affected in a dose-dependent manner by majority of drugs; though, there are differences in susceptibility to individual members.

1. *Bone marrow* Depression of bone marrow results in granulocytopenia, agranulocytosis, thrombocytopenia, aplastic anaemia. This is the most serious toxicity; often limits the dose that can be employed. Infections and bleeding are the usual complications.

2. *Lymphoreticular tissue* Lymphocytopenia and inhibition of lymphocyte function results in suppression of cell mediated as well as humoral immunity.

Because of action (1) and (2) + damage to epithelial surfaces, the host defence mechanisms (specific as well as nonspecific) are broken down → susceptibility to all infections is increased. Of particular importance are the opportunistic infections due to low pathogenicity organisms. Infections by fungi (*Candida* and others causing deep mycosis), viruses (*Herpes zoster*, cytomegalovirus), *Pneumocystis jiroveci* (a fungus) and *Toxoplasma* are seen primarily in patients treated with anticancer drugs.

3. *Oral cavity:* The oral mucosa is particularly susceptible to cytotoxic drugs because of high epithelial cell turnover. Many chemotherapeutic drugs, particularly fluorouracil, methotrexate, daunorubicin, doxorubicin produce stomatitis as an early manifestation of toxicity. The gums and oral mucosa are regularly subjected to minor trauma, and breaches are common

during chewing. Oral microflora is large and can be the source of infection. Neutropenia and depression of immunity caused by the drug indirectly increase the chances of oral infections. Thrombocytopenia may cause bleeding gums. Xerostomia due to the drug may cause rapid progression of dental caries.

4. *GIT* Diarrhoea, shedding of mucosa, haemorrhages occur due to decrease in the rate of renewal of the gastrointestinal mucous lining. Drugs that prominently cause mucositis are—bleomycin, actinomycin D, daunorubicin, doxorubicin, fluorouracil and methotrexate.

Nausea and vomiting are prominent with many cytotoxic drugs. This is due to direct stimulation of CTZ by the drug, as well as generation of emetic impulses/mediators from the upper g.i.t. and other areas (*see* Ch. 48).

Emetogenic potential of cytotoxic drugs

High	*Moderate*	*Mild*
Cisplatin	Carboplatin	Bleomycin
Mustine	Cytarabine	Chlorambucil
Cyclophosphamide	Procarbazine	Busulfan
Actinomycin D	Vinblastine	Fluorouracil
Dacarbazine	Doxorubicin	6-Thioguanine
Lomustine	Daunorubicin	Hydroxyurea
	Ifosfamide	Vincristine
	6-Mercapto-purine	Methotrexate
	Paclitaxel	Etoposide
		l-Asparaginase

5. *Skin* Alopecia occurs due to damage to the cells in hair follicles. Dermatitis is another complication.

6. *Gonads* Inhibition of gonadal cells causes oligozoospermia and impotence in males; inhibition of ovulation and amenorrhoea are common in females.

Damage to the germinal cells may result in mutagenesis.

7. *Foetus* Practically all cytotoxic drugs given to pregnant women profoundly damage the developing foetus. This may lead to abortion, foetal death or teratogenesis.

8. *Carcinogenicity* Secondary cancers, especially leukaemias, lymphomas and histocytic tumours appear with greater frequency many years after the use of cytotoxic drugs. This may be due to depression of cell mediated and humoral *blocking factors* against neoplasia.

9. *Hyperuricaemia* This is secondary to massive cell destruction (uric acid is a product of purine metabolism) and is especially likely to occur in leukaemias and bulky lymphomas. Acute renal failure, gout and urate stones in the urinary tract may develop. Allopurinol is protective by decreasing uric acid synthesis.

In addition to these general toxicities, individual drugs may produce specific adverse effects, e.g. vincristine causes neuropathy, doxorubicin produces cardiomyopathy, cyclophosphamide causes alopecia and cystitis.

NOTES ON INDIVIDUAL DRUGS

ALKYLATING AGENTS

These compounds produce highly reactive carbonium ion intermediates which transfer alkyl groups to cellular macromolecules by forming covalent bonds. The position 7 of guanine residues in DNA is especially susceptible, but other molecular sites are also involved. Alkylating agents may react with carboxyl, hydroxyl, amino, sulfhydryl and phosphate groups of biomacromolecules. Alkylation results in cross linking/abnormal base pairing/scission of DNA strand. Cross linking of nucleic acids with proteins can also take place.

Alkylating agents have cytotoxic and radiomimetic (like ionizing radiation) actions. Most agents are cell cycle non-specific, i.e. act on dividing as well as resting cells. Some have CNS stimulant and cholinergic properties.

Mechlorethamine (Mustine HCl) It is the first nitrogen mustard; highly reactive and local vesicant. Because of marked acute effects, it is no longer used systemically. Mustine is now occasionally used by topical application on cutaneous T cell lymphoma.

Cyclophosphamide It is inactive as such: produces few acute effects and is not locally damaging. Transformation into active

metabolites (aldophosphamide, phosphoramide mustard) occurs in the liver, and a wide range of antitumour actions is exerted. It has prominent immunosuppressant property. Thus, it is one of the most popular alkylating agents useful in many solid tumours. It is less damaging to platelets, but alopecia and cystitis (due to another metabolite acrolein) are prominent.

Dose: 2–3 mg/kg/day oral; 10–15 mg/kg i.v. every 7–10 days, i.m. use also possible.

ENDOXAN, CYCLOXAN 50 mg tab; 200, 500, 1000 mg inj.

Ifosfamide This congener of cyclophosphamide has a longer and dose-dependent t½. It has found utility in bronchogenic, breast, testicular, bladder, head and neck carcinomas, osteogenic sarcoma and some lymphomas. Ifosfamide produces greater neurotoxicity (mental changes, hallucinations, seizures, coma) and haemorrhagic cystis than other alkylating agents. To protect the bladder, MESNA, a –SH compound is mostly given with it. Mesna is excreted in urine—binds and inactivates the vasicotoxic metabolites of ifosfamide and cyclophosphamide. Ifosfamide causes less alopecia and is less emetogenic than cyclophosphamide.

HOLOXAN-UROMITEXAN 1 g vial + 3 amps of mesna 200 mg inj.; HOLOXAN, IPAMIDE 1 g inj.

Chlorambucil It is a very slow acting alkylating agent, especially active on lymphoid tissue: Myeloid tissue is largely spared. It is the drug of choice for long-term maintenance therapy for chronic lymphatic leukaemia; non-Hodgkin lymphoma and few solid tumours also resolve. It has some immunosuppressant property.

Dose: 4–10 mg (0.1–0.2 mg/kg) daily for 3–6 weeks, then 2 mg daily for maintenance; LEUKERAN 2, 5 mg tab.

Melphalan It is very effective in multiple myeloma and has been used in advanced ovarian cancer. Bone marrow depression is the most important toxicity. Infections, diarrhoea and pancreatitis are the complications.

Dose: 10 mg daily for 7 days or 6 mg/day for 2–3 weeks—4 weeks gap—2 to 4 mg daily for maintenance orally. ALKERAN 2, 5 mg tab, 50 mg per vial for inj.

Bendamustine This nitrogen mustard alkylating agent is indicated in chronic lymphatic leukaemia and non-Hodgkin lymphoma. After i.v. infusion, it is rapidly degraded with a plasma t½ of 30 min. Myelosuppression caused by bendamustine reverses rapidly. Other adverse effects are nausea, vomiting, fever, fatigue and dyspnoea.

Dose: 100–120 mg/m² i.v. daily for 2 days in 28 day cycles.

XYOTIN 100 mg/vial inj.

Thio-TEPA It is an ethylenimine, that does not require to form an active intermediate. Thio-TEPA has high toxicity: seldom used now in ovarian and bladder cancer.

Altretamine It is hexamethyl melamine (HMA) which acts by alkylating DNA and proteins. Altretamine is indicated in recurrent ovarian carcinoma for palliative treatment. The major toxicity is bone marrow depression and neurological effects (mental confusion, ataxia, hallucinations, peripheral neuritis). Kidney dysfunction is dose limiting toxicity.

Dose: 260 mg/m²/day oral in 4 divided doses for 2–3 weeks.

CANTRET 50 mg cap.

Busulfan This alkylating agent is highly specific for myeloid elements; granulocyte precursors being the most sensitive, followed by those of platelets and RBC. It produces little effect on lymphoid tissue and g.i.t. Hyperuricaemia is common; pulmonary fibrosis and skin pigmentation are the specific adverse effects of busulfan. Sterility also occurs. It is now the 2nd choice drug to imatinib for chronic phase of myelocytic leukaemia.

Dose: 2–6 mg/day (0.06 mg/kg/day) orally.

MYLERAN, BUSUPHAN 2 mg tab.

Nitrosoureas These are highly lipid soluble alkylating agents with a wide range of antitumour activity. They cross blood-brain barrier—are effective in meningeal leukaemias and brain cancer. Nausea, vomiting are common and CNS effects also occur. Bone marrow depression is characteristically delayed taking nearly 6 weeks to develop. Visceral fibrosis and renal damage can occur:

Lomustine (CCNU): 100–130 mg/m² BSA single oral dose every 6 weeks;

LOMUSTINE, MOOSTIN 40, 100 mg cap.

Dacarbazine (DTIC) After activation in liver, it acts by methylating DNA and interfering with

its function. Dacarbazine is primarily used in combination regimens for Hodgkin's disease and in malignant melanoma. Nausea, vomiting, flu-like symptoms, neuropathy and myelosuppression are the prominent adverse effects.

Dose: For Hodgkin's disease 3.5 mg/kg i.v. on day 1 and 15 of 4 weeks cycles; for malignant melanoma 3.5 mg/kg/day i.v. for 10 days, repeat after 4 weeks.

DACARIN 100, 200, 500 mg inj; DACARZINE 200 mg/vial inj.

Temozolomide This orally active triazine methylating agent is the drug of choice for glioma and other malignant brain tumours; also utilized in melanoma. Adverse effects are similar to dacarbazine.

Dose: 100–250 mg/day; GLIOZ, GLIOGREY 20, 100, 250 mg caps, 100 mg/vial inj.

Procarbazine It is not a classical alkylating agent, but has similar properties. After metabolic activation (it is inactive as such), procarbazine methylates and depolymerizes DNA causing chromosomal damage. Inhibition of nucleic acid synthesis also occurs. Beause of damage to DNA, mutagenic and carcinogenic potential has been detected. It is a component of combination regimens for Hodgkin's and related lymphomas, and is an alternative drug for brain tumours.

Procarbazine is a weak MAO inhibitor; produces sedation and other CNS effects, and can interact with foods and drugs. Alcohol causes hot flushing and a disulfiram-like reaction in patients taking procarbazine. Males may suffer sterility. Vomiting, leucopenia, thrombocytopenia are the prominent toxicities.

Dose: 100 mg/m^2/day for 14 days in 28 days cycles.

INDICARB 20 mg cap, NEOZINE, P-CARZINE 50 mg cap.

PLATINUM COORDINATION COMPLEXES

Cisplatin The platinum coordination complexes enter cells and are hydrolysed intracellularly to produce a highly reactive moiety which causes cross linking of DNA. The favoured site is N^7 of guanine residue. It can also react with–SH groups of cytoplasmic and nuclear proteins. The effects resemble those of alkylating agents and radiation. Cisplatin is slowly excreted unchanged in urine with a t½ of about 72 hrs. Negligible amounts enter brain.

A copper transporter CTR1 is involved in the entry of platinum complexes into the tumour cells. The complexes are extruded from cells by the transporter MRP1 as well as by copper efflux proteins. Resistance to cisplatin can be imparted by alteration in the levels of these proteins.

Cisplatin is very effective in metastatic testicular and ovarian carcinoma. It is widely used in many other solid tumours. e.g. those of lung, bladder, esophagus, stomach, liver, head and neck.

Cisplatin is administered by slow i.v. infusion 50–100 mg/m^2 BSA every 3–4 weeks; CISPLATIN, CISPLAT, PLATINEX 10 mg/10 ml, 50 mg/50 ml vial.

Cisplatin is a highly emetic drug. Antiemetics are routinely administered before infusing it. The most important toxicity is renal impairment which is dependent on total dose administered. Normal saline (1–2L) is infused i.v. before cisplatin to reduce its renal toxicity. Tinnitus, deafness, sensory neuropathy and hyperuricaemia are other problems. A shock-like state sometimes occurs during i.v. infusion.

Carboplatin It is a less reactive second generation platinum compound that is better tolerated and has a toxicity profile different from cisplatin, but mechanism of action and clinical utility are similar. Nephrotoxicity, ototoxicity and neurotoxicity are low. Nausea and vomiting is milder and is delayed; It infrequently limits the dose. The dose-limiting toxicity is thrombocytopenia and less often leucopenia. Liver dysfunction may occur. Because of lesser plasma protein binding, it is rapidly eliminated by the kidney with a plasma t½ of 2–4 hours. A small fraction that is bound is excreted over days. It is primarily indicated in ovarian carcinoma of epithelial origin, and has shown promise in squamous carcinoma of head and neck, small cell lung cancer, breast cancer and seminoma.

ONCOCARBIN 150 mg inj, KEMOCARB 150, 450 mg/vial inj. 400 mg/m^2 as an i.v. infusion over 15–60 min, to be repeated only after 4 weeks.

Oxaliplatin This third generation platinum complex differs significantly from cisplatin.

It appears to target different biomolecules. Pathways which confer resistance to cisplatin are not operative in its case. Resistance does not easily develop to oxaliplatin, and it retains activity against tumours that have become resistant to cisplatin. Oxaliplatin is highly effective in colorectal cancer, and 5-fluorouracil markedly synergises with it. Gastroesophageal and pancreatic cancers also respond.

The dose limiting toxicity is peripheral neuropathy. Sensory paresthesias involving arms, legs, mouth and throat are common. An acute form of neuropathy is usually triggered by exposure to cold. Myelosuppression is modest, but diarrhoea and acute allergic reactions are reported.
Dose: 85 mg/m^2 i.v. every 2 weeks.
KINAPLAT, OPLATIN 50 mg in 25 ml and 100 mg in 50 ml vial.

ANTIMETABOLITES

These are analogues related to the normal components of DNA or of coenzymes involved in nucleic acid synthesis. Antimetabolites competitively inhibit utilization of the normal substrate or get themselves incorporated forming dysfunctional macromolecules.

1. Folate antagonist

Methotrexate (Mtx)

This folic acid analogue is one of the oldest and highly efficacious antineoplastic drugs which acts by inhibiting dihydrofolate reductase (DHFRase), thus blocking the conversion of dihydrofolic acid (DHFA) to tetrahydrofolic acid (THFA). Utilizing the folate carrier it enters into cells and is transformed to more active polyglutamate form by the enzyme folypolyglutamate synthase (FPGS). Tetrahydrofolic acid is an essential coenzyme required for one carbon transfer reactions in *de novo* purine synthesis and amino acid interconversions. The inhibition is pseudoirreversible because Mtx has 50,000 times higher affinity for the enzyme than the normal substrate.

Methotrexate has cell cycle specific action—kills cells in S phase. In addition to DHFRase it inhibits thymidylate synthase as well, so that DNA synthesis is primarily affected, but synthesis of RNA and protein also suffers. It exerts major toxicity on bone marrow—low doses given repeatedly cause megaloblastic anaemia, but high doses produce pancytopenia. Mucositis and diarrhoea are common side effects. Desquamation and bleeding may occur in the g.i.t.

Methotrexate is absorbed orally, 50% plasma protein bound, little metabolized and largely excreted unchanged in urine. Salicylates, sulfonamides, dicumerol displace it from protein binding sites. Aspirin and sulfonamides enhance toxicity of Mtx by decreasing its renal tubular secretion.

The toxicity of Mtx cannot be overcome by folic acid, because it will not be converted to the active coenzyme form. However, *Folinic acid* (N5 formyl THFA or cirtrovorum factor) rapidly reverses the effects. Thymidine also counteracts Mtx toxicity.

Methotrexate is apparently curative in choriocarcinoma: 15–30 mg/day for 5 days orally or 20–40 mg/m^2 BSA i.m. or i.v. twice weekly. High dose Mtx can induce remission in childhood acute lymphoblastic leukaemia (ALL) and is also effective in maintenance of remission; so that the disease may be cured. Mtx is widely used in non-Hodgkin lymphoma, breast, bladder, head and neck cancers, osteogenic sarcoma, etc. It has prominent immunosuppressant property useful in rheumatoid arthritis, psoriasis and many other antoimmune disorders (*see* Ch. 65).
NEOTREXATE 2.5 mg tab, 50 mg/2 ml inj; BIOTREXATE 2.5 mg tab, 5, 15, 50 mg/vial inj; FOLITREX 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg tabs, 15 mg/ml and 50 mg/2 ml inj.

The use of folinic acid *rescue* has permitted much higher doses of Mtx and has enlarged its scope to many difficult-to-treat neoplasms. A nearly 100 times higher dose (250–1000 mg/m^2 BSA) of Mtx is infused i.v. over 6 hours, followed by 3–15 mg i.v. calcium leucovorin within 3 hours, repeated as required. This procedure can be repeated weekly.

Pemetrexed This newer congener of Mtx primarily targets the enzyme thymidylate

synthase. Though, it is also a DHFRase inhibitor, the pool of THFA is not markedly reduced. Like Mtx it utilizes the folate carrier to enter cells and requires transformation into polyglutamate form by FPGS for activity enhancement. Adverse effects (mucositis, diarrhoea, myelosuppression) are similar to Mtx, but a painful, itching erythematous rash, mostly involving the hands and feet, 'hand-foot syndrome' is quite common. Dexamethasone can relieve it, and pretreatment can reduce its incidence. Low dose folic acid and vit B_{12} pretreatment is recommended to limit pemetrexed-induced myelosuppression. NSAIDs should be avoided as they decrease pemetrexed clearance and may increase toxicity.

In combination with cisplatin, pemetrexed is approved for treatment of mesoepithelioma and non-small cell lung carcinoma. In combinations it has been used for breast, bladder and colorectal cancer.

Dose: 500 mg/m^2 i.v. every 3 weeks.

PEMEX 500 mg vial for i.v. inj., PEXITAZ 100 mg, 500 mg/vial inj.

2. Purine antagonists

Mercaptopurine (6-MP) and thioguanine (6-TG) These are highly effective antineoplastic drugs. After synthesis in the body to the corresponding monoribonucleotides, these drugs inhibit the conversion of inosine monophosphate to adenine and guanine nucleotides that are the building blocks for RNA and DNA. There is partial feedback inhibition of *de novo* purine synthesis. They also get incorporated into RNA and DNA which becomes dysfunctional.

6-MP and 6-TG are especially useful in childhood acute leukaemia, choriocarcinoma and have been employed in some solid tumours as well. In acute leukaemia, both have been used in combination regimens to induce remission and 6-MP for maintaining remission as well.

All antipurines are absorbed orally (though incompletely). Azathioprine and 6-MP are oxidised by xanthine oxidase and their metabolism is inhibited by allopurinol; dose has to be reduced to ¼–½ if allopurinol is given concurrently. Thioguanine is not a substrate for xanthine oxidase. It follows a different (S-methylation) metabolic path and its dose need not be reduced if allopurinol is given.

Methylation by thiopurine methyl transferase (TPMT) is an additional pathway of 6-MP metabolism. Genetic deficiency of TPMT makes the individual more susceptible to 6-MP induced myelosuppression, mucositis and gut damage, while over expression of TPMT is an important mechanism of 6-MP resistance in acute leukaemia cells. Toxicity of azathioprine is also enhanced in TPMT deficiency.

The main toxic effect of antipurines is bone marrow depression, which develops slowly. Mercaptopurine causes more nausea and vomiting than 6-TG. It also produces a high incidence of reversible jaundice. Hyperuricaemia occurs with both, which, and can be reduced by allopurinol.

Dose

6-Mercaptopurine: 2.5 mg/kg/day, half dose for maintenance; PURINETHOL, EMPURINE, 6-MP, MERCAPTHOL 50 mg tab.

6-Thioguanine: 100–200 mg/m^2/day for 5–20 days; 6-TG 40 mg tab.

Azathioprine This antipurine acts by getting converted to 6-MP, but has more prominent immunosuppressant action (*see* p. 942), probably because of selective uptake into immune cells and intracellular conversion to 6-MP, which is further synthesized into the nucleic acid inhibitory neucleotides. Azathioprine primarily suppresses cell mediated immunity (CMI) and is used mainly in autoimmune diseases (rheumatoid arthritis, ulcerative colitis, etc.) as well as in organ transplantation.

Dose: Azathioprine 3–5 mg/kg/day, maintenance 1–2 mg/kg/day; IMURAN, AZORAN, AZOPRINE 50 mg tab.

Fludarabine This newer purine antimetabolite is phosphorylated intracellularly to the active triphosphate derivative which then inhibits DNA polymerase and ribonucleotide reductase, interferes with DNA repair as well as gets incorporated to form dysfunctional DNA. Tumour cell apoptosis is promoted by multiple mechanisms confering activity even in slow growing neoplasms. It is indicated in

chronic lymphatic leukaemia and non-Hodgkin's lymphoma that have recurred after treatment. Prominent adverse effects are chills, fever, myalgia, arthralgia and vomiting after each injection, myelosuppression and opportunistic infections (it is a potent suppressant of CMI).
Dose: 25 mg/m² BSA daily for 5 days every 28 days by i.v. infusion.
FLUDARA 50 mg/vial inj.

3. Pyrimidine antagonists

Pyrimidine analogues have varied applications as antineoplastic, antifungal and antipsoriatic agents.

Fluorouracil (5-FU) It is converted in the body to the corresponding nucleotide 5-fluoro-2-deoxyuridine monophosphate (FdUMP), which forms a covalent ternary complex with methyl-THFA and tymidylate synthase (TS) resulting in irreversible inhibition of TS. Consequently conversion of deoxyuridilic acid to deoxythymidylic acid is blocked. Selective failure of DNA synthesis occurs due to non-availability of thymidylate. Accordingly, thymidine can partially reverse 5-FU toxicity. The triphosphate of 5-FU (FUTP) gets incorporated into RNA, interferes with RNA synthesis as well as RNA function, contributing to its cytotoxicity. Even resting cells are affected, though rapidly multiplying ones are more susceptible. Since inhibition of TS by 5-FU is dependednt on the presence of THFA, concurrent infusion of leucovorin enhances the efficacy of 5-FU. Cisplatin and oxaliplatin also synergise with 5-FU. Most protocols now employ 5-FU along with leucovorin and cisplatin/oxaliplatin, e.g. leucovorin + 5FU + oxaliplatin (FOLFOX) protocol.

Currently, 5-FU is a commonly used anticancer drug for many solid malignancies, especially of colon, rectum, stomach, pancreas, liver, urinary bladder, head and neck. Oral absorption of 5-FU is unreliable. It is mostly used by i.v. infusion. 5-FU is rapidly metabolized by dihydropyrimidine dehydrogenase (DPD) resulting in a plasma t½ of 15–20 min after i.v. infusion. Genetic deficiency of DPD predisposes to severe 5-FU toxicity. Major toxicity of 5-FU is exerted on the bone marrow and g.i.t. causing myelosuppression, mucositis, diarrhoea, nausea and vomiting. Peripheral neuropathy (hand-foot syndrome) also occurs.
Dose: 500 mg/m² i.v. infusion over 1–3 hours weekly for 6–8 weeks, or 12 mg/kg/day i.v. for 4 days followed by 6 mg/kg i.v. on alternate days, 3–4 doses.
FLURACIL, FIVE FLURO, FIVOCIL 250 mg/5 ml and 500 mg/10 ml vial, ONCOURCIL 250 mg/5 ml inj.

A 1% topical solution applied twice daily for 3–6 weeks has yielded gratifying results in superficial basal cell carcinoma, and in actinic keratosis.

Capecitabine This is an orally active prodrug of 5-FU. After absorption it is converted to deoxy-5-fluorouridine in the liver and released in blood. Taken up by cells, it is hydrolysed to 5-FU by thymidine phosphorylase. Because many breast and colorectal cancer cells express large quantity of this enzyme, they generate more 5-FU and suffer higher toxicity than normal cells. A combined regimen of capecitabine + oxaliplatin is frequently used in metastatic colorectal cancer. It has also been utilized in 2nd line treatment of metastatic breast cancer along with docetaxel. Hand-foot syndrome and diarrhoea are prominent adverse effects, but bone marrow depression and mucositis are less marked.
Dose: 2.5 g/m² in 2 divided doses with food daily for 2 weeks—then 1 week rest in cycles of 3 weeks.
CAPIIBINE, CAPXCEL 150 mg, 500 mg tab.

Doxyfluridine This is a 2nd generation oral prodrug of 5-FU which is approved in India and some Asian countries, but not yet by US-FDA. It circumvents the rapid degradation of 5-FU by dihydropyrimidine dehydrogenase in the gut wall and is orally active. Inside the cell it is converted to 5-FU by pyrimidine phosphorylase, high levels of which are expressed in esophageal, breast, hepatic and pancreatic carcinoma cells. Alone or in combination, doxyfluridine is indicated in gastrointestinal cancers metastatic to liver, hepatic and breast carcinoma. Adverse effects are diarrhoea, stomatitis, bone marrow depression, hearing loss and neuritis.
Dose: 800 mg 3 times a day.
CORCIDOX 200 mg cap.

Cytarabine (Cytosine arabinoside, *Ara-C*) This cytidine analogue is phosphorylated in the body to the corresponding nucleotide which inhibits DNA synthesis. The triphosphate of cytarabine is an inhibitor of DNA

polymerase, as well as blocks production of cytidilic acid. However, its incorporation into DNA is now considered to be more important for the expression of its cytotoxicity. DNA repair is also affected. Cytarabine is cell cycle specific and acts primarily during 'S' phase. It is useful only in leukaemias and lymphomas, and is not effective in solid tumours. It is the most effective drug for induction of remission in acute myelogenous as well as lymphoblastic leukaemia in children and in adults. Cytarabine is also used for blast crisis in chronic myelogenous leukaemia and for non-Hodgkin's lymphoma. Because cytarabine is rapidly deaminated and cleared from plasma, it is administered either by rapid i.v. injection (100 mg/m^2) 2–3 times daily for 5–10 days, or by continuous i.v. infusion over 5–7 days. A high dose regimen of 1–3 g/day has also been used.

CYTABIN, CYTOSAR, BIOBIN, REMCYTA 100, 500, 1000 mg inj.

Major toxic effects are due to bone marrow suppression—leukopenia, thrombocytopenia, anaemia, mucositis and diarrhoea. Delayed pulmonary complications may occur.

Gemcitabine It is a difluoro analogue of deoxycytidine that utilizes nucleoside transporters to enter cells and gets converted to mono-, di- and tri-phosphate nucleotides. In contrast to cytarabine, it affects multiple phases of cell cycle, causes DNA strand termination and interferes with DNA repair. After i.v. infusion, it is rapidly deaminated and excreted in urine with a t½ of 15 min. Myelosuppression is the most prominent toxicity. Other adverse effects are nausea, vomiting, paresthesias, fever, renal and hepatic impairment. Gemcitabine is indicated in nonresectable or metastatic carcinoma of pancreas, non-small cell lung cancer, ovarian and bladder carcinoma.

Dose: 1000 mg/m^2 by 10 mg/min i.v. infusion every week for upto 7 weeks.

CELGEM, GEMAZ, ONCOGEM 200 mg and 100 mg/vial inj.

MICROTUBULE DAMAGING AGENTS

Vinca alkaloids

These are mitotic inhibitors which bind to microtubular protein—'tubulin', prevent its polymerization and assembly of microtubules, cause disruption of mitotic spindle and interfere with cytoskeletal function. The chromosomes fail to move apart during mitosis: metaphase arrest occurs. They are cell cycle specific and act in the mitotic phase. Vincristine and vinblastine, though closely related chemically, have different spectrum of antitumour activity and toxicity.

Vincristine (oncovin) It is a rapidly acting drug, very useful for inducing remission in childhood acute lymphoblastic leukaemia, but is not good for maintenance therapy. Other indications are acute myeloid leukaemia, Hodgkin's disease, Wilms' tumour, Ewing's sarcoma, neuroblastoma and carcinoma lung. Prominent adverse effects are peripheral neuropathy and alopecia. Vincristine also causes ataxia, nerve palsies, autonomic dysfunction (postural hypotension, paralytic ileus, urinary retention) and seizures. Bone marrow depression is minimal, but syndrome of inappropriate secretion of ADH (SIADH) can occur.

Dose: 1.5–2 mg/m^2 BSA i.v. weekly.

ONCOCRISTIN, CYTOCRISTIN 1 mg/vial inj.

Vinblastine It is primarily employed along with other drugs in Hodgkin's disease, Kaposi sarcoma, neuroblastoma, non-Hodgkin's lymphoma, breast and testicular carcinoma. Bone marrow depression is more prominent, while neurotoxicity and alopecia are less marked than with vincristine. SIADH has been noted. It can cause local tissue necrosis if extravasation occurs during i.v. infusion.

Dose: 0.1–0.15 mg/kg i.v. weekly × 3 doses.

UNIBLASTIN, CYTOBLASTIN 10 mg/vial inj.

Vinorelbine This is a newer semisynthetic vinblastine analogue with similar mechanism of action inhibiting microtubule assembly and causing metaphase arrest. As a single agent or combined with others, its primary indication is non-small cell lung cancer. As a second line drug, it is useful in advanced breast and ovarian carcinoma. Neutropenia is the dose limiting toxicity. Thrombocytopenia and neurotoxicity are less marked.

Dose: 25–30 mg/m^2 weekly by slow i.v. injection over 10 min.

VINOTEC, RELBOVIN, ONCOBINE 10 mg, 50 mg vial.

Taxanes

Paclitaxel It is a complex diterpin taxane obtained from bark of the Western yew tree,

which exerts cytotoxic action by a novel mechanism. It binds to β-tubulin and enhances its polymerization to form excess of microtubules: a mechanism opposite to that of vinca alkaloids. The microtubules are stabilized and their depolymerization is prevented. This stability disrupts the normal dynamic reorganization of the microtubule network that is essential for interphase and mitotic functions. Abnormal arrays or 'bundles' of microtubules are produced throughout the cell cycle. Cytotoxic action of paclitaxel emphasizes the importance of tubulin-microtubule dynamic equilibrium.

The approved indications of paclitaxel are metastatic ovarian and breast carcinoma after failure of first line chemotherapy and relapse cases. It has also shown efficacy in advanced cases of head and neck cancer, small cell lung cancer, esophageal adenocarcinoma, urinary and hormone refractory prostate cancer. AIDS related Kaposi's sarcoma also responds.

Dose: 135–175 mg/m^2 by i.v. infusion over 3 hr, repeated every 3 weeks.

ALTAXEL, MITOTAX, ONCOTAXEL 30 mg, 100 mg, 260 mg as 6 mg/ml in cremophor (polyoxyethylated castor oil + alcohol + water) emulsion.

Acute anaphylactoid reactions occur because of the cremophor solvent. Pretreatment with dexamethasone, H_1 and H_2 antihistaminics is routinely used to suppress the reaction.

The major toxicity is reversible myelosuppression (mainly granulocytopenia) and 'stocking and glove' neuropathy. Nausea, chest pain, arthralgia, myalgia, mucositis and edema can be troublesome.

Docetaxel It is a more potent congener of paclitaxel with the same mechanism of action. Docetaxel has been found effective in breast and ovarian cancer refractory to first line drugs. Small cell cancer lung, pancreatic, gastric and head/neck carcinomas are the other indications. Major toxicity is neutropenia (more than paclitaxel), but neuropathy is less frequent. Arrhythmias, fall in BP and fluid retention occur with repeated courses.

Dose: 75–100 mg/m^2 i.v. over 1 hr; repeat at 3 weeks.

DOCECAD, DOCETERE, DOXEL 20 mg, 80 mg, 120 mg/vial inj.

Docetaxel is formulated in polysorbate medium which produces less acute hypersensitivity reactions.

Estramustine It is a complex of *estradiol* with a nitrogen mustard *normustine*, which has weak estrogenic but no alkylating property. Rather, it binds to β-tubulin and interferes with its organization into microtubules, exerting antimitotic action. Estramustine gets concentrated in prostate, and the only indication is advanced or metastatic prostate cancer that is nonresponsive to hormone therapy. It is orally active, undergoes first pass metabolism in liver into active as well as inactive metabolites, which are eliminated mainly in faeces. A small amount is hydrolysed into estradiol and normustine producing myelosuppression and estrogenic adverse effects, *viz.* gynaecomastia, impotence, fluid retention, increased risk of thromboembolism and impaired glucose tolerance. Angioedema and other hypersensitivity reactions also occur.

Dose: 4–5 mg/kg orally 3 times daily.

ESMUST, ESTRAM 140 mg cap.

TOPOISOMERASE-2 INHIBITOR

Etoposide It is a semisynthetic derivative of podophyllotoxin, a plant glycoside. It is not a mitotic inhibitor, but arrests cells in the G_2 phase and causes DNA breaks by affecting DNA topoisomerase-2 function. While the cleaving of double stranded DNA is not interfered, the subsequent resealing of the strand is prevented. Etoposide is used in testicular tumours, lung cancer, Hodgkin's and other lymphomas, carcinoma bladder and stomach. Alopecia, leucopenia and g.i.t. disturbances are the main toxicity. Oral bioavailability is 50%; oral dose is double than i.v. dose.

Dose: 50–100 mg/m^2/day i.v. for 5 days, 100–200 mg/day oral.

PELTASOL 100 mg in 5 ml inj., LASTET 25, 50, 100 mg cap, 100 mg/5 ml inj, ACTITOP 50, 100 mg cap, 100 mg/5 ml inj.

TOPOISOMERASE-1 INHIBITORS

Camptothecin analogues

Topotecan, Irinotecan These are two semisynthetic analogues of camptothecin, an antitumour substance obtained from a Chinese tree. They act in a manner similar to etoposide,

but interact with a different enzyme (DNA topoisomerase-1). Their binding to this nuclear enzyme allows single strand breaks in DNA, but not its resealing after the strand has untwisted. They damage DNA during replication; act in the S phase and arrest cell cycle at G_2 phase.

Topotecan It is used in metastatic carcinoma of ovary and small cell lung cancer after primary chemotherapy has failed. Combined with cisplatin, it has been used in cervical cancer. The major toxicity is bone marrow depression, especially neutropenia. Other adverse effects are pain abdomen, vomiting anorexia and diarrhoea.
Dose: 1.5 mg/m^2 i.v. over 30 min daily for 5 days every 3 weeks, 4 or more cycles. TOPOTEC, CANTOP 2.5 mg inj.

Irinotecan It is a prodrug which is decarboxylated in liver to the active metabolite SN-38. Cholinergic effects are produced in some patients because it inhibits AChE. These effects can be suppressed by prior atropinization. Irinotecan is primarily indicated in metastatic/advanced colorectal carcinoma; also in cancer lung/cervix/ovary and stomach. It has been combined with 5-FU and leucovorin. Dose limiting toxicity is diarrhoea. Neutropenia, thrombocytopenia, haemorrhage, bodyache and weakness are the other adverse effects.
The active metabolite SN-38 is inactivated by glucuronidation in the liver. Individuals expressing the UGT1A1*28 allele of glucuronyl transferase enzyme are more susceptible to irinotecan induced diarrhoea and neutropenia, because they fail to inactivate SN-38.
Dose: 125 mg/m^2 i.v. over 90 min, weekly for 4 weeks.
IRINOTEL, IRNOCAM 40 mg (2 ml), 100 mg (5 ml) inj.

ANTIBIOTICS

These are products obtained from microorganisms and have prominent antitumour activity. Practically all of them intercalate between DNA strands and interfere with its template function.

Actinomycin D (Dactinomycin) It is a very potent peptide antineoplastic drug, highly efficacious in Wilms' tumour and childhood rhabdomyosarcoma. Dactinomycin has been combined with Mtx for cure of choriocarcinoma, or may be used in Mtx resistant cases. Good results have also been obtained in Ewing's sarcoma and metastatic testicular carcinoma. In addition to blocking RNA transcription (due to interference with template function of DNA) dactinomycin causes single strand breaks in DNA. Prominent adverse effects are vomiting, stomatitis, diarrhoea, erythema and desquamation of skin, alopecia and bone marrow depression.
Dose: 15 µg/kg i.v. daily for 5 days.
DACMOZEN 0.5 mg/vial inj.

Daunorubicin (Rubidomycin), Doxorubicin These are anthracycline antibiotics having antitumour activity. Whereas, utility of daunorubicin is limited to acute myeloid and lymphoblastic leukaemia (in which it is highly active), doxorubicin, in addition, is effective in many solid tumours, such as breast, thyroid, ovary, bladder and lung cancers, sarcomas and neuroblastoma. These drugs intercalate between DNA strands and block DNA as well as RNA synthesis. However, their more prominent action is to combine with and activate topoisomerase-2 causing breaks in DNA. They also generate quinone type free radicals. As such, they have mutagenic and carcinogenic potential. Maximum action is exerted at S phase, but toxicity is usually exhibited in G_2 phase.

Both, daunorubicin and doxorubicin, produce cardiotoxicity as a unique adverse effect. This can manifest either acutely within 2–3 days, causing ECG changes, arrhythmias and hypotension, all of which are reversible; or be delayed and produce congestive heart failure (related to the total dose administered). CHF is due to cardiomyopathy, which may be fatal. Marrow depression, alopecia, stomatitis, vomiting and local tissue damage (on extravasation) are the other adverse effects. Urine may be coloured red.
Daunorubicin: 25–50 mg/m^2 BSA i.v. daily for 3 days, repeat every 3–4 weeks.
DAUNOCIN, DAUNOMYCIN 20 mg/vial inj.
Doxorubicin: 60–75 mg/m^2 BSA slow i.v. injection every 3 weeks; ADRIAMYCIN, DOXORUBICIN, ONCODRIA 10 mg, 50 mg per vial inj.

Idarubicin This analogue of daunorubicin is less cardiotoxic, but bone marrow depression, stomatitis, alopecia, vomiting, abdominal cramps and other toxicities, as well as mechanism of action are similar to daunorubicin. The primary

indication of idarubicin is acute myeloid leukaemia in which it is generally combined with cytarabine.

Dose: 12 mg/m²/daily for 3 days by slow i.v. injection.

ZAVEDOS 5 mg/vial inj.

Epirubicin This is a newer anthracycline with mechanism of action and properties similar to doxorubicin. Epirubicin has been primarily used as a component of regimen for adjuvant therapy of breast carcinoma. Other indications are gastroesophageal, pancreatic, ovarian, hepatic and bladder carcinoma. Alopecia, hyperpigmentation of skin and oral mucosa, painful oral ulcers, fever and g.i. symptoms are the common adverse effects. Urine may turn red. Cardiotoxicity is dose related.

Dose: 60–90 mg/m² i.v. over 5 min, repeated at 3–4 weeks, total dose < 900 mg/m² to avoid cardiotoxicity.

ALRUBICIN, EPIRUBITEC 10, 50 mg vials, for reconstitution as 2 mg/ml soln. with diluent.

Aclarubicin It is a recently introduced anthracycline, not yet approved by US-FDA, that is indicated in haematological malignancies. Aclarubicin intercalates in DNA and interacts with both topoisomerase 1 and 2 to inhibit RNA and protein synthesis. It is claimed to be less cardiotoxic. Adverse effects are mucositis, alopecia and hyperuricaemia.

Dose: 25–100 mg/m² slow i.v. injection.

KLASINOMYCIN 20 mg/vial inj.

Mitoxantrone It is an anthracycline derivative related to doxorubicin with lower cardiotoxicity, probably because it does not produce quinone type free radicals. However, it does bind to DNA, inhibits topoisonerase-2 causing strand breaks and inhibiting DNA as well as RNA synthesis. Clinical utility is restricted mostly to acute myeloid leukaemia, advanced hormone-refractory prostate cancer and occasionally in breast and hepatic carcinoma, non-Hodgkin lymphoma. It has been found useful in late stage multiple sclerosis as well. Though cardiomyopathy can occur, major toxicity is marrow depression and mucosal inflammation. Discolouration of nails and eye may occur.

ONCOTRON 20 mg/10 ml inj; 14 mg/m² single i.v. dose, repeat at 3 weeks. For induction in acute leukaemia 12 mg/m²/day for 3 days with cytarabine.

Bleomycin This is a mixture of closely related glycopeptide antibiotics having potent antitumour activity. Bleomycin chelates copper or iron, produces superoxide ions and intercalates between DNA strands—causes chain scission and inhibits repair. It is highly effective in testicular tumour and is generally combined with cisplatin + vinblastine or etoposide. It is also useful in squamous cell carcinoma of skin, oral cavity, head and neck, genitourinary tract and Hodgkin's lymphoma. Rate of fluid collection in malignant pleural or peritoneal effusion can be reduced by intrapleural/intraperitoneal injection of bleomycin.

Mucocutaneous toxicity and pulmonary fibrosis which can be life threatening, but minimal myelosuppression are the special features. Allergic and hypotensive reaction can occur after bleomycin injection.

Dose: 30 mg twice weekly i.v. or i.m. (total dose ≤ 250 mg to minimise risk of pulmonary toxicity); BLEOCIN, ONCOBLEO 15 mg inj.

Mitomycin C This highly toxic drug is now used only in anal cancer. It is usually combined with 5-FU, cisplatin and radiation. Superficial bladder tumours are treated by intravesical instillation of mitomycin C. It is transformed intracellularly to a form which acts as an alkylating agent and crosslinks DNA. It also generates free radicals which damage DNA. Bone marrow and g.i.t. are the primary targets of toxicity. Myelosuppression is typically delayed. Injections are repeated only after 6 weeks or more. A haemolytic-uremic syndrome is reported.

Dose: 10 mg/m² BSA, infused i.v. in one day.

MITOCIN, ALMITO 2, 10 mg inj.

MISCELLANEOUS CYTOTOXIC DRUGS

These drugs (except L-asparaginase) have been developed by random synthesis and testing for antitumour activity.

Hydroxyurea It blocks the conversion of ribonucleotides to deoxyribonucleotides by inhibiting the enzyme ribonucleoside diphosphate reductase (RNR), thus interferes with DNA synthesis and exerts S-phase specific action. Its primary therapeutic value is in chronic myeloid leukaemia, psoriasis and polycythaemia vera. Hydroxyurea is occasionally used in some solid tumours and is also employed as a radiosensitizer before radiotherapy. It is a first-line drug for sickle cell disease in adults. Hydroxyurea is well absorbed orally and is eliminated in urine with a plasma t½ of ~ 4 hours. Myelosuppression is the major toxicity. Gastrointestinal disturbances and cutaneous reactions, including pigmentation, also occur.

Dose: 20–30 mg/kg daily or 80 mg/kg twice weekly; CYTODROX, HONDREA, UNIDREA 500 mg cap.

L-Asparaginase (L-ASPase) This enzyme was introduced on the basis of a difference observed between normal cells and those from childhood lymphoblastic leukaemia, *viz.* the leukaemia cells were found to be deficient in L-asparagine synthase enzyme and depended on the supply of L-asparagine from the medium. The enzyme L-ASPase (from *E. coli.*) degrades L-asparagine to L-aspartic acid, depriving the leukaemic cells of an essential metabolite, and causes cell death. L-asparaginase is a component of regimen for inducing remission in acute lymphoblastic leukaemia along with Mtx., prednisolone, vincristine, etc. However, resistance develops to L-ASPase mostly by induction of L-asparagine synthase in the leukaemic cells. Moreover, L-ASPase is antigenic, produces neutralizing antibodies which inactivate and clear the enzyme rapidly, so that clinical response is lost. A polyethylene glycol conjugated L-ASPase (Peg-asparaginase) has been produced which has very slow clearance from the body, is injected every 2 weeks and is more effective. It is also less antigenic.

Many of the typical adverse effects of anticancer drugs do not occur with L-ASPase (no leukopenia, alopecia, or mucosal damage), but it produces effects due to defective protein synthesis—hyperglycaemia, raised triglyceride levels, pancreatitis, liver damage, clotting defects and CNS symptoms. A significant number of recipients develop allergic reactions (urticaria, chills, fever, rash), including anaphylaxis; deaths are reported.

Dose: 50–200 KU/kg i.v., also i.m. twice weekly for 3–4 weeks.
LEUNASE, HOILASP 10,000 KU per vial inj.

Tretinoin It is all trans-retinoic acid, a form of vit A acid (*see* Ch. 69) which acts as a differentiating agent and has recently emerged as a highly effective treatment (usually in combination with daunorubicin or doxorubicin) for acute promyelocytic leukaemia (APL). This subtype of acute myelocytic leukaemia (AML) is associated with production of a fusion gene *PML-RARα* due to a specific chromosomal translocation. The normal retinoic acid receptor RARα-RXR dimerization needed for cell differentiation is prevented and APL is produced. Tretinoin given in relatively higher doses binds tightly to RARα-RXR diamer and prevents formation of PML-RARα dimerization. It also promotes degradation of already formed PML-RARα fusion gene. As a result, blockade of myeloid precursor cell differentiation into cells of different lineages is overcome and prolonged remission is induced in APL. Though, tretinoin alone can induce temporary remission in APL, induction therapy with tretinoin + daunorubicin/doxorubicin produces complete remission in upto 95% patients of APL. Tretinoin has also been shown to promote stem cell renewal in bone marrow. A course of 45 mg/m^2/day tretinoin is administered till one month after remission occurs (or max. 90 days).

Adverse effects of tretinoin are dryness of skin, eye, nose, mouth, pruritus, epistaxis, rise in serum lipids, hepatic transaminases and intracranial pressure. The most serious adverse effect is 'retinoic acid syndrome' comprising of breathlessness, fever, pleural/pericardial effusion and pulmonary infiltrates. Pretreatment with dexamethasone largely prevents occurrence of this syndrome.

Arsenic trioxide Arsenic has been a traditional poison for ages. Ehrlich produced organic arsenicals for cure of syphilis, and some organic arsenicals were used in amoebiasis till 1960s. Lately therapeutic value of small doses of arsenic trioxide in APL has been recognized. It probably acts by enhancing reactive oxygen free radical generation in APL cells. Arsenic is primarily used in resistant/relapsed cases of APL after tretinoin treatment, but now arsenic trioxide is also being included in the 1st line therapy of APL along with tretinoin + an anthracycline, particularly in high risk cases and in those who have initial WBC count of > 10,000/μL. With such triple therapy ~ 90% APL patients have remained in long-term remission.

Though, arsenic trioxide is absorbed orally, it is administered as 0.15 mg/kg daily i.v. infusion over 2 hours till remission is induced or maximum 2 months. Further treatment may be given after a gap. Adverse effects of arsenic are nausea, dizziness, malaise, fatigue, sensory disturbances, effusions, breathlessness, hyperglycaemia, Q-T prolongation, A-V block. Corticosteroid treatment provides considerable relief from these adverse effects.

TARGETED DRUGS

In the recent years fundamental studies of cancer biology and molecular mechanisms of carcinogenesis have identified several targets which can be attacked to selectively kill/inhibit cancer cells. Designing and development of drugs to attack these targets is an active area of current research. Several new drugs have been introduced while a large number are in the pipe line. These drugs are primarily of two types:

- Specific monoclonal antibodies that need to be given parenterally and attack cell surface targets or tumour antigens.
- Synthetic small molecular compounds, given orally, which penetrate cells and affect cancer-specific enzymes or pathways.

Only a sample of these drugs, especially those available in India, are presented here.

1. BCR–ABL tyrosine kinase inhibitors

Imatinib It is the first selectively targeted drug to be introduced for treatment of a malignancy. Imatinib inhibits a specific tyrosine protein kinase labelled 'BCR-ABL' tyrosine kinase expressed by chronic myeloid leukaemia (CML) cells and related receptor tyrosine kinases. These include platelet derived growth factor (PDGF) receptor that is constitutively active in dermatofibrosarcoma protuberans, stem cell receptor and *c-kit* receptor active in gastrointestinal stromal tumour (GIST)—a rare tumour. BCR-ABL tyrosine kinase is responsible for uncontrolled cell division in these tumours. Imatinib is found to be strickingly successful in the chronic phase of CML (remission is induced in >90% cases) and in metastatic c-kit-positive GIST, in which it is the drug of choice. A relatively higher dose may elicit response in accelerated phase of CML as well. Imatinib is also indicated in dermatofibrosarcoma protuberans. Resistance to imatinib develops by point mutations in BCR-ABL tyrosine kinase affecting its affinity for imatinib.

Imatinib is well absorbed orally, metabolized in liver, one active metabolite is also produced. The major degrading enzyme is CYP3A4, and potential interactions can occur with inducers and inhibitors of this isoenzyme. All metabolites are excreted in faeces through bile. The t½ of imatinib is 18 hours while that of its active metabolite is double. Adverse effects are abdominal pain, vomiting, fluid retention, periorbital edema, pleural effusion, myalgia, liver damage and CHF.

Dose: 400 mg/day with meals; accelerated phase of CML 600–800 mg/day.

SHANTINIB, GLEE-VEC, IMATIB α 100 mg cap; UNITINIB 100, 400 mg cap.

Dasatinib It is a second generation BCR-ABL kinase inhibitor. While imatinib binds to and fixes the BCR-ABL kinase enzyme in the inactive state, dasatinib binds to both active and inactive states of the enzyme. It is also a more potent inhibitor (has a lower IC_{50} value). The plasma t½ of dasatinib is much shorter (3–5 hours) than that of imatinib. Dasatinib is approved for use in newly diagnosed Philadelphia chromosome +ive cases of CML which are unresponsive to, or intolerant to imatinib. It is effective in both chronic as well as accelerated phases of the disease. Adverse effects are low blood counts, bleeding, hypertension and pleural effusion. It can prolong Q-T interval.

Dose: 100–400 mg/day, to be swallowed without crushing.

DISANAT 20 and 50 mg tab.

Nilotinib Another second generation BCR-ABL, PDGF-receptor β and c-kit receptor tyrosine kinase inhibitor with 20–50 fold higher affinity for these kinases than imatinib. Thus, it can overcome resistance to imatinib due to BCR-ABL mutation and is effective in chronic CML nonresponsive to imatinib. It is only 30% bioavailable orally, but absorption is improved by food. Nilotinib is also useful in accelerated phase of CML. Thus, it is an alternative drug in imatinib nontolerant or resistant cases of CML, and has now been used as a first line drug as well. Adverse effects are similar to imatinib; Q-T prolongation has been noted.

2. EGF receptor (HER 1) inhibitors

Gefitinib Epidermal growth factor (EGF) receptor (also called 'human epidermal growth factor receptor1' or HER1 or Erbβ$_1$) is a transmembrane receptor-tyrosine-kinase which regulates growth and differentiation of epitheilal cells. Binding of ligand (EGF) to the extracellular domain of the receptor induces dimerization leading to activation of tyrosine kinase activity of the intracellular domain (*see* Fig. 4.8) resulting in autophosphorylation of the kinase and phosphorylation of several cytoplasmic regulatory proteins which modify gene transcription to regulate growth. Certain epithelial cancers over-express EGF receptor or have an active *EGFR* mutation. Their growth is critically dependent upon activation of this receptor.

Gefitinib is a synthetic compound that penetrates cells, binds to the tyrosine kinase domain of the EGF receptor and prevents phosphorylation of regulatory proteins. Gefitinib has been found effective in selected patients of non-small cell lung cancer which has EGFR activating mutation. Lung cancers in non-smokers and in women are generally of this mutant type. In such cases, it has been found to be more effective than cytotoxic drugs. However,

response in non-mutant type of lung cancer is disappointing. Gefitinib monotherapy has been used for locally advanced or metastatic lung cancers after cisplatin and docetaxal have failed.

Oral bioavailability of gefitinib is 60%. It is primarily metabolized by CYP3A4 with t½ of ~ 40 hours. Drug interactions with inducers/inhibitors of CYP3A4 are likely.

Dose: 250 mg/day orally;

GEFONIB, GEFTINAT 250 mg tab/cap.

The most common adverse effect is skin rash and diarrhoea. Others are nausea, anorexia, itching and rise in serum transaminase. Interstitial lung disease is an infrequent, but serious complication.

Erlotinib It is similar to gefitinib in action, pharmacokinetics, adverse effects and efficacy in a subtype of non-small cell lung cancer. Erlotinib has been combined with gemcitabine for advanced/metastatic pancreatic cancer as well. Few cases of serious hepatic dysfunction have occured in patients with preexisting liver disease.

Dose: 100–150 mg OD to be taken 1 hour before or 2 hours after meal.

ERLOTEC, ERLONAT 100, 150 mg tabs.

Cetuximab This inhibitor of EGF receptor is a chimeric monoclonal antibody directed to the extracellular domain of the EGF receptor. Binding to the receptor, it prevents transmembrane signalling resulting in blockade of cell growth, proliferation and metastasis. Survival of tumour cells is jeopardised. Infused i.v. in a loading dose followed by weekly or fortnightly maintenance doses, cetuximab is approved for advanced/metastatic squamous carcinoma of head and neck in combination with radiation and/or cisplatin based chemothrapy. EGF receptor positive metastatic colorectal cancer is another indication in which cetuximab is used either in combination with irinotecan ± cisplatin or as monotherapy in resistant cases. Adverse effects are acneform skin rash, itching, headache and diarrhoea. Anaphylactoid reactions may occur during infusion. Hypomagnesemia and interstitial lung disease are infrequent.

EGFR/HER2 inhibitors

Trastuzumab It is a humanized monoclonal antibody which binds to the extracellular domain of another subtype of EGFR termed HER2 (human epidermal growth factor receptor 2) and inhibits signal transduction. Immune cell mediated cytotoxicity has also been observed in HER2 over-expressing tumours. Trastuzumab is indicated in early stage HER2 positive but ER/PR negative carcinoma breast that has spread to lymph node. It is also useful in HER2 over expressing gastric carcinoma. Trastuzumab is generally used alongwith taxanes, or may be used alone in relapse cases. The long (~6 days) t½ of trastuzumab permits weekly dosing. An acute reaction following the i.v. infusion consisting of flu-like symptoms, chills, fever, malaise, back/neck pain and dyspnoea, is common. The specific toxicity is decrease in LVEF and cardiomyopathy which may lead to CHF in ~1% patients. Monitoring of LVEF is recommended.

Dose: 2–8 mg/kg by i.v. infusion, every week.

HERCEPTIN 440 mg in 50 ml inj.

Lapatinib This is a synthetic orally active inhibitor of EGFR/HER2 which penetrates cells and blocks tyrosine kinase activity of the liganded HER2 and thus interferes with signal transduction. Lapatinib is indicated in metastatic HER2 positive breast cancer that is nonresponsive to trastuzumab and is used in combination with capecitabine. Selected cases of metastatic postmenopausal breast cancers that are ER positive and overexpress HER2 may be treated with lapatinib combined with an aromatase inhibitor. Adverse effects are fatigue, abdominal pain, diarrhoea, decreased LVEF, heart failure and Q-T prolongation. However, lapatinib is considered to be less cardiotoxic than trastuzumab.

Dose: 1250–1500 mg/day.

TYKERB 250 mg tab.

3. Angiogenesis inhibitors

Angiogenesis (proliferation of new blood vessels) is essential for growth and metastasis of cancers. The vascular endothelial growth factor (VEGF) is the most important stimulus for neovascularization and increase in microvessel density within solid tumours. VEGF interacts with cell surface VEGF receptor, that is another receptor tyrosine kinase, which promotes angiogenesis by phosphorylating intracellular regulatory proteins. Several cancers over-express VEGF-receptor, and inhibitors of this receptor have been developed as antitumour drugs. However, all angiogenesis inhibitors carry the risk of vascular injury, bleeding, perforations and defective healing.

Bevacizumab It is a humanized monoclonal antibody that binds VEGF-A and hinders

its access to the VEGF receptor, interrupting angiogenic signalling. Combined with 5-FU, bevacizumab is used in metastatic colorectal cancer. Added to conventional chemotherapy, it improves survival in metastatic non-small cell lung cancer, breast cancer, clear cell renal carcinoma and glioblastoma. Deafness due to neurofibromatosis can be reversed by growth inhibitory effect of bevacizumab.

Being an antibody, bevacizumab is administered by i.v. infusion every 2–3 weeks. Adverse effects are—rise in BP, arterial thromboembolism leading to heart attack and stroke, vessel injury, nose bleeds, rectal bleed and other haemorrhages, heart failure, proteinurea, gastrointestinal perforations, and healing defects.

Dose: 5–10 mg/kg i.v. infusion over 30–90 min.

AVASTIN 100, 400 mg per vial inj.

Intravitreous injection of bevacizumab is used to delay loss of vision in persons having 'wet' type of age-related macular degeneration.

Sunitinib This is a small molecular synthetic VEGF receptor-2 inhibitor, which enters cells and competitively blocks ATP binding to the tyrosine kinase domain, thereby preventing phosphorylation of angiogenic regulatory proteins. Sunitinib inhibits multiple receptor tyrosine kinases like platelet derived growth factor (PDGF) receptor α and β, c-KIT, RET, etc. It is used in metastatic renal cell carcinoma and imatinib resistant g.i. stromal tumour (GIST). Sunitinib is administered orally daily in 4 week cycles, but now 2 week on-one week off cycle is also being used. It is metabolized by CYP3A4 and t½ is ~100 hours. Because sunitinib inhibits multiple tyrosine kinases, adverse effects are more common and of a wider range than that with bevacizumab. Adverse effects are hypertension, rashes, diarrhoea, fatigue, weakness, bleeding, proteinurea, hypothyroidism, neutropenia, rarely CHF.

Dose: 37.5–50 mg OD oral.

SUTENT 12.5 mg, 25 mg, 50 mg caps.

Sorafenib Another orally active synthetic VEGF receptor tyrosine kinase inhibitor that, like sunitinib, inhibits several other tyrosine-kinases as well. It is indicated in advanced/metastatic renal cell carcinoma as a second choice drug to sunitinib. In addition, sorafenib is approved for hepatocellular cancer as well as for progressive/metastatic papillary carcinoma of thyroid that is refractory to radioactive iodine. Common adverse effects are anorexia, weakness, arthralgia, flu-like illness, hand-foot skin reaction, hypertension, haemorrhages and proteinuria, but CHF and myelosuppression are infrequent.

Dose: 400 mg BD, may be reduced to 400 mg OD.

SORANIB, NEXAVAR 200 mg tab.

4. Proteasome inhibitor

Proteasomes are packaged complexes of proteolytic enzymes which degrade several intracellular signalling proteins that control cell cycle, apoptosis and survival response.

Bortezomib It is a unique boron containing compound that covalently binds to proteasome and inhibits its proteolytic activity, disrupting many intracellular signalling pathways. The most important of these is nuclear factor-κB (NF-κB) mediated signalling. NF-κB is a transcription factor that normally resides in the cytoplasm bound to an inhibitory protein IκB. Hypoxia, cytotoxic drugs, DNA breaks and other stressful stimuli activate proteasome which cleaves and degrades IκB to release NF-κB which then translocates to the nucleus and transcripts certain genes to produce molecules that oppose apoptosis and promote cell proliferation. Some neoplasms overexpress NFκB which plays an important role in their survival. By inhibiting proteasome, bortezomib prevents the breakup and degradation of IκB, so that NFκB is not released to transcript survival molecules. It also causes build up of 'Bax', an apoptosis promoting protein, and affects other regulators of cell cycle.

The prime indication of bortezomib is multiple myeloma which over expresses NFκβ, both for first line combined therapy (along with cytotoxic drugs), as well as for relapsed disease. It is also used for refractory mantle cell lymphoma. The most prominent adverse effect is peripheral neuropathy. Others are diarrhoea, fatigue, bone marrow depression, especially thrombocytopenia.

Dose: 1.3 mg/m^2 i.v. bolus injection (can be injected s.c. also), 4 doses at 3 day intervals in cycles of 3 weeks.

EGYBORT 3.5 mg vial for inj, MYEZOM 2 mg, 3.5 mg per vial inj.

5. CD20 inhibitor

Malignant cells express certain antigens on their surface to which monoclonal antibodies (MAbs) could be developed. CD20 is one such antigen.

Rituximab It is a chimerized MAb that binds to the CD20 B-cell antigen expressed on the

surface of B-lymphocytes, plasma cells and B-cell lymphomas. Rituximab binding to the antigen promotes apoptosis through transmembrane signalling as well as by antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) mechanisms. It is indicated in B-cell lymphoma, non-Hodgkin lymphoma and chronic lymphocytic leukaemia, both as single agent as well as in combination with cytotoxic chemotherapy. Survival benefits have been obtained both when it is used as initial therapy as well as in relapsed cases. Rituximab is also being used in some autoimmune diseases. It is administered as slow i.v. infusion every week for 4 weeks when used as single agent, followed by 6 monthly maintenance doses. In combination, it is given every 3–4 weeks (max 8 doses). Adverse effects are infusion reactions consisting of chills, fever, urticarial rashes, pruritus, dyspnoea and hypotension. Severity of the reaction varies, and is also related to rate of infusion. Pretreatment with antihistaminics and corticosteroids dampens the reaction. Late onset neutropenia and depletion of B-lympocytes as well as severe skin reactions are the other problems.

Dose: Initially 50–375 mg/m^2 by slow i.v. infusion, then 500 mg/m^2.

REDITUX 100, 500 mg/vial inj.

mTOR inhibitors

Everolimus (oral) and *Temsirolimus* (i.v.) are mTOR inhibitors (described in Ch. 65) that are approved for use in advanced renal cell cancer, refractory mantle cell lymphoma and advanced hormone receptor positive but HER2 negative breast cancer.

HORMONAL DRUGS

Hormones and related drugs are not cytotoxic, but modify the growth of hormone-dependent tumours. All hormones are only palliative.

Glucocorticoids They have marked lympholytic action and are primarily used in acute childhood leukaemia and lymphomas. They induce remission rapidly, but relapses inevitably occur after variable intervals and gradually the responsiveness is lost. Considerable palliative effects are obtained in Hodgkin's disease. Glucocorticoids have a secondary role in some hormone responsive breast cancers as well.

Corticosteroids are also valuable for the control of malignany and chemotherapy associated complications like hypercalcaemia, haemolysis, bleeding due to thrombocytopenia, retinoic acid syndrome, increased intracranial tension and mediastinal edema due to radiotherapy. Moreover, they afford symptomatic relief by antipyretic and mood elevating action and potentiate the antiemetic action of ondansetron/metoclopramide. Prednisolone or dexamethasone are most commonly used; doses are high—hypercorticism may occur (*see* Ch. 20).

Estrogens They produce symptomatic relief in carcinoma prostate (*see* p. 336), which is an androgen-dependent tumour. However, relapses occur, but life is prolonged. Estrogens have been superseded in carcinoma prostate by GnRH agonists used with an antiandrogen.

Selective estrogen receptor modulators (tamoxifen)

Selective estrogen receptor down regulators (fulvestrant)

Aromatase inhibitors (letrozole, etc).

The above three classes of drugs are the sheet anchor of adjuvant and palliative therapy of carcinoma breast, as well as for primary and secondary prevention of breast cancer (*see* Ch. 22).

Antiandrogen Flutamide and bicalutamide (*see* p. 326) antagonise androgen action on prostate carcinoma cells and have palliative effect in advanced/metastatic cases. Because they increase androgen secretion by antagonizing androgenic action in pituitary, combination with orchiectomy or GnRH analogues is required to produce full therapeutic effect.

5-α reductase inhibitor Finasteride and dutasteride (*see* p. 326–27) inhibit conversion of testosterone to dihydrotestosterone in prostate (and other tissues), have palliative effect in advanced carcinoma prostate; occasionally used.

GnRH agonists (*see* p. 264) They indirectly inhibit estrogen/androgen secretion by suppressing

FSH and LH release from pituitary and have palliative effect in advanced estrogen/androgen dependent carcinoma of breast and prostate. They are generally used in combination with antiandrogens or SERMs.

Progestins (*see* p. 344) They bring about temporary remission in some cases of advanced or recurrent (after surgery/radiotherapy) and metastatic endometrial carcinoma. High doses are needed. They have also been used in palliative treatment of metastatic carcinoma breast that has become unresponsive to tamoxifen.

GENERAL PRINCIPLES IN CHEMOTHERAPY OF CANCER

1. In cancer chemotherapy, analogy is drawn with bacterial chemotherapy; the malignant cell being viewed as an invader. However, there are two main differences—

(a) Bacterial metabolism differs markedly from that of the host, while malignant cells are in fact host cells with deranged regulation of growth and differentiation and relatively minor other differences. Therefore, selectivity of drugs is limited. A number of measures which enhance selectivity of the drugs for the tumour need to be utilized. However, lately some unique tumour antigens and oncogenes (like the BCR-ABL tyrosine kinase gene in CML cells) have been identified, which provide specific targets for drug therapy.

(b) Infecting microorganisms are amenable to immunological and other host defence mechanisms. This is absent or minimal against cancer cells.

Human interferon α-2 (*see* p. 856-57) and other cytokines (interleukin-2, tumour necrosis factor, etc.) that can modify the biological responses to tumour cells are being used as adjuvants in treating neoplasms. They appear to have some direct inhibitory effect on malignant cells, in addition to reinforcing immunological defence against these.

2. A single clonogenic malignant cell is capable of producing progeny that can kill the host. To effect cure, all malignant cells must be killed or removed. Survival time is related to the number of cells that escape chemotherapeutic attack.

3. In any cancer, subpopulations of cells differ in their rate of proliferation and susceptibility to cytotoxic drugs. These drugs kill cancer cells by first order kinetics, i.e. a certain fraction of cells present are killed by one treatment.

4. Drug regimens or number of cycles of combined chemotherapy which can effectively palliate large tumour burdens may be curative when applied to minute residual tumour cell population after surgery and/or irradiation. This is the basis of the combined modality approach (*see* Fig. 64.1).

5. Whenever possible, complete remission should be the goal of cancer chemotherapy: drugs are often used in maximum tolerated doses. Intensive regimens used at an early stage in the disease yield better results.

6. Formerly cancers were treated with one drug at a time, and most cancers could not be cured or palliated durably. Now a combination of 2–5 drugs is given in intermittent pulses to achieve *total tumour cell kill*, giving time in between for normal cells to recover (Fig. 64.1). However, few tumours are still treated with a single drug.

Synergistic combinations and rational sequences are devised by utilizing:

- Drugs which are effective when used alone.
- Drugs with different mechanisms of action.
- Drugs with differing toxicities.
- Empirically by trial and error; optimal schedules are mostly developed by this procedure.
- Drugs with different mechanisms of resistance.
- Drugs with known synergistic biochemical interactions.
- *Kinetic scheduling*: On the basis of cell cycle specificity/nonspecificity of the drugs and the phase of cell cycle (*see* box on p. 935) at which the drug exerts its toxicity.

Cytotoxic drugs are either cell cycle nonspecific (CCNS) or cell cycle specific (CCS).

(a) *Cell cycle nonspecific* These drugs kill resting as well as dividing cells, e.g. bendamustine, cyclophosphamide, chlorambucil,

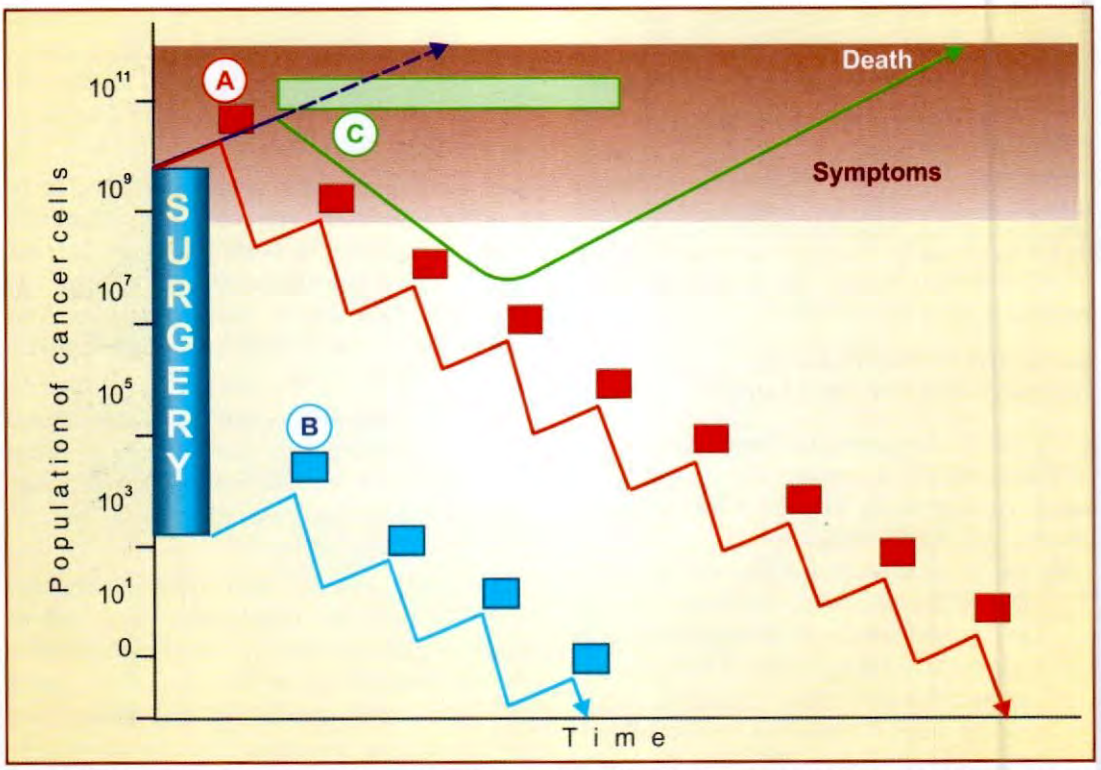


Fig. 64.1: Illustration of cancer cell dynamics with three chemotherapeutic approaches. The shaded area depicts symptoms, before which the cancer remains subclinical. The broken purple line indicates no treatment.
A. A rationally designed combination of 2–5 chemotherapeutic drugs (red bar) is given cyclically. Each cycle kills 99% tumour cells, reducing the tumour cell mass by 2 log units each time. Some regrowth occurs during the rest interval, but the rate of cell kill is more than regrowth and resistance does not develop. If the cycles are continued well beyond all symptoms disappear, cure may be achieved. Radiation may be used to supplement chemotherapy.
B. The cancer (in case of solid tumours) is resected surgically and the small number of residual cancer cells (at the primary site or in metastasis) are killed by relatively few cycles of adjuvant combination chemotherapy (blue bar). This may be supplemented by radiation (in case of radiosensitive tumours).
C. The chemotherapy is begun relatively late with a single but effective drug given continuously (green bar). It causes slower tumour cell kill, but symptom relief may occur. Resistance soon develops, and the tumour starts regrowing even with continued chemotherapy. Symptoms reappear and increase in severity. Ultimately failure of therapy and death occur.

carmustine, dacarbazine, busulfan, melphalan, lomustine, temozolomide, L-asparaginase, cisplatin, procarbazine, actinomycin D, doxorubicin, daunorubicin.

(b) *Cell cycle specific* These drugs kill only actively dividing cells. Their toxicity is generally expressed in S phase. However, these drugs may show considerable phase selectivity, e.g.—

G_1: Etoposide.

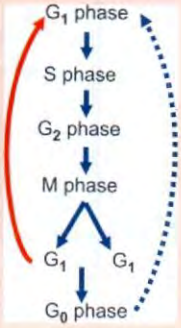
S : Mtx, cytarabine, fludarabine, 6-TG, 6-MP, 5-FU, hydroxyurea, capecitabine, gemcitabine.

G_2: Bleomycin, etoposide, topotecan, irinotecan.

M: Vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel.

It is logical to use cell cycle specific drugs in short courses (pulses) of treatment. This allows noncycling cells (which are generally less susceptible to drugs) to re-enter the cycle

Phases of cell cycle



Pre (nucleic acid) synthesis interval.

Synthesis of DNA occurs.

Post synthetic interval.

Mitosis occurs—two G1 cells are produced, which either directly re-enter next cycle or pass into the nonproliferative (G0) phase.

Nonproliferating cells; a fraction of these are clonogenic—may remain quiescent for variable periods, but can be recruited in cell cycle if stimulated later.

between drug courses. The CCS drugs are generally scheduled after a course of CCNS drug(s) to improve the cell kill. The CCS drugs are more effective in haematological malignancies and in solid tumours with a large growth fraction, while the CCNS drugs are effective in these as well as in solid cancers with a small growth fraction.

Many regimens have been devised by taking into consideration the above factors and by observing patient response.

When cyclic treatment is given, 6–11 cycles may be needed for optimum response. It has been found that maintenance therapy thereafter does not produce additional benefit.

Many regimens have been devised for different tumours. Some of these are:

VAMP : Vincristine + Amethopterine (Mtx) + 6-MP + Prednisolone (used in acute leukaemia).

COAP : Cyclophosphamide + Oncovin (Vincristine) + Ara-C (Cytarabine) + Prednisolone.

FOLFIRI : 5-FU + Leucovorin + Irinotecan (for colon cancer)

FOLFOX : 5-FU + Leucovorin + Oxaliplatin (for colon cancer).

ABVD : Adriamycin (Doxorubicin) + Bleomycin + Vinblastine + Dacarbazine (for Hodgkin's disease).

CHOP-R : Cyclophosphamide + Hydroxydaunorubicin (Doxorubicin) + Oncovin (Vincristine) + Prednisolone + Rituximab (for non-Hodgkin's lymphoma)

BEP : Bleomycin + Etoposide + Platinum (Cisplatin) (for testicular cancer).

7. Tumours often become resistant to any drug that is used repeatedly due to selection of less responsive cells. Such selection is favoured if low dose of a single drug is used.

Several mechanisms of tumour resistance have been recognized. Mutations altering the target biomolecule confer specific (to that particular drug) resistance. An important mechanism of multidrug resistance is overexpression of MDR 1 gene which increases the concentration of P-glycoprotein (an efflux transporter) on the surface of cancer cells, resulting in pumping out of the chemotherapeutic agents. This mechanism is particularly applicable to natural products like vinca alkaloids, anthracycline antibiotics, taxanes, etc.

Toxicity amelioration

High doses and intensive regimens are being employed aiming at cure of the malignancy. The associated toxicity may be ameliorated to some extent by—

1. Toxicity blocking drugs:
   - *Folinic acid* rescue has permitted administration of > 100 fold dose of Mtx (*see* p. 921). It is professed that normal cells are rescued more than the cancer cells, and therapeutic index is increased.
   - Cystitis caused by cyclophosphamide and ifosphamide can be blocked by systemically administered *mesna* and by irrigating the bladder with *acetylcysteine*. Both these drugs are–SH containing compounds that combine with and detoxify the excreted toxic metabolites in the bladder. Generous fluid intake and frequent bladder voiding also helps.
   - For controlling cytotoxic drug induced vomiting, *ondansetron*, a 5-HT_3 antagonist, has surpassed the efficacy of metoclopramide, which nevertheless is still used (*see* Ch. 48). Addition of dexamethasone and/or lorazepam or aprepitant further enhances the protection against vomiting.
   - The anthracycline antibiotics (doxorubicin, etc.) produce cumulative total dose related cardiotoxicity (usually at doses

>300 mg/m^2). *Dexrazoxane* is an iron chelating agent which infused i.v. before doxorubicin has been found to reduce risk of such toxicity. However, it may also compromise the anticancer efficacy of doxorubicin. Dexrazoxane can also be used to ameliorate anthracycline infusion site reaction due to extravasation.

2. *Amifostine* It is an organic thiophosphate which on activation by alkaline phosphatase acts as a cytoprotective against cancer chemotherapy and radiotherapy. Amifostine is particularly used for prophylaxis of cisplatin induced neuro/nephro-toxicity, and radiotherapy related xerostomia.

Dose: 910 mg/m^2 i.v. before cisplatin infusion
200 mg/m^2 i.v. before radiotherapy.

CYTOFOS, NAPROFOS, ETHYFOS 500 mg/vial inj.

Short term side effects of amifostine itself are nausea, vomiting, hypotension and infusion related reaction. Delayed adverse effect is hypocalcaemia.

Vigorous hydration of the patient before, during and after cisplatin infusion also reduces nephrotoxicity.

3. Hyperuricaemia occurring as a consequence of rapid destruction of bulky tumour masses and degradation of large amount of purines can be reduced by *allopurinol*, alkalinization of urine and plenty of fluids. Corticosteroids also reduce hyperuricaemia.

4. Hypercalcaemia occurring as a complication of certain malignancies like myeloma, cancer breast/prostate, etc. may be aggravated by chemotherapy. This is treated by vigorous hydration and i.v. bisphosphonates (*see* Ch. 24).

5. Drugs given in pulses with 2–3 week intervals for normal cells to recover improve the efficacy of the therapy, because malignant cells recover more slowly.

6. Selective exposure of tumour to the drug by intraarterial infusion into a limb or head and neck, or intrapleural/intraperitoneal injection—especially for rapidly accumulating pleural effusion or ascitis; topical application on the lesion for lesions on skin, buccal mucosa, vagina, etc. may reduce systemic toxicity.

7. Platelet and/or granulocyte transfusion after treatment—to prevent bleeding or infection.

8. Use of *biological agents* like recombinant GM-CSF/G-CSF hastens recovery from cytotoxic drug induced myelosuppression.

Filgrastim (GRAFEEL, NEUPROGEN 300 µg/vial or prefilled syringe).

It is recombinant human granulocyte-colony stimulating factor (G-CSF). Started one day after myelosuppressive chemotherapy and injected s.c. or i.v. (5 µg/kg) daily, till neutrophil count normalizes, may be used to shorten recovery time from neutropenia.

Molgramostim (LEUCOMAX 150, 300, 400 µg/vial for s.c./i.v. inj) It is a granulocyte-macrophage colony stimulating factor (GM-CSF). Injected daily beginning one day after last dose of myelosuppressant chemotherapy, it hastens recovery of neutrophil count.

Interleukin-2 (Il-2) is a cytokine biological agent that itself has antitumour property by amplifying killer T-cell response.

9. Bone marrow transplantation after treatment with high doses of myelosuppressant drugs.

10. *Thalidomide* (banned in 1961 for its teratogenic effect, but reintroduced as immunomodulator, and angiogenesis inhibitor antitumour drug) has anxiolytic, antiemetic, adjuvant analgesic/antipyretic properties and has been found to counteract cancer associated cachexia and retard tumour growth by inhibiting angiogenesis. It probably acts by suppressing TNFα and by modulating IL-2. Thalidomide is also useful in erythema nodosum leprosum (ENL) (*see p. 837*).

MISCELLANEOUS DRUGS

Chapter 65 Immunosuppressant Drugs

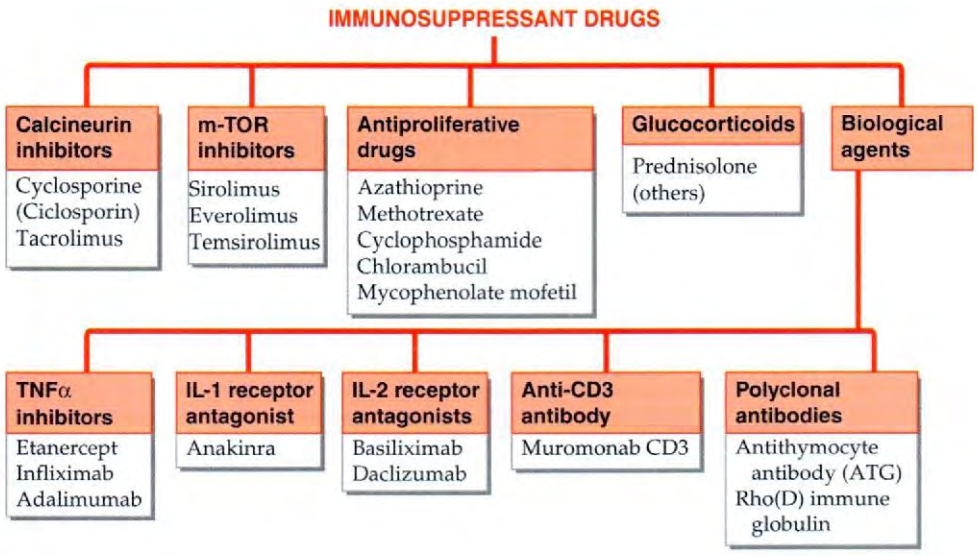
Immunosuppressants are drugs which inhibit cellular/humoral or both types of immune responses, and have their major use in organ transplantation and autoimmune diseases. The important drugs are grouped in the chart.

Several other immunosuppressants and immunomodulators have also been produced.

The development of immune response and the sites of action of different immunosuppressants are summarized in Figure 65.1.

CALCINEURIN INHIBITORS

Cyclosporine It is a cyclic polypeptide with 11 amino acids, obtained from a fungus and introduced in 1977 as a highly selective immunosuppressant which markedly increased the success of organ transplantations. Cyclosporine profoundly and selectively inhibits T lymphocyte proliferation, IL-2 and other cytokine production as well as response of inducer T cells to



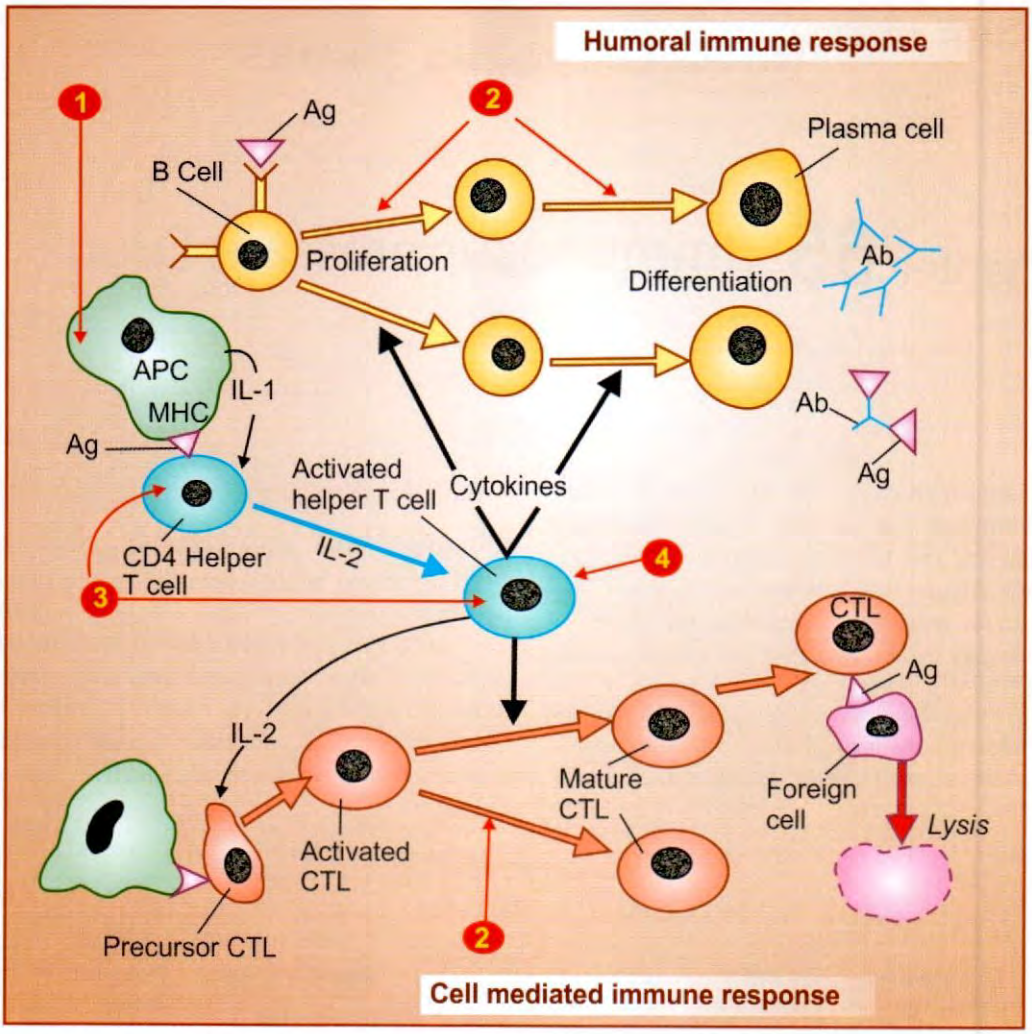


Fig. 65.1: Simplified depiction of generation of humoral and cell-mediated immune response and sites of action of immunosuppressant drugs.

The antigen (Ag) is processed by macrophages or other antigen presenting cells (APC), coupled with class II major histocompatibility complex (MHC) and presented to the CD4 helper T-cell which are activated by interleukin-I (IL-1), proliferate and secrete cytokines—these in turn promote proliferation and differentiation of antigen activated B cells into antibody (Ab) secreting plasma cells. Antibodies finally bind and inactivate the antigen.

In cell-mediated immunity—foreign antigen is processed and presented to CD4 helper T cell which elaborate IL-2 and other cytokines that in turn stimulate proliferation and maturation of precursor cytotoxic lymphocytes (CTL) that have been activated by antigen presented with class I MHC. The mature CTL (Killer cells) recognize cells carrying the antigen and lyse them.

- Glucocorticoids inhibit MHC expression and IL-1, IL-2, IL-6 production so that helper T-cells are not activated.
- Cytotoxic drugs block proliferation and differentiation of T and B cells.
- Cyclosporine, tacrolimus and sirolimus inhibit antigen stimulated activation and proliferation of helper T cells as well as expression of IL-2 and other cytokines by them.
- Antibodies like muromonab CD3, antithymocyte globulin specifically bind to helper T cells, prevent their response and deplete them.

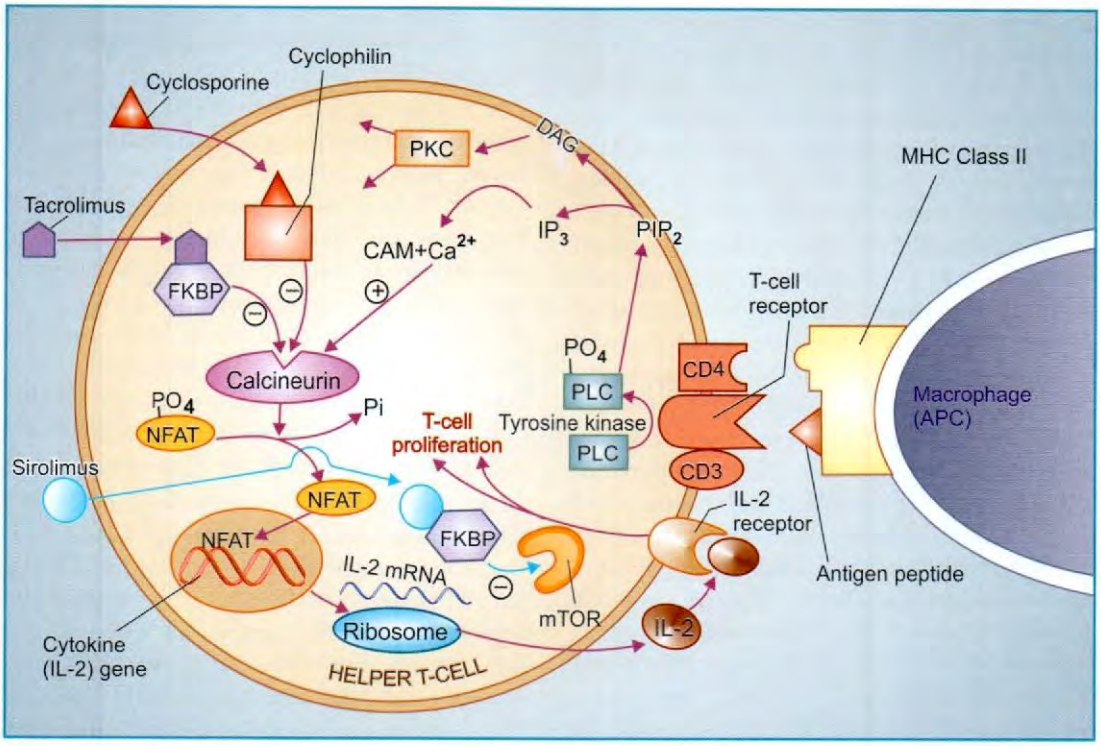


Fig. 65.2: Interaction between macrophage antigen presenting cell (APC) and helper T-cell in the immune response and mechanism of action of cyclosporine, tacrolimus and sirolimus.

Cyclosporine binds to an intracellular protein 'Cyclophilin' and this complex inhibits Ca^{2+}-Calmodulin (Ca^{2+}-CAM) activated phosphatase 'Calcineurin'. Tacrolimus as well inhibits calcineurin, but after binding to a different protein FKBP (FK binding protein). Normally, after activation through T-cell receptor, calcineurin dephosphorylates a 'nuclear factor of activated T-cells' (NFAT) which translocates to the nucleus and triggers transcription of cytokine genes resulting in production of IL-2 and other cytokines. IL-2 diffuses out and acts on IL-2 receptor to stimulate T-cell proliferation and other processes, carrying forward the immune response.

Sirolimus also binds to FKBP, but this complex acts at a later stage, *viz.* it binds to and inhibits another kinase termed m-TOR (mammalian target of rapamycin) which is a key factor for progression of cell proliferation.

PLC—phospholipase C; PIP_2—phosphatidyl inositol bisphosphate; DAG—diacyl glycerol; PKC—protein kinase C.

IL-1, without any effect on suppressor T-cells. Lymphocytes are arrested in G_0 or G_1 phase.

The CD4 molecule associated with T cell receptor on helper T cells anchors the major histocompatibility complex class II (MHC II) carrying the antigen peptide so that it is able to activate the T cell receptor (Fig. 65.2). Stimulation of T cell receptor phosphorylates PLc, which hydrolyses PIP_2 to generate DAG and IP_3. While DAG activates PKc to produce MAPkinase dependent and other actions, IP_3 releases intracellular Ca^{2+}. After binding to calmodulin this Ca^{2+} activates a membrane associated serine/threonine phosphatase called *calcineurin* which dephosphorylates regulatory protein 'nuclear factor of activated T-cell' (NFAT), permitting its intranuclear migration and transcription of cytokine genes leading to production of IL-2 along with other interleukins, GM-CSF, TNFα, interferon, etc. IL-2 is the major cytokine for T-cell multiplication and differentiation. Cyclosporine enters target cells and binds to *cyclophilin,* an immunophilin class of protein. The complex then binds to and inactivates calcineurin so that response of the helper T cell to antigenic stimulation fails.

Cyclosporine also enhances expression of transforming growth factor β (TGFβ), an inhibitor of IL-2 which attenuates IL-2 stimulated T-cell proliferation and production of killer lymphocytes. Cyclosporine is most active when administered before antigen exposure, but can, in addition, suppress the responses of primed helper T cells; hence useful in autoimmune diseases as well.

Cyclosporine selectively suppresses cell-mediated immunity (CMI), prevents graft rejection and yet leaves the recipient with enough immune activity to combat bacterial infection. Unlike cytotoxic immunosuppressants, it is free of toxic effects on bone marrow and RE system. Humoral immunity remains intact. However, it is nephrotoxic, which is its major limitation. It also impairs liver function. Other adverse effects are sustained rise in BP, precipitation of diabetes, anorexia, lethargy, hyperkalaemia, hyperuricaemia, opportunistic infections, hirsutism, gum hyperplasia, tremor and seizures.

Cyclosporine is a highly effective drug for prevention of graft rejection reaction. It is the standard drug for use in renal, hepatic, cardiac, bone marrow and other transplantations. For induction it is started orally 12 hours before the transplant and continued for as long as needed. If graft rejection has started, it can be given i.v., because oral bioavailability is low, dependent on presence of bile and is highly variable. Blood level monitoring is required for effective therapy. Cyclosporine is concentrated in WBCs and RBCs, metabolized in liver by CYP3A4 and excreted in bile. The plasma t½ is biphasic 4–6 hr and 12–18 hr.

Dose: 10–15 mg/kg/day with milk or fruit juice till 1–2 weeks after transplantation, gradually reduced to maintenance dose of 2–6 mg/kg/day. Therapy may be started with 3–5 mg/kg i.v. infusion.

IMUSPORIN, GRAFTIN SOFGEL 25, 50, 100 mg soft gelatin cap. Absorption from this preparation is slower and more variable. A newer microemulsion formulation SANDIMMUN NEORAL, PANIMUN BIORAL 25, 50, 100 mg caps, has more consistent bioavailability.

For i.v. use cyclosporine is dispersed in cremaphor emulsion: SANDIMMUN, PANIMUN 100 mg/ml inj in 1 ml, 5 ml, 50 ml vial, which is diluted and infused over 4–6 hours. An acute reaction consisting of chills, fever, bodyache and dyspnoea often occurs because of the solvent; i.v. cyclosporine is used only in emergency, and is substituted by oral medication as soon as possible.

Cyclosporine is a second line drug to other immunosuppressants in autoimmune diseases, like severe rheumatoid arthritis, uveitis, bronchial asthma, inflammatory bowel disease, dermatomyositis, etc. and in psoriasis, especially to suppress acute exacerbations. It is generally used along with corticosteroids or Mtx. Good results have been obtained in some cases of aplastic anaemia. For these conditions, lower doses (2–5 mg/kg/day) are needed and adverse effects are milder. However, it is not curative and relapses occur when the drug is withdrawn.

Drug interactions Cyclosporine can interact with a large number of drugs. All nephrotoxic drugs like aminoglycosides, vancomycin, amphotericin B and NSAIDs enhance its toxicity. By depressing renal function, it can reduce excretion of many drugs. Phenytoin, phenobarbitone, rifampin and other enzyme inducers lower its blood levels so that transplant rejection may result. On the other hand, CYP3A4 inhibitors erythromycin, ketoconazole and related drugs inhibit its metabolism to increase bioavailability and cause toxicity. Potassium supplements and K^+ sparing diuretics can produce marked hyperkalaemia in patients on cyclosporine.

Tacrolimus (FK506) This immunosuppressant is chemically different (a macrolide) from cyclosporine, but has the same mechanism of action, and is ~100 times more potent. It binds to a different cytoplasmic immunophilin protein labelled 'FK 506 binding protein (FKBP)', but the subsequent steps are the same, i.e. inhibition of helper T cells *via* calcineurin.

Tacrolimus is administered orally as well as by i.v. infusion. Oral absorption is variable and decreased by food. It is metabolized by CYP3A4 and excreted in bile with a t½ of 12 hours. Therapeutic application, clinical efficacy as well as toxicity profile are similar to cyclosporine. Tacrolimus also requires blood level monitoring for dose adjustment. However, due to higher potency (may be some-what higher

efficacy as well), and easier monitoring of blood levels, it is preferred now for organ transplantations. Tacrolimus may be useful in patients whose rejection reaction is not suppressed by cyclosporine. It is particularly valuable in liver transplantation because its absorption is not dependent on bile. Being more potent, it is also suitable for suppressing acute rejection that has set in.

Tacrolimus is also used in fistulating Crohn's disease. A 10 week course may induce remission. Topically, it is useful in atopic dermatitis. Hypertension, hirsutism, gum hyperplasia and hyperuricaemia are less marked than with cyclosporine, but tacrolimus is more likely to precipitate diabetes, cause neurotoxicity, alopecia and diarrhoea. Dose limiting toxicity is renal.

Dose: 0.05–0.1 mg/kg BD oral (for renal transplant), 0.1–0.2 mg/kg BD (for liver transplant). It can also be given i.v. (but no i.v. preparation is available in India); 0.03–0.1% topically.

TACROMUS, PANGRAF 0.5, 1.0, 5.0 mg caps; TACRODERM, TACREL 0.03, 0.1% oint.

mTOR INHIBITORS

Sirolimus This newer and potent immunosuppressant is a macrolide antibiotic (like tacrolimus), which was earlier named *Rapamycin*. It binds to the same immunophillin FKBP as tacrolimus, but the sirolimus-FKBP complex inhibits another kinase called 'mammalian target of rapamycin' (mTOR), and does not interact with ~~calcineurin~~ (Fig. 65.2). The kinase mTOR is an important link in the cascade of signalling pathways which lead to proliferation and differentiation of T-cells activated by IL-2 and other cytokines. Thus, sirolimus arrests the immune response at a later stage than cyclosporine, and may be considered an antiproliferative drug.

Sirolimus is absorbed orally, but fatty meal reduces absorption. It is extensively metabolized, mainly by CYP3A4, so that systemic bioavailability is only 15–20%. Elimination occurs primarily by the biliary route; the t½ is ~60 hours. Inhibitors and inducers of CYP3A4 significantly alter its blood level, which needs to be monitored. Cyclosporine shares the same isoenzyme and raises the blood level of sirolimus.

For prophylaxis and therapy of graft rejection reaction, sirolimus can be used alone, but is generally combined with lower dose of cyclosporine/tacrolimus and/or corticosteroids and mycophenolate mofetil. The latter combination avoids use of a calcineurin inhibitor, and is particularly suitable for patients developing renal toxicity with cyclosporine. Sirolimus is effective in some steroid refractory cases, and has been used in stem cell transplant as well. However, it is not recommended for ~~liver transplant~~. *Sirolimus coated stents* are being used to reduce the incidence of coronary artery restenosis, by inhibiting endothelial proliferation at the site.

Significantly, sirolimus is not nephrotoxic, but it can suppress bone marrow, mainly causing thrombocytopenia. Rise in serum lipids is common. Other adverse effects are diarrhoea, liver damage and pneumonitis. The antiproliferative action of sirolimus may impair wound healing, and exert antineoplastic effect in skin cancer and few other cancers.

Dose: Initially loading dose 1 mg/m^2 daily, followed by titrated lower doses for maintenance.

RAPACAN 1 mg tab.

Everolimus This newer congener of sirolimus has similar mechanism of action, immunosuppressant property, drug interaction potential and adverse effects, but is better absorbed orally and has more consistent bioavailability. Its shorter t½ (40 hours) permits steady-state levels to be reached earlier. In addition to use for prophylaxis of kidney and liver transplant rejection, everolimus is indicated in advanced renal cell cancer, hormone receptor positive, but HER-2 negative advanced breast cancer and pancreatic neuroendocrine tumours.

Dose: For preventing transplant rejection: 0.5–1 mg BD. For cancer therapy: 5–10 mg daily.

CERTICAN 0.25 mg, 0.5 mg, 0.75 mg tab

AFINITOR, EVERTOR 5 mg, 10 mg tab.

Temsirolimus This ester analogue of sirolimus is converted in the body to sirolimus, and acts as a mTOR inhibitor. It is metabolised by CYP3A4 with a t½ of 30 hrs, while its major active matabolite sirolimus has a t½ of 60 hours. Temsirolimus is approved for use in advanced renal cell carcinoma and in refractory mantle cell lymphoma.

Dose: 25 mg i.v. weekly.

TORISEL 25 mg/vial inj.

ANTIPROLIFERATIVE DRUGS
(Cytotoxic immunosuppressants)

Certain cytotoxic drugs used in cancer chemotherapy exhibit prominent immunosuppressant property, mainly by preventing clonal expansion of T and B lymphocytes (*see* Fig. 65.1).

Azathioprine (*see* p. 922) It is a purine antimetabolite which has more marked immunosuppressant than antitumour action. The basis for this difference is not clear, but may be due to its selective uptake into immune cells and intracellular conversion to the active metabolite 6-mercaptopurine, which then undergoes further transformations to inhibit *de novo* purine synthesis and damage to DNA. Azathioprine selectively affects differentiation and function of T cells and inhibits cytolytic lymphocytes; CMI is primarily depressed.

The most important application of azathioprine is prevention of renal and other graft rejection, but it is less effective than cyclosporine; generally combined with it or used in patients developing cyclosporine toxicity. Relatively lower doses (1–2 mg/kg/day) are used in progressive rheumatoid arthritis (*see* p. 228), and it is frequently employed for maintening remission in inflammatory bowel disease (*see* p. 736). Recently, azathioprine has been found effective for restoring near-normal pigmentation in patients with *vitiligo*, and may be usefully administered orally along with a topical corticosteroid. It may be an alternative drug to long-term steroids in some other autoimmune diseases as well.

Methotrexate (Mtx. *see* p. 921) This folate antagonist is a potent immunosuppressant which markedly depresses cytokine production and cellular immunity. Mtx has antiinflammatory property as well. It has been used as a first line drug in many autoimmune diseases like rapidly progressing rheumatoid arthritis (*see* p. 228), severe psoriasis, pemphigus, myasthenia gravis, uveitis, chronic active hepatitis. Low dose Mtx maintenance therapy is relatively well tolerated.

Cyclophosphamide (*see* p. 918–19) This cytotoxic drug has more marked effect on B cells and humoral immunity compared to that on T cells and CMI. It has been particularly utilized in bone marrow transplantation in which a short course of high dose is generally given. In other organ transplants it is employed only as a reserve drug. In rheumatoid arthritis, it is rarely used, only when systemic manifestations of the disease are marked. Low doses are occasionally employed for maintenance therapy in pemphigus, systemic lupus erythematosus and idiopathic thrombocytopenic purpura.

Mycophenolate mofetil (MMF) This immunosuppressant is a prodrug of mycophenolic acid which selectively inhibits *inosine monophosphate dehydrogenase*, an enzyme essential for *de novo* synthesis of guanosine nucleotides in the T and B cells (these cells, unlike others, do not have the purine salvage pathway). Lymphocyte proliferation, antibody production and CMI are inhibited. As 'add on' drug to cyclosporine + glucocorticoid in renal transplantation, it has been found as good or even superior to azathioprine, but should not be combined with azathioprine. It can help to reduce the dose of cyclosporine and thus its toxicity. MMF + glucocorticoid + sirolimus is a non-nephrotoxic combination that is utilized in patients developing renal toxicity with cyclosporine/tacrolimus. MMF is rapidly absorbed orally and quickly converted to the active metabolite mycophenolic acid. This is then slowly inactivated by glucuronidation with a t½ of ~ 16 hours. The glucuronide is excreted in urine. Vomiting, diarrhoea, leucopenia and predisposition to CMV infection, g.i. bleeds are the prominent adverse effects.

Dose: 1.0 g BD oral; CELLMUNE, MYCEPT, MYCOPHEN 250, 500 mg tab/cap.

Glucocorticoids (*see* Ch. 20)

Glucocorticoids have potent immunosuppressant and antiinflammatory action. They inhibit several components of the immune response

(*see* p. 310–11). They particularly inhibit MHC expression (Fig. 65.1) and activation/proliferation of T lymphocytes. Expression of several IL and other cytokine genes is regulated by corticosteroids and production of adhesion molecules is depressed. The short-lived rapid lymphopenic effect of steroids is due to sequestration of lymphocytes in tissues. Accordingly, they have marked effect on CMI but little effect on humoral immunity.

The corticosteroids are widely employed as companion drug to cyclosporine or other immunosuppressants in various organ transplants. Glucocorticoids are the most effective drugs for the treatment of graft *vs* host reaction. In case graft rejection sets in—large doses of corticoids i.v. are employed for short periods. They are used in practically all cases of severe autoimmune diseases, especially during exacerbation. Long-term complications are the greatest limitations of steroid use; and it is maintenance of remission for which other immunosuppressants often prove safer.

BIOLOGICAL AGENTS

These are biotechnologically produced recombinant proteins or polyclonal/monoclonal antibodies directed to cytokines or lymphocyte surface antigens which play a key role in immune response. They are important recent additions, mostly as supplementary or reserve drugs for severe and refractory cases of autoimmune diseases and graft versus host reaction.

TNFα inhibitors

TNFα is secreted by activated macrophages and other immune cells to act on TNF receptors ($TNFR_1$, $TNFR_2$) which are located on the surface of neutrophils, fibroblasts, endothelial cells as well as found in free soluble form in serum and serous fluids. TNFα amplifies immune inflammation by releasing other cytokines and enzymes like collagenases and metalloproteinases. The TNFα inhibitors are mainly used in autoimmune diseases, and are briefly described with disease modifying drugs for rheumatoid arthritis in Ch.15.

Etanercept This fusion protein of human TNF receptor and Fc portion of human IgG_1 neutralizes both TNFα and TNFβ. It prevents activation of macrophages and T-cells during immune reaction. It is used mostly in combination with Mtx in rheumatoid arthritis patients who fail to respond adequately to the latter alone (*see* p. 230). Etanercept is also approved for severe/refractory ankylosing spondylitis, polyarticular idiopathic juvenile arthritis and plaque psoriasis.

Infliximab It is chimeral monoclonal antibody against TNFα which binds and inactivates TNFα. Used by i.v. infusion every 4–8 weeks along with Mtx and other conventional therapy, it has proven useful in refractory rheumatoid arthritis, fistulating Crohn's disease, ulcerative colitis, psoriasis and ankylosing spondylitis.

Adalimumab It is fully human recombinant anti-TNFα antibody indicated in the same range of autoimmune diseases as infliximab, and like the latter, does not bind TNFβ, but is less antigenic. It can be added to Mtx or other conventional drugs for additional benefit.

IL-1 receptor antagonist

Stimulated macrophages and other mononuclear cells elaborate IL-1 which activates helper T-cells and induces production of other ILs, metalloproteinases, etc. An endogenous IL-1 receptor antagonist has been isolated and several of its recombinant variants have been produced for clinical use.

Anakinra This recombinant human IL-1 receptor antagonist prevents IL-1 binding to its receptor and has been approved for use in refractory rheumatoid arthritis (*see* p. 230) not controlled by conventional DMARDs. Anakinra along with continued Mtx has been used alone as well as added to TNFα antagonists, because its clinical efficacy as monotherapy is lower.

IL-2 receptor antagonist

The CD-25 molecule is expressed on the surface of immunologically activated, but not resting T-cells. The CD-25 acts as a high affinity receptor for IL-2 through which cell proliferation and differentiation are promoted. Some anti CD-25 antibodies have been developed as IL-2 receptor antagonist to specifically arrest the activated T-cells.

Daclizumab It is a highly humanized chimeric monoclonal anti CD-25 antibody which binds to and acts as IL-2 receptor antagonist. Combined with glucocorticoids, calcineurin antagonists and/or azathioprine/MMF, it is used to prevent renal and other transplant rejection reaction. The plasma t½ of daclizumab is long (3 weeks), and it has also been used in combination regimens for maintenance of graft.

Basiliximab This is another anti CD-25 antibody with higher affinity for the IL-2 receptor, but shorter plasma t½ (1 week). Clinical use of basiliximab is similar to that of daclizumab.

Dose: 20 mg i.v.

SIMULECT (Basiliximab) 20 mg/vial inj.

Both daclizumab and basiliximab can cause anaphylactic reactions and promote opportunistic infection. Peripheral edema, fever, headache, dyspnoea are the side effects.

Anti-CD3 antibody

Muromonab CD3 It is a murine monoclonal antibody against the CD3 glycoprotein expressed near to the T cell receptor on helper T cells (*see* Fig. 65.2). Binding of muromonab CD3 to the CD3 antigen obstructs approach of the MHCII-antigen complex to the T-cell receptor. Consequently, antigen recognition is interfered, and participation of T-cells in the immune response is prevented. Following antibody binding, the T-cell receptor is internalized and the T-cells get rapidly depleted from blood, partly by cytolysis and partly by their migration to non-lymphoid organs. An immune blocked state results.

Muromonab CD3 is the oldest (developed in the 1980s) monoclonal antibody that is still occasionally used clinically, though newer humanized anti CD3 monoclonal antibodies have been produced which are less antigenic. Muromonab CD3 is now primarily used for acute transplant rejection reaction, particularly in steroid-resistant cases. Daily i.v. injection of muromonab CD3 is given for 2 weeks along with corticosteroids and other immunosuppressants. Subsequent courses are not recommended, because the first course produces antibodies against mouse protein which neutralise it. Use of muromonab CD3 for induction therapy of organ transplantation is infrequent now, since better alternatives are available. It has also been used to deplete T cells from the donor bone marrow before transplantation.

Initial doses of muromonab CD3 are associated with 'cytokine release syndrome' with flu-like symptoms, *viz.* chills, rigor, high fever, wheezing, malaise, etc. which is due to release of TNFα, ILs and interferon. The symptoms decrease in severity with subsequent doses. High-dose corticosteroid pretreatment attenuates the reaction, and is a part of the usual protocol while administering muromonab CD3.

Polyclonal antibodies

Antithymocyte globulin (ATG) It is a polyclonal antibody purified from horse or rabbit immunized with human thymic lymphocytes which contains antibodies against many CD antigens as well as HLA antigens. It binds to T lymphocytes and depletes them by complement dependent as well as cell mediated cytotoxicity. It also interferes with lymphocyte function. ATG is a potent immunosuppressant and has been used primarily to suppress acute allograft rejection episodes, especially in steroid-resistant cases. It is mostly combined with other immunosuppressants, including steroids. It can also be used in induction regimens, but this has the potential to produce serum sickness or anaphylaxis.

LYMPHOGLOBULIN (equine) 100 mg/vial inj.; 10 mg/kg/day i.v.;
THYMOGLOBULIN (rabbit) 25 mg/vial inj.; 1.5 mg/kg/day.
ATG 100 mg inj; 200 mg i.v./day.

Anti-D immune globulin It is human IgG having a high titer of antibodies against Rh (D) antigen. It binds the Rho antigens and does not allow them to induce antibody formation in Rh negative individuals. It is used for prevention of postpartum/post-abortion formation of antibodies in Rho-D negative, DU negative women who have delivered or aborted a Rho-D positive, DU positive baby/foetus. Administered within 72 hours of delivery/abortion, such treatment prevents Rh haemolytic disease in future offspring. It has also been given at 28th week of pregnancy to prevent neonatal haemolytic jaundice due to Rh incompatibility between mother and the baby.

Dose: 250–350 µg i.m. of freez dried preparation.
RHESUMAN, RHOGAM, IMOGAM 300 µg per vial/prefilled syringe.

Higher doses (1000–2000 µg) are needed for Rh negative recipients of inadvertantly administered Rh positive blood. It should never be given to the infant or to Rho-D positive, DU positive individuals.

IMMUNOSUPPRESSION IN ORGAN TRANSPLANTATION

Use of immunosuppressants is essential for successful organ transplantation. In general 3 types of regimens are used depending upon the stage of transplantation.

1. *Induction regimen* This is given in the perioperative period: starting just before the transplant to about 2–12 weeks after it. Accelerated rejection develops in the first week, while acute rejections are most likely from 2–12 weeks. The most common regimens include triple therapy with cyclosporine/tacrolimus/sirolimus + prednisolone + MMF/azathioprine. Use of 3 drugs which target different steps of the immune response permits reduction of dose, and thus toxicity of each component. The sirolimus + prednisolone +

MMF combination avoids risk of renal toxicity. Two drug and single drug regimens are also used, but intensive induction regimens improve chances of graft survival, and may need lower dose maintenance regimens. Many experts do not give cyclosporine/tacrolimus preoperatively, and try to delay its induction as far as possible to avoid nephrotoxicity, particularly in renal transplantation. The newer biological agents are being increasingly used in induction regimens. If no rejection develops, the doses are gradually reduced after 2 weeks and this phase merges imperceptably with the maintenance phase.

2. *Maintenance regimen* This is given for prolonged periods, may be life-long. Triple drug regimen consisting of maintenance doses of any three of the following choices—cyclosporine/tacrolimus, sirolimus, prednisolone, azathioprine/MMF are generally favoured, because each component is needed in lower doses—reduces toxicity and cost. Nephrotoxicity is often the limiting factor with cyclosporine/tacrolimus, while long-term steroid therapy has its own problems. The component which produces toxicity in a given patient is curtailed or dropped. Two drug and one drug regimens are also used, but are associated with more episodes of acute rejection. After 1 year, cyclosporine is generally dropped, but its continuation is associated with fewer acute rejections. In case of intolerance to the first line drugs *viz.* cyclosporine, tacrolimus, sirolimus, MMF, azathioprine and prednisolone, the second line drugs like cyclophosphamide, chlorambucil or daclizumab/basiliximab are substituted.

3. *Antirejection regimen* This is given to suppress an episode of acute rejection. Steroid pulse therapy (methylprednisolone 0.5–1 g i.v. daily for 3–5 days) is effective in majority of cases. In case of no response, muromonab CD3/ATG is given as rescue therapy or the antibodies are combined with the steroid. Tacrolimus, sirolimus, MMF have also been used in rescue therapy of steroid resistant rejection. If the maintenance regimen had not included cyclosporine, its addition can treat acute rejection, but can be damaging to the transplanted kidney.

Adverse effects The two general untoward effects of immunosuppressant therapy are:

(a) Increased risk of bacterial, fungal, viral (especially CMV) as well as opportunistic infections.

(b) Development of lymphomas and related malignancies after a long latency due to weakening of immunological surveillance against neoplasia.

Chapter 66 Drugs Acting on Skin and Mucous Membranes

A variety of drugs applied topically to the skin or mucous membranes produce therapeutic effects localized to the site of application. They act primarily by virtue of their physical/mechanical/chemical/biological attributes and may be divided into several categories designated by the most prominent action.

DEMULCENTS

Demulcents are inert substances which sooth inflamed or denuded mucosa or skin by preventing contact with air/irritants in the surroundings. They are, in general, high molecular weight substances and are applied as thick colloidal/viscid solutions in water. Some, like *gum acacia, gum tragacanth* produce foam with water, reduce surface tension and act as suspending/emulsifying agents.

Glycyrrhiza is a sweet tasting root (liquorice); used in cough lozenges to sooth the throat and as sweetening/flavouring agent in mixtures. It contains a glycoside *glycyrrhizin* which has steroid like salt retaining action when taken orally.

Methylcellulose It is a synthetic cellulose derivative used as bulk purgative, in nose drops and contact lens solutions.

CADILOSE 0.5% drops in 10 ml bottle.

Propylene glycol is a clear, viscous liquid, miscible with water as well as some oils, and is used in cosmetics and as occlusive dressing for ichthyosis, etc.

Glycerine is a clear, sweet, viscous liquid. Undiluted glycerine has dehydrating property—produces a warm sensation and irritates mucous membranes. Applied to anal canal as suppository it induces evacuation. Applied to dry skin and cracked lips (50% in water) it acts as emollient and is a popular vehicle for gum/throat paints. It is also used orally/per rectum (50–75%) or intravenously (10%) to reduce intraocular/intracranial tension.

EMOLLIENTS

Emollients are bland oily substances which sooth and soften skin. They form an occlusive film over the skin, preventing evaporation, thus restoring elasticity of cracked and dry skin. Olive oil, arachis oil, sesame oil, cocoa butter, hard and soft paraffin, liquid paraffin, wool fat, bees wax and spermaceti are the commonly employed emollients. They are also used as vehicles for topically applied medicaments and as ointment bases.

Wool fat may cause allergy in some patients.

ADSORBANTS AND PROTECTIVES

Adsorbants are finely powdered, inert and insoluble solids capable of binding to their surface (adsorbing) noxious and irritant substances. They are also called protectives because they afford physical protection to the skin or mucosa. Other protectives form a continuous, adherent and flexible occlusive coating on the skin. Demulcents and emollients also serve as protectives.

Magnesium/zinc stearate Their particles have very smooth surface—prevent friction, and are not water wettable. They can be used on exuding surfaces, because they allow evaporation of water and do not form a crust.

Talc It is native hydrous magnesium silicate, which spreads easily—used in talcum/face powders. Entering raw surfaces, it can form granulomas—should not be sprinkled on wound or used for surgical gloves.

Calamine It is native zinc carbonate tinted pink with ferric oxide. Calcined calamine is zinc oxide. It has mild astringent and antiseptic action and is a good soothing and protective agent. Used in calamine lotion along with zinc oxide and bentonite (native hydrated aluminium silicate) which have similar properties, as cosmetic, on sunburn, insect bite, urticaria and contact dermatitis.

CALACREME 5% cream, CALAMINOL 5% and CALAMYL 10% emulsion, CALAK 15% with zinc oxide 5%, bentonite 3% sodium citrate 0.5%, glycerol 5% (calamine lotion).

Starch It is used in dusting powders and for surgical gloves, but should not be used on exuding surfaces because it absorbs moisture, crusts on drying and encourages fermentation.

Boric acid It is a smooth and fine powder; has mild antiseptic (*see* Ch. 67), antipruritic and deodorant actions, and is a common ingredient of prickly heat powders.

Aloe vera gel It is a mucilaginous preparation from the fleshy leaves of *Aloe vera* plant with soothing and moisturising property, widely included in cosmetic and skin care products. Therapeutic claims in acne, psoriasis and many other conditions have been made.

ALOVIT: Aloe extract 10% + vit E 0.5% cream.

Polyvinyl polymer When allowed to dry, its solution forms an occlusive pellicle-like coating on abraded skin. Used as a spray on abrasions and minor cuts, it protects from dust and exposure.

HEALEX SPRAY, Polyvinyl polymer: 2.5% + benzocaine 0.36% as aerosol wound dressing.

Feracrylum It is a water-soluble biodegradable polymer which forms gel-like complexes on coming in contact with blood. Applied to fresh abrasions, it stops oozing of blood and protects the wound by acting as a physical barrier. A mild antiseptic action is also exerted.

SEPGARD GEL: 1% gel, to be applied as a thin film on the abrasion/wound; 3% gel for postoperative cuts and wounds.

Dimethicone (Dimethyl polysiloxane, Simethicone) It is a silicone polymer—a viscous, amphiphilic liquid, that is pharmacologically inert, nonirritating and has water repellent and surface tension reducing properties (collapses froth). Applied to the skin, it adheres and protects it. The specific use of dimethicone is to prevent maceration and excoriation of skin due to soiling with urine (suprapubic cystostomy). Also used on bedsores, ulcers and burns.

BARRIER-SF: Dimethiocone 15%, vit E 0.18% cream.

Sucralfate (topical) This aluminium salt of sulfated sucrose used primarily as peptic ulcer protective (*see* p. 704), has been formulated as a topical gel. Applied on burns, bedsores, diabetic/radiation/aphthous ulcers, excoriated skin, sores, etc. It adheres and serves to protect damaged tissue—facilitates healing.

PEPSIGARD LIGHT GEL 10% gel; to be applied on the ulcer 3-4 times a day.

ASTRINGENTS

Astringents are substances that precipitate proteins, but do not penetrate cells, thus affecting the superficial layer only. They toughen the surface making it mechanically stronger and decrease exudation. Drugs are:

Tannic acid and tannins Tannic acid is present in many plants but is generally obtained from nutgalls of oak. Tannins are found in tea, catechu, nutmeg, areca nut (betel nut), etc. They denature proteins forming protein tannate. Uses are:

Bleeding gums—as glycerine of tannic acid.

Bleeding piles—as tannic acid suppository.

Alkaloidal poisoning—precipitates ingested alkaloids as tannates.

(Its use on burns has been abandoned because it forms a crust under which bacteria could grow. Sufficient systemic absorption often occurred to cause centrilobular necrosis of the liver.)

Alcohol Ethanol and methanol are good astringents at 50–90% concentration. Denatured spirit rubbed on the skin prevents bedsores, but should not be applied on the sores once these have formed, as it is highly irritating to raw surfaces. Ethanol is also used as after-shave and on minor cuts.

Mineral astringents Heavy metal ions are astringent and antiseptic. Alum has been used as after-shave and as local haemostatic on minor cuts. Other salts of aluminium, zinc and zirconium are used as antiperspirants. They diffuse through the sweat ducts, reduce secretion from glands and partially block the ducts as well. Their antibacterial action prevents decomposition of sweat by bacteria, reducing body odour.

IRRITANTS AND COUNTER-IRRITANTS

Irritants stimulate sensory nerve endings and induce inflammation at the site of application.

Depending on their nature, concentration and sensitiveness of the site, they produce cooling sensation or warmth, pricking and tingling, hyperaesthesia or numbness and local vasodilatation. Irritants which cause local hyperemia with little sensory component are called *Rubefacients*. Stronger irritants which in addition increase capillary permeability and cause collection of fluid under the epidermis (forming raised vesicles) are termed *Vesicants*. Certain irritants that also produce a remote effect which tends to relieve pain and inflammation in deeper organs are called *Counter-irritants*.

Mechanism of counterirritation Cutaneous sensations are precisely localized. Deeper sensations from muscles, joints and viscera are perceived more diffusely. A spinal segment, receiving afferent impulses from the surface as well as from deeper organs, modulates them—preferentially conducting the former to the higher centers. When a counter-irritant is applied to the area of skin supplied by nerves from the same segment as the deeper organ from which pain impulses are coming, the cutaneous impulses obscure the deeper sensation.

Irritation of afferent nerve endings produces arteriolar dilatation in the adjoining areas of skin by axon reflex (which mediates flare in triple response). Through segmental association of afferents, vasodilatation also occurs in the corresponding deeper organ. Increased blood supply helps to fight the cause of pain and inflammation in the deeper organ.

Counterirritants are generally rubbed to relieve headache, muscular pain (torticollis, backache, sprain), joint pain, pleural/peritoneal pain, colics, etc. Drugs are:

Volatile oils (essential oils) These are terpene hydrocarbons of plant origin having a characteristic odour. They have variable properties, but all are irritants. Stearoptenes are solid volatile oils.

Turpentine oil Obtained by distilling *Pinus* oleoresin and used as counterirritant in the form of liniment or 'stupes'.

Clove oil Applied by cotton swab for toothache.

Eucalyptus oil Used in pain balms.

Camphor It is obtained from the bark of *Cinnamomum camphora* or produced synthetically. Camphor produces cooling sensation on skin and is mildly anaesthetic—relieves itching. It is added in liniments and pain balms. Taken internally—small doses produce a warm and comforting sensation in epigastrium; larger doses are emetic. Systemically it produces excitement and convulsions (especially in children).

Thymol Obtained from *Thymus vulgaris*, it has a pungent taste. It is included in pain balms.

Menthol From mint or prepared synthetically, has cooling and soothing action. It is added to pain balms, throat paints, throat lozenges and inhalers for relief of nasal congestion. It is also a carminative.

Mustard seeds It contains a glycoside *sinigrin* and an enzyme *myrosin*. When ground seeds are soaked in water, myrosin hydrolyses sinigrin to release *allyl isothiocyanate* which is a strong irritant. Mustard plaster has been used as rubefacient and counterirritant. As a suspension in water 4–8 g of ground seeds are emetic.

Capsicum (Chillies) It is a powerful irritant, hot in taste. The active principle is *capsaicin*. It is a popular condiment in Indian cooking, and is included in some counterirritant preparations. After initial stimulation, capsaicin depletes afferent nerve endings of the transmitter substance P, and may relieve post-herpetic neuralgia on local application.

Canthridin It is a crystalline solid obtained from Spanish fly. Canthridin is a strong irritant, higher concentrations damage the epithelium and cause vesication. It has been used to remove warts, etc. Added to hair tonics, it is claimed to increase vascularity of scalp and promote hair growth.

Methyl salicylate (oil of wintergreen) In contrast to other salicylates, it is not used internally (induces vomiting, gastritis and systemic toxicity). It is combined with other irritants in liniments and ointments for muscle and joint pain.

Alcohol Produces rubefaction when rubbed on skin and is a vehicle for liniments.

Some counterirritant combinations

ALGIPAN: Capsicum oleoresin 0.1%, histamine 0.1%, methyl nicotinate 1%, glycol salicylate 5% cream.

ARJET SPRAY: Methyl salicylate 875 mg, menthol 1.6 g, camphor 1.5 g, benzyl nicotinate 20 mg, squalance 250 mg, glycol salicylate 875 mg per 50 ml spray.

RELISPRAY: Winter green oil 20%, clove oil 1%, menthol 4%,

nilgiri oil 6%, camphor 10%, cinnamon oil 0.5%, turpentine oil 10% spray.
EUTHERIA: Eucalyptol 7.2%, menthol 4.7%, methylsalicylate 11.25% balm.
MEDICREME: Methylsalicylate 8%, menthol 2%, adrenaline 0.03%, mephenesin 2.5%, chlorpheniramine 0.2%, cream.
RELAXYL: Capsicum oleoresin 0.05%, mephenesin 10% methyl nicotinate 1% ointment.
VICKS VAPORUB: Menthol 2.8%, camphor 5.25%, thymol 0.1% turpentine oil 5.5% ointment.
IODEX: Methylsalicylate 5%, iodine 4% nonstaining ointment.
AMRUTANJAN: Eucalyptus oil 17%, camphor 10%, thymol 1%, menthol 4.5%, methylsalicylate 7% ointment.
CAPSIGYL-D: Capsaicin 0.075%, methyl salicylate 20%, menthol 10%, camphor 5%, eucalyptus oil 5%, diclofenac 1% gel.

CAUSTICS AND ESCHAROTICS

Caustic means corrosive and *Escharotic* means cauterizer. These chemicals cause local tissue destruction and sloughing. An escharotic, in addition, precipitates proteins that exude to form a scab—gets fibrosed to form a tough scar. They are used to remove moles, warts (including genital warts) condylomata, papillomas and on keratotic lesions. Care is needed in their application to avoid ulceration. It is believed that all microorganisms are killed during cauterization, but this is not always so.

Podophyllum resin It is used as 10–25% alcoholic solution or suspension in mineral oil.

PODOWART 20% paint; CONDYLINE 0.5% podophyllotoxin soln.

Silver nitrate It is used in the form of toughened silver nitrate sticks or pencils.

Phenol It is carefully touched on the lesion as 80% w/w solution.

Trichloroacetic acid As crystals or 10–20% solution it is used to cauterise adenoids; dilute solution is used to promote peeling of frackled skin.

Glacial acetic acid Undiluted can cause peeling of skin.

KERATOLYTICS

Keratolytics dissolve the intercellular substance in the horny layer of skin. The epidermal cells swell, soften and then desquamate. These drugs are used on hyperkeratotic lesions like corns, warts, psoriasis, chronic dermatitis, ringworm, athletes foot, etc.

Salicylic acid It is used as 10–20% solution in alcohol or propylene glycol for dissolving corns. It is more effective when applied under occlusive dressing. *Propylene glycol* is hygroscopic. Applied under polyethylene occlusive dressing, it causes maceration of skin and acts as a keratolytic, supplementing the action of salicylic acid.

CORNAC 16.5% liquid, CORN CAP 40% oint in adhesive tape; SALACTIN: Salicyclic acid 16.7% + lactic acid 16.7% in flexible collodion paint (for corn).

Lower concentrations (3–5%) are used in other conditions, e.g. in Whitfield's ointment.

RINGCUTTER 3% ointment with 5% benzoic acid.

It is also mildly antiseptic and antifungal.

Resorcinol Has antiseptic, antifungal, local irritant and keratolytic properties; 3–10% is used in eczema, seborrheic dermatitis, ringworm, etc.

Urea Applied at a concentration of 5–20% in cream/ointment base, urea acts as a humectant by its hygroscopic and water retaining property. It causes softening and solubilization of keratin, facilitating its removal from hyperkeratinized lesions like ichthyosis, lichen planus. Inclusion of urea enhances the penetration of the concurrently applied topical steroid.

ANTI-SEBORRHEICS

These are drugs effective in seborrheic dermatitis which affects areas rich in sebaceous glands (scalp, face, trunk) and is characterized by erythematous, scaling lesions. Dandruff is the commonest complaint. A causal role of the yeast *Pityrosporum ovale* has been shown, but various trigger factors like change in quantity and composition of sebum, increase in alkalinity of skin (due to increased sweating), external local factors, emotional stress, genetic predisposition appear to be needed to transform the yeast from a commensal to a noninvasive pathogenic organism. Drugs used are:

Selenium sulfide Applied to the scalp as a 2.5% lotion or shampoo, it slows epidermal proliferation and scaling. It is also antikeratolytic and fungicidal to *P. ovale*. Dryness, folliculitis and dandruff are benefited, but > 50% patients relapse on discontinuation. Systemic absorption and toxicity can occur if it is applied to inflamed or damaged skin. Some individuals develop sensitivity reactions.

SELSUN 2.5% susp., SELDRUFF PLUS 2.5% susp. with clotrimazole 1%.

Zinc pyrithione It reduces epidermal turnover and inhibits *P. ovale*. Weekly shampoo (1%)

reduces dandruff, but symptoms do not resolve completely.

It is often combined with ketoconazole.

SCALPE: Zinc pyrithione 1%, Ketoconazole 2% shampoo.

Corticosteroids Massaged in the scalp as a lotion, topical steroids are highly effective in relieving symptoms of seborrheic dermatitis including dandruff. Pityrosporal yeasts are reduced in the affected skin. However, relapse rates are high on discontinuation and prolonged use can produce adverse effects like atrophy, poor healing, purpura, etc.

Imidazole antifungals Among several of these compounds, ketoconazole (KTZ) was found to be the most effective against *P. ovale*. Orally (200 mg/day for 4 weeks) it has been found to improve seborrhoea. But because this is often a chronic relapsing condition and prolonged oral KTZ therapy is considered unwarranted, KTZ has been formulated into 2% cream/shampoo/scalp gel. Good to excellent results have been obtained with these preparations without skin irritation, contact sensitivity, phototoxicity or systemic adverse effects.

KETOVATE, NIZRAL, OCONA 2% cream, 2% shampoo.

Clotrimazole 1% solution may be used in its place.

Sulfur, Resorcinol, Coaltar, Ammoniated mercury These drugs are mildly effective. They have minimal antiyeast action: may benefit seborrhoea by keratolytic and antiseptic properties.

Salicylic acid It is keratolytic, has mild effect in seborrhoea, probably by removing the scales and by improving penetration of other drugs.

MELANIZING AGENTS

Melanizing agents are drugs that increase sensitivity to solar radiation and promote repigmentation of vitiliginous areas of skin. Psoralens are furocoumarins which on photoactivation stimulate melanocytes and induce their proliferation.

Psoralen It is obtained from fruit of *Ammi majus*.

MANADERM 10 mg tablet, 1% ointment, PSORLINE 5 mg tablet, 0.25% solution and ointment.

Methoxsalen (MACSORALEN 10 mg tab, 1% solution, MALANOCYL 10 mg tab, 0.75% soln.) and *Trioxsalen* (NEOSORALEN 5 mg, 25 mg tablets and 0.2% lotion) are synthetic psoralens.

These agents sensitize the skin to sunlight which then induces erythema, inflammation and pigmentation. They are applied topically as well as given orally. Methoxsalen is absorbed better, undergoes less first pass metabolism and is more effective than trioxsalen. Their plasma t½ is short (~ 1 hr); sensitization of skin is maximal at 1–2 hours, but lasts for 8 hours or more.

Topical therapy The solution/ointment is carefully painted on the small well defined vitiliginous lesion—which is then exposed to sunlight for 1 minute and then occluded by bandage or sun screen ointment. Weekly treatment with longer exposures is given. Pigmentation usually begins to appear after a few weeks; months are needed for satisfactory results. Then periodic maintenance treatment may be needed. This therapy should be undertaken only under direct supervision of physician because longer exposure causes burning and blistering.

Oral therapy On alternate days after 2 hours of a 0.3–0.6 mg/kg (usually 20 mg) oral dose of a psoralen, skin is exposed to sunlight (or artificial UV light), initially for 15 minutes—gradually increasing to 30 minutes over days. Eyes, lips and other normally pigmented areas should be protected during exposure to sunlight.

DRUGS FOR PSORIASIS

Psoriasis is an immunological disorder manifesting as localized or widespread erythematous scaling lesions or plaques. There is excessive epidermal proliferation attended by dermal inflammation. Periodic flareups are common. Drugs can diminish the lesions, but cannot cure the disease. Therapy has to be prolonged and adjusted to the body surface area involved as well as to the severity of disease. Topically applied emollients, keratolytics, antifungals afford variable symptomatic relief, but *topical corticosteroids* are the primary drugs used. They are very effective in mild-to-moderate disease, and initially even in severe cases. Most patients respond within 3 weeks, and the response may be hastened by applying the steroid under occlusion. Therapy is started with a high potency steroid which is substituted after improvement by either weekly application or by a milder preparation. However, topical steroids carry their

own local and systemic adverse effects, and lesions may progressively become refractory. Systemic therapy with corticosteroids and/or immunosuppressants is reserved for severe and refractory cases. Other topically used drugs are:

Calcipotriol It is a synthetic nonhypercalcaemic vit D analogue effective topically in plaque type psoriasis. Calcipotriol binds to the intracellular vit D receptor in epidermal keratinocytes and suppresses their proliferation while enhancing differentiation. On absorption through the skin, it is inactivated rapidly by metabolism so that little systemic effect on calcium metabolism is exerted. Benefit in psoriasis is slow; but most cases respond in 4–8 weeks. Response is maintained till treatment is continued. Efficacy of calcipotriol in psoriasis is rated comparable to a moderate potency topical steroid. Combination with a steroid is more effective than either drug alone. Side effects are skin irritation, erythema and scaling. Hypercalcaemia is rare. It is a safe and effective alternative to steroids, but expensive.
DAIVONEX 0.005% oint; apply over psoriatic lesions twice daily.

Tazarotene This synthetic retinoid applied as a topical gel (0.05–0.1%) is moderately effective in psoriasis. It is a prodrug which is hydrolysed in the skin to tezarotenic acid that exerts antiproliferative and antiinflammatory action by binding to the intracellular retinoic acid receptor and modification of gene function. Combination with a topical steroid/calcipotriol may benefit refractory cases. Skin irritation, burning sensation, peeling are common. These side effects can be minimized by careful application to the plaques only. It is teratogenic.
LATEZ 0.05%, 0.1% gel; TAZRET 0.05% gel, 0.1% cream; 0.05–0.1% application once daily in the evening.

Coaltar This crude preparation containing many phenolic compounds exerts a phototoxic action on the skin when exposed to light, especially UVA, and retards epidermal turnover. Applied as ointment or alcoholic solution on psoriatic plaques (generally with salicylic acid) and exposed to sunlight daily, it induces resolution of psoriatic lesions in majority of cases, but relapses are common. Use of coaltor has declined now because of strong smell, cosmetic unacceptability, skin irritation, allergy, and potential for photosensitivity and carcinogenicity.
EXETAR: coaltar 6%, salicylic acid 3%, sulfur ppt. 3%, oint. TARSYL: coaltar 1%, salicylic acid 3% lotion. IONAX-T: coaltar 4.25%, salicylic acid 2% scalp lotion.

Photochemotherapy (PUVA: Psoralen ultraviolet A) Photoactivated psoralen undergoes O_2 independent as well as O_2 dependent reactions and binds to pyrimidine bases, which interfere with DNA synthesis and epithelial cell turnover. PUVA therapy has produced gratifying results in severely debilitating psoriasis, but relapses occur when treatment is stopped. Oral methoxasalen is followed 1–2 hours later by UVA exposure on alternate days. However, there are serious concerns regarding potential of PUVA to cause skin cancer, cataracts and immunological damage. Being inconvenient and carrying risks, it is reserved for severe cases or extensive surface area of psoriasis only.

Psoralens have also been used to accelerate tanning—a maximum of 2 weeks treatment has been advised for this purpose. Other applications of PUVA are in lichen planus, urticaria pigmentosa, atopic dermatitis and cutaneous T cell lymphoma.

Adverse effects: Mottling, erythema, burns, blistering, premature ageing of skin, gastric discomfort, nervousness and insomnia.

Acitretin It is a synthetic retinoid for oral use in psoriasis, lichen planus, severe ichthyosis, etc. Acitretin acts by binding to 'retinoic acid receptor' in epidermal cells and regulating their proliferation and maturation. Inflammation is suppressed. Because of frequent and potentially serious adverse effects, use of acitretin is restricted to recalcitrant, pustular and other forms of severe psoriasis. Combination with topical antipsoriatic drugs is advised.
Dose: 0.5–0.75 mg/kg/day oral;
ACITRIN, ACETEC, ACERET 10, 25 mg tab.

Dryness of skin and eyes, gingivitis, erythema and scaling of skin, alopecia, arthralgia, myalgia, lipid abnormalities and liver damage are the important adverse effects. Elimination of acitretin is very slow (taking months) because of accumulation in body fat. It is highly teratogenic. Women taking acitretin must not conceive during and till 3 years after stopping it. Drinking alcohol should be prohibited during and till 3 months after acitretin use.

Etanercept, Infliximab These are TNFα inhibitor immunosuppressive drugs, also used in psoriasis. They are described in Ch. 15 and Ch. 65.

DEMELANIZING AGENTS

These drugs lighten hyperpigmented patches on skin.

Hydroquinone It is a weak hypopigmenting agent. It inhibits tyrosinase and other melanin forming enzymes, decreases formation of and increases degradation of melanosomes. Regular application (as 2–6% lotion or cream) for months is required in melasma, chloasma of pregnancy, etc. The response is often incomplete and pigmentation may recur when it is discontinued, especially if exposed to sunlight; sunscreens are frequently combined with hydroquinone. Skin irritation, rashes and allergy are possible. Care is to be taken to avoid its entry in eyes.
EUKROMA 4% cream, MELALITE: Hydroquinone 2% with glycerylester of PABA 2.8% cream. BRITE: hydroquinone 4%, glyceryl PABA 2.8% cream.

Monobenzone This derivative of hydroquinone is a potent demelanizing agent—destroys melanocytes and may cause permanent depigmentation. Full effect takes 4–6 months; treated areas should be protected from sunlight by a sunscreen. Its bleaching action is somewhat irregular: ugly depigmented patches can appear. Erythema and eczema may also result. Therefore, its use should be restricted to post-inflammatory melasma; 5% lotion or 20% ointment is applied 2–3 times daily.
BENOQUIN 20% ointment.

Azelaic acid It is a drug for acne (*see* p. 954) that is also effective in hyperpigmentary disorders including melasma. It inhibits the melanin forming enzyme tyrosinase. However, it is a weak demelanizing agent with reversible hypopigmentary action.

Azelaic acid is used as a 10%, 20% cream. The only side effect is mild and transient local irritation.

SUNSCREENS

Sunscreens are substances that protect the skin from harmful effects of exposure to sunlight.

(a) Chemical sunscreens They absorb and scatter UV rays that are responsible for sunburn and phototoxicity, but allow longer wave lengths to penetrate, so that tanning occurs.

Efficacy of a sunscreen formulation is quantified by its 'Sun protection factor' (SPF) which is the ratio of the dose of UVB radiation that will produce minimal erythema on protected skin to the dose required for the same on unprotected skin. Most commercial preparations have a SPF of 15 or more. Period for which they remain effective depends on the vehicle.

Para-aminobenzoic acid (PABA) and its esters: PABA and glyceryl mono amino benzoate absorb UVB (290–320 nm). PABA is used as 5% solution in alcohol/propylene glycol (PABALAK) or as 10% cream (PARAMINOL).

Benzophenones (such as oxybenzone 2–6%) block UVA (320–400 nm); are highly protective; therefore higher concentrations prevent tanning as well.

Cinnamates (such as octyl methoxy cinnamate) are included in sunscreens.
SUNSHIELD: Octyl methoxycinnamate 5%, vit E 0.25% lotion. EUKROMA-SG: Oxybenzone 3%, Octyl methoxy cinnamate 5%, hydroquinone 2% cream.

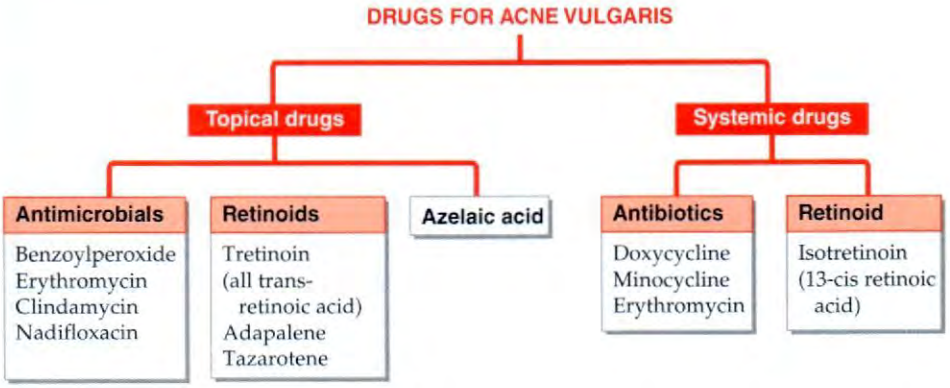
Uses Chemical sunscreens are used as adjuncts in vitiligo therapy, drug induced phototoxicity and to facilitate tanning while preventing sunburn. There is some evidence that they can prevent skin cancer and premature ageing of skin.

(b) Physical sunscreens Heavy petroleum jelly, titanium dioxide, zinc oxide and calamine are opaque substances that stop and scatter not only UV but also visible light. They are also called 'sun shades' and have to be applied as a thick lotion/cream which may be cosmetically disagreeable. They withhold longer wave lengths also, which are mostly involved in photoallergy. Not only sunburn, but tanning as well is prevented.

Chloroquine taken orally is effective in actinic eruptions, but should be reserved for severe cases only.

DRUGS FOR ACNE VULGARIS

Acne vulgaris is the most common skin disease in adolescent boys and girls. Under androgenic stimulation the sebaceous follicles of face and neck produce excess of sebum and get colonized by bacteria and yeast (*Propionibacterium acnes, Staph. epidermidis, Pityrosporum ovale*). Bacterial lipases produce fatty acids from sebum, which irritate the follicular ducts causing retention of secretions and hyperkeratosis— 'comedones' are formed which may rupture into the dermis causing inflammation and pustulation.



I. Topical Therapy

1. Benzoyl peroxide It is one of the most effective and widely used drugs in acne. It gradually liberates oxygen (in the presence of water) which kills bacteria, especially anaerobic/microaerophilic ones. Benzoyl peroxide is used almost exclusively for acne because of its high efficacy against *P. acnes* as well as additional keratolytic and comedolytic properties. *P. acnes* or other bacteria do not develop resistance to benzoyl peroxide. It induces mild desquamation, the comedone caps are shed and production of irritant fatty acids in the sebum is reduced. Benzoyl peroxide is a mild irritant of the skin—burning and stinging sensation is often felt initially, localized erythema may occur. Most patients gradually develop tolerance to these actions; if not, use should be discontinued. Avoid contact with eyes, lips, mucous membranes and denuded skin. Benzoyl peroxide can bleach hair and coloured fabric.

Adverse effects are excessive dryness of skin, marked scaling, erythema, edema and contact sensitization (in 1–2% patients). It is used as 5–10% cream, gel or lotion. The duration and frequency of application is guided by the degree of irritation produced and tolerated; start with 15 min once daily.

PERSOL, PERNOX, BENZAC-AC 2.5% and 5% gel; in PERSOL FORTE 10% cream with sulfur ppt. 5%.

2. Retinoic acid (all trans vitamin A acid, Tretinoin) It is a potent comedolytic: promotes lysis of keratinocytes and prevents horny cells from binding to each other. Hence comedones, which are horny impactions in follicles, cannot form. Epidermal cell turnover is stimulated resulting in peeling. No antibacterial action is exerted. Retinoic acid is highly efficacious in comedonal acne and one of the first line drugs, but response is delayed (may take 6–10 weeks). Tretinoin has potential to irritate the skin, therefore, start with the lower concentration applied once daily.

Side effects are feeling of warmth, stinging, excessive redness, edema and crusting. Used as a 0.025–0.05% gel or cream, it can be alternated with benzoyl peroxide (one in the morning the other at night), but both should not be applied together because benzoyl peroxide accelerates degradation of tretinoin. Teratogenic risk with topical retinoic acid is minor because of low blood levels produced; but it should be used during pregnancy only if essential.

Tretinoin has been shown to prevent photoageing of skin. Dry scaly surface, mottling, wrinkles, rough and leathery texture, sagging of loose skin that develop due to excessive exposure to sun are arrested and pigmented spots tend to fade. However, the risk-benefit ratio of long-term prophylactic therapy is not clear.

EUDYNA 0.05% cream. RETINO-A 0.025% and 0.05% cream.

3. Adapalene It is a newer synthetic tretinoin-like drug which binds directly to the nuclear retinoic acid receptor and modulates keratinization and differentiation of follicular

epithelial cells. It also exerts antiinflammatory action; comedone formation is suppressed. In acne vulgaris it is as effective but less irritating than tretinoin. Adapalene, unlike tretinoin, remains stable in the presence of benzoyl peroxide; can be combined with it.

ADAFERIN, ADAPEN, ADAPLE, ACLENE 0.1% gel; apply once daily at bed time.

Tazarotene (*see* p. 951) is another topical retinoid with therapeutic effect in acne vulgaris in addition to that in psoriasis.

4. Topical antibiotics Clindamycin, erythromycin and tetracyclines are less effective against *P. acnes* than benzoyl peroxide. They are appropriate for cases with inflamed papules, rather than in non-inflamed comedones. They do not irritate skin but can cause sensitization.

Erythromycin: ACNEDERM 2% lotion and oint; ERYTOP 3% lotion and cream; ACNESOL 4% gel, 2% lotion, ACNELAK-Z 4% lotion and gel with zinc acetate 2%.

Clindamycin: CLINDAC-A, CLINCIN, ACNESOL 1% gel.

Nadifloxacin is a newer topical quinolone broad-spectrum antibiotic which has exerted therapeutic benefit in inflamed acne and folliculitis.

NADIBACT, NADOXIN 1% cream for topical application.

5. Azelaic acid It is a natural product from *Malassezia furfur* that has been developed for topical treatment of acne. Many aerobic and anaerobic microorganisms, especially *P. acnes* present on acne bearing skin are inhibited. Azelaic acid reduces cutaneous bacterial density, free fatty acid content of skin surface lipids, proliferation of keratinocytes and has mild comedolytic property. Used as 10% or 20% cream, its efficacy in acne approaches that of benzoyl peroxide, but response is delayed. Pigmentation of melasmic patches may be reduced.

AZIDERM 10%, 20% cream

II. Systemic Therapy

Systemic use of drugs in acne is indicated only in severe cases with cysts and pustules which are likely to form scars.

1. Antibiotics Tetracycline, doxycycline, minocycline or erythromycin have been used. After initial control of pustules and cysts, smaller maintenance doses may be continued for months. However, long-term systemic antibiotic therapy has its own complications. Recently risk of intracranial hypertension after use of tetracyclines for > 2 months has been emphasized.

2. Isotretinoin (13-cis retinoic acid) is an orally administered retinoid that reduces production of sebum (skin bacteria decrease secondarily), corrects abnormal keratinization of follicles and causes dramatic improvement. A 20 week course of 0.5–1 mg/kg daily brings about remission in most cases of cystic acne. Relapses occur after variable intervals, but can be treated similarly. Side effects are frequent—cheilitis, dryness of skin, eyes, nose and mouth, epistaxis, pruritus, conjunctivitis, paronychia, rise in serum lipids and intracranial tension, and musculoskeletal symptoms. Therefore, isotretinoin should be reserved for unresponsive cases of severe acne.

Isotretinoin is highly teratogenic; upto 25% exposed foetuses had birth defects, like craniofacial, heart and CNS abnormalities (ACCUTANE embryopathy). It is contraindicated in women likely to become pregnant during therapy and one month after. The t½ of isotretinoin is ~18 hours, and it is not accumulated like other retinoids.

ISOTROTIN, SOTRET 10, 20 mg cap, IRET 20 mg cap.

Isotretinoin is also effective in the prevention and treatment of skin cancers. Oral leucoplakia, actinic keratoses and other premalignant lesions can be treated, but benefit-risk ratio is not clear.

TOPICAL STEROIDS

Glucocorticoids are used topically for a large variety of dermatological conditions. They benefit by virtue of their antiinflammatory, immunosuppressive, vasoconstrictor and antiproliferative (useful for scaling lesions) actions. The intensity of action depends on the extent of absorption to the deeper layers. As such, lipophilicity of the compound determines potency to a great extent. Fluorinated compounds and lipid soluble esters, e.g. hydrocortisone butyrate are potent. The available preparations may be roughly graded as:

Potent

Beclomethasone dipropionate	0.025%	BECLATE cream.
Betamethasone benzoate	0.025%	TOPICASONE cream, oint.
Betamethasone valerate	0.12%	BETNOVATE cream, oint.

		BETASONE cream.
Halcinonide	0.1%	CORTILATE, HALOG cream
Clobetasol propionate	0.05%	LOBATE, TENOVATE, DERMOTYL cream
Dexamethasone sod. phosphate	0.1%	DECADRON cream (with Neomycin 0.35%).
Dexamethasone trimethyl-acetate	0.1%	MILLICORTENOL cream.
Fluocinolone acetonide	0.025%	FLUCORT oint., LUCI oint.
Fluocortolone	0.5%	ULTRALAN oint.
Triamcinolone acetonide	0.1%	LEDERCORT oint.
Moderately potent		
Fluocinolone acetonide	0.01%	FLUCORT-H oint. and skin lotion.
Clobetasol butyrate	0.05%	EUMOSONE cream
Fluocortolone	0.25%	COLSIPAN oint.
Mometasone	0.1%	MOMATE, CUTIZONE oint, cream
Fluticasone propionate	0.05%	FLUTIVATE, MOLIDERM cream
Prednicarbate	0.1-0.25%	DERMATOP, STEROTOP cream
Triamcinolone acetonide	0.05%	DESOWEN, DESONIDE cream/ lotion
Hydrocortisone + urea 12%	1%	COTARYL-H cream.
Hydrocortisone acetate	2.5%	WYCORT oint.
Mild		
Hydrocortisone acetate	0.1–1.0%	LYCORTIN 1% oint., in CORTOQUINOL 1% with quiniodochlor 4% cream, GENTACYN-HC TOPICAL 1% with gentamicin 0.1%. CORTISON-KEMICETINE 0.5% with chloramphenicol 0.5%.
Hydrocortisone butyrate	0.001%	LOCOID cream

General guidelines for the use of topical steroids

1. Penetration of the steroid at different sites differs markedly. It is high at axilla, groin, face, scalp and scrotum; medium at limbs and trunk: low at palm, sole, elbow and knee. Areas of high penetration easily develop adverse effects, therefore potent preparations should be avoided. Areas of low penetration do not generally respond to milder agents.

2. Absorption into the skin also depends on the nature of the lesion; high in atopic and exfoliative dermatitis, low in hyperkeratinized and plaque forming lesions. Milder drugs should be used on acute lesions; stronger ones are reserved for chronic lesions.

3. Choice of vehicle is important. Lotions and creams (to some extent) are better for exudative lesions, because they allow evaporation, have a cooling, drying and antipruritic effect. Sprays and gels are appropriate for hairy regions. Ointments form an occlusive film and are good for chronic, scaly conditions.

4. Occlusive dressing markedly enhances absorption of the steroid (as much as 10 fold), retains moisture and results in maceration of the horny layer. Chronic, hypertrophied lesions may be occluded intermittently (12 hours at a time). Continuous occlusion promotes bacterial and fungal growth; should be avoided.

5. Absorption is greater in infants and young children—milder agents should be used.

6. Routine use of potent steroids is not justified. Very potent preparations should be restricted to severe inflammatory conditions, unresponsive eczema, psoriasis, etc., and that too only for short periods till the lesion resolves. The mildest preparation that will control the lesion should be used.

7. Use of potent preparations should be short term or intermittent to prevent adverse effects and tachyphylaxis. Sudden discontinuation should be avoided. Upon improvement a less potent preparation may be substituted or the steroid may be alternated with an emollient till the lesion resolves.

8. More than 2 applications a day do not afford additional benefit. Generally twice daily application is satisfactory.

A combination of steroid with an antimicrobial may be used for—impetigo, furunculosis, secondary infected dermatoses, napkin rash, otitis externa, intertriginous eruptions.

Popular combinations are:

Containing Neomycin (0.3–0.5%):
BECLATE-N, BETASONE-N, COLSIPAN-N, DECADRON, KENACOMB, KENALOG-S SKIN, TOPICASONE.

Containing Chinoform or Quiniodochlor (3–4%):
BECLATE-C, BETASONE-C, BETNOVATE-C, CORTOQUINOL, FLUCORT-C

Containing Gentamicin (0.1%):
GENTICYN-HC TOPICAL, DERMOTYL-G, LOBATE-G

Containing Chloramphenicol (1%):
CORTISON-KEMICETINE

Containing Povidone iodine (1%):
ECZO-BETADINE

Containing Miconazole (2%):
FLUCORT-MZ, TENOVATE-M

Containing Clotrimazole (1%): CLOBEN

Indications for topical steroids

Lesions that usually respond well	*Lesions requiring potent steroids, respond slowly*
Atopic eczema	Cystic acne
Allergic contact dermatitis	Alopecia areata
	Discoid LE
Lichen simplex	Hypertrophied scars, keloids
Primary irritant dermatitis	Lichen planus
Seborrheic dermatitis	Nail disorders
Psoriasis of face, flexures	Psoriasis of palm, sole, elbow, knee
Varicose eczema	

Local adverse effects of topical steroids

Thinning of epidermis
Dermal changes—atrophy
Telangiectasia, Striae
Easy bruising
Hypopigmentation
Delayed wound healing
Fungal and bacterial infections

} Related to the potency of preparation and duration of treatment; skin of face is more susceptible. Potent halogenated steroids not to be used on face.

Systemic adverse effects of topical steroids

Adrenal pituitary suppression can occur if large amounts are applied repeatedly. Infants and children are particularly susceptible. Rarely, Cushing's syndrome has been reported. With proper use, the systemic risks are minimal.

Chapter 67 Antiseptics, Disinfectants and Ectoparasiticides

ANTISEPTICS AND DISINFECTANTS

The terms *antiseptic* and *disinfectant* connote an agent which inhibits or kills microbes on contact. Conventionally, agents used on living surfaces (skin, mouth) are called *antiseptics* while those used for inanimate objects (instruments, privies, water supply) are called *disinfectants*. There is considerable overlap and many agents are used in either way. A practical distinction between the two on the basis of a *growth inhibiting versus direct lethal* action is futile because these are often concentration dependent actions. The term *Germicide* covers both category of drugs.

There, however, is difference between 'disinfection' and 'sterilization'. While sterilization means complete killing of all forms of microorganisms, including spores, disinfection refers to reduction in the number of viable pathogenic microbes to a level that they do not pose a risk to individuals with normal host defence. The terms 'sanitization' (used for inanimate surfaces or environment) and 'decontamination' also have similar connotation. Thus, in ordinary usage, disinfectants do not eliminate all microbes.

The era of antiseptics and disinfectants was heralded by Semmelweiss (washing of hands in chlorinated lime) and Lister (antiseptic surgery by the use of phenol) in the 19th century. These germicides differ from systemically used antimicrobials by their low parasite selectivity, i.e. they are too toxic for systemic use. However, many systemic antimicrobials are applied topically as well, and some antibiotics (bacitracin, neomycin) are restricted to topical use, but are generally not enumerated with the antiseptics. A strict distinction is thus impossible.

A good antiseptic/disinfectant should be:

1. Chemically stable.
2. Cheap.
3. Nonstaining with agreeable colour and odour.
4. Cidal and not merely static, destroying spores as well.
5. Active against all pathogens—bacteria, fungi, viruses, protozoa.
6. Require brief time of exposure.
7. Able to spread through organic films and enter folds and crevices.
8. Active even in the presence of blood, pus, exudates and excreta.

A disinfectant in addition should not corrode or rust instruments and be easily washable. An antiseptic in addition should be:

- Rapid in action and exert sustained protection.
- Nonirritating to tissues, should not delay healing.
- Nonabsorbable or produce minimum toxicity if absorbed.
- Nonsensitizing (no allergy).
- Compatible with soaps and other detergents.

Spectrum of activity of majority of antiseptic-disinfectants is wide, reflecting nonselectivity of action. However, some are rather selective, e.g. hexachlorophene, chlorhexidine, quaternary ammonium antiseptics, gentian violet and acriflavine are more active on gram-positive than on gram-negative bacteria; silver nitrate is highly active against gonococci and benzoyl peroxide against *P. acnes*.

Mechanisms of action of germicides are varied, but can be grouped into:

(a) Oxidation of bacterial protoplasm.
(b) Denaturation of bacterial proteins including enzymes.
(c) Detergent like action increasing permeability of bacterial membrane.

Factors which modify the activity of germicides are:

- Temperature and pH.
- Period of contact with the microorganism.
- Nature of the microbe involved.
- Size of innoculum.
- Presence of blood, pus or other organic matter.

Potency of a germicide is generally expressed by its *phenol coefficient* or *Rideal Walker coefficient*, which is the ratio of the minimum concentration of test drug required to kill a 24 hour culture of *B. typhosa* in 7.5 minute at 37.5°C to that of phenol under similar conditions. This test has only limited validity, particularly in relation to antiseptics which have to be tested on living surfaces.

Therapeutic index of an antiseptic is defined by comparing the concentration at which it acts on microorganisms with that which produces local irritation, tissue damage or interference with healing.

CLASSIFICATION

1. *Phenol derivatives*: Phenol, Cresol, Chloroxylenol, Hexachlorophene.
2. *Oxidizing agents*: Pot. permangnate, Hydrogen peroxide, Benzoyl peroxide.
3. *Halogens*: Iodine, Iodophores, Chlorine, Chlorophores.
4. *Biguanide*: Chlorhexidine.
5. *Quaternary ammonium (Cationic)*: Cetrimide, Benzalkonium chloride, Dequalinium chloride.
6. *Soaps*: of Sod. and Pot.
7. *Alcohols*: Ethanol, Isopropanol.
8. *Aldehydes*: Formaldehyde, Glutaraldehyde.
9. *Acids*: Boric acid.
10. *Metallic salts*: Silver nitrate, Silver sulfadiazine, Zinc sulfate, Calamine, Zinc oxide.
11. *Dyes*: Gentian violet, Acriflavine, Proflavine.
12. *Furan derivative*: Nitrofurazone.

1. PHENOLS

Phenol (Carbolic acid) It is one of the earliest used antiseptics and still the standard for comparing other germicides. It is a relatively weak agent (bacteriostatic at 0.2%, cidal at >1%, poor action on bacterial spores). Phenol is a general *protoplasmic poison*, injuring microbes and tissue cells alike—at higher concentrations it causes skin burns and is a caustic. It acts by disrupting bacterial membranes and denaturing bacterial proteins. Organic matter diminishes its action slightly while alkalies and soaps do so profoundly (carbolic soaps are not more germicidal than soap itself). It is now seldom employed as an antiseptic, but being cheap, it is used to disinfect urine, faeces, pus, sputum of patients and is sometimes included in antipruritic preparations because of its mild local anaesthetic action.

Cresol It is methyl-phenol; more active (3–10 times) and less damaging to tissues. Used for disinfection of utensils, excreta and for washing hands.

LYSOL is a 50% soapy emulsion of cresol.

Chloroxylenol It has a phenol coefficient of 70; does not coagulate proteins, is noncorrosive, nonirritating to intact skin, but efficacy is reduced by organic matter. It is poorly water soluble; the commercial 4.8% solution (DETTOL) is prepared in 9% terpinol and 13% alcohol, that is used for surgical antisepsis. A 0.8% skin cream and soap, 1.4% lubricating obstetric cream (for vaginal examination, use on forceps, etc.), and a mouthwash (DETTOLIN 1% with menthol 0.45%) are also available. These preparations lose activity if diluted with water and kept for a time.

Hexachlorophene This chlorinated phenol acts by inhibiting bacterial enzymes and (at high concentration) causing bacterial lysis. It is odourless, nonirritating, does not stain, and activity is reduced by organic matter but not by soap. Hexachlorophene is commonly incorporated in soap and other cleansing antiseptics for surgical scrub, patient's skin, etc., but is narrow spectrum; kills gram-positive but not gram-negative bacteria or spores. The degerming action is slow but persistent due to deposition on the skin as a fine film that is not removed by rinsing with water. Incorporated in toilet products, it is a good deodorant.

Use of a 3% solution for baby bath markedly reduced the incidence of staphylococcal infections, but produced brain damage (especially in premature neonates). Around 1970 several fatalities occurred in USA. Since then use of preparations containing > 2% hexachlorophene have been banned.

2. OXIDIZING AGENTS

Potassium permanganate It occurs as purple crystals, highly water soluble, liberates oxygen which oxidizes bacterial protoplasm. The available oxygen and germicidal capacity is used up if much organic matter is present—the solution gets decolourised. A 1:4000 to 1:10,000 solution (Condy's lotion) is used for gargling, douching, irrigating cavities, urethra and wounds. The action is rather slow and higher concentrations cause burns and blistering—popularity therefore has declined.

Pot. permanganate has also been used to disinfect water (wells, ponds) and for stomach wash in alkaloidal poisoning (except atropine and cocaine which are not efficiently oxidized). It promotes rusting and is not good for surgical instruments.

Hydrogen peroxide It liberates nacent oxygen which oxidizes necrotic matter and bacteria. A 3.0% solution produces 10 volumes of oxygen, much of which escapes in the molecular form. Catalase present in tissues speeds decomposition resulting in foaming. This helps in loosening and removing slough, ear wax, etc. Hydrogen peroxide has poor penetrability and a weak, transient action. It loses potency on keeping. Use therefore is much restricted.

Benzoyl peroxide It is specifically active against *P. acnes* and used on acne vulgaris (*see* p. 953).

3. HALOGENS

Iodine It is a rapidly acting, broad-spectrum (bacteria, fungi, viruses) microbicidal agent that has been in use for more than a century. Acts by iodinating and oxidizing microbial protoplasm. A 1 : 20,000 solution kills most vegetative forms within 1 min. Even bacterial spores are killed with higher concentrations/longer contact. Organic matter retards but does not abolish its germicidal action.

Iodine crystals are corrosive, stronger solutions (> 5%) cause burning and blistering of skin. *Tincture iodine* (2% in alcohol) stings on abrasions. It is used on cuts, for degerming skin before surgery, and to treat ring worm.

Mandel's paint (1.25% iodine dissolved with the help of Pot. iodide forming soluble I_3^--ions) is applied on sore throat.

A *nonstaining iodine ointment* (IODEX 4%) is popular as antiseptic and counterirritant. Some individuals are sensitive to iodine—rashes and systemic manifestations occur in them.

Iodophores These are soluble complexes of iodine with large molecular organic compounds that serve as carriers—release free iodine slowly. The most popular is:

Povidone (Polyvinylpyrrolidone) iodine: It is nonirritating, nontoxic, nonstaining and exerts prolonged germicidal action. Treated areas can be bandaged or occluded without risk of blistering. It is used on boils, furunculosis, burns, otitis externa, ulcers, tinea, monilial/trichomonal/nonspecific vaginitis and for surgical scrubbing, disinfection of endoscopes and instruments.

BETADINE 5% solution, 5% ointment, 7.5% scrub solution, 200 mg vaginal pessary; PIODIN 10% solution, 10% cream, 1% mouthwash; RANVIDONE AEROSOL 5% spray with freon propellant.

Chlorine A highly reactive element and a rapidly acting potent germicide, 0.1–0.25 ppm kills most pathogens (but not ~~*M. tuberculosis*~~) in 30 sec. However, the degerming action is soon exhausted, and it lacks substantivity. It is used to disinfect urban water supplies. Organic matter binds chlorine, so that excess has to be added to obtain free chlorine concentration of 0.2–0.4 ppm. This is known as the 'chlorine demand' of water. Chlorine is more active in acidic or neutral medium.

Chlorophores These are compounds that slowly release hypochlorous acid (HOCl). Because of ease of handling, they are used in preference to gaseous chlorine.

(i) *Chlorinated lime (bleaching powder)* It is obtained by the action of chlorine on lime (CaO); resulting in a mixture of calcium chloride and calcium hypochlorite. On exposure, it decomposes releasing 30–35% W/W chlorine. Chlorinated lime is used as disinfectant for drinking water, swimming pools and sanitizer for privies, etc.

(ii) *Sodium hypochlorite solution* Contains 4–6% sodium hypochlorite, that is a powerful disinfectant used in dairies for milk cans, other equipment and for infant feeding bottles. It is unstable and too irritant to be used as antiseptic, except for root canal therapy in dentistry.

4. BIGUANIDE

Chlorhexidine A powerful, nonirritating, cationic antiseptic that disrupts bacterial cell membrane. A secondary action is denaturation of microbial proteins. It is relatively more active against gram-positive bacteria. Like hexachlorophene, chlorhexidine persists on the skin. Present in SAVLON (*see* below), it is extensively used

for surgical scrub, neonatal bath, mouthwash, obstetrics and as general skin antiseptic.

Chlorhexidine is the most widely employed antiseptic in dentistry. As 0.12–0.2% oral rinse or 0.5–1% toothpaste, it is highly active in preventing/treating gingivitis. Twice daily chlorhexidine oral rinse markedly reduces oral infections in immunocompromised patients, including AIDS. However, it may leave an unpleasant after taste, and repeated application causes brownish discolouration of teeth.

5. QUATERNARY AMMONIUM (CATIONIC) ANTISEPTICS

These are detergents; cidal to bacteria, fungi and viruses. However, many gram-negative bacteria (especially *Pseudomonas*), *M. tuberculosis* and bacterial spores are relatively resistant. Cationic antiseptics act by altering permeability of cell membranes and denaturing of bacterial proteins. Soaps, being anionic, neutralize their action, while alcohol potentiates. They spread through oil and grease, have cleansing and emulgent properties. They are nonirritating and mildly keratolytic. However, the germicidal action is rather slow and bacteria may thrive under a film formed by them on the skin. Pus, debris and porous material like cotton, polyethylene reduce their activity. Occasionally sensitization occurs. These disadvantages not withstanding, they are widely used as sanitizers, antiseptic and disinfectant for surgical instruments, gloves, etc, but should not be considered sterilizing.

Cetrimide It is a soapy powder with a faint fishy odour. Used as 1–3% solution. cetrimide has good cleansing action, efficiently removing dirt, grease, tar and congealed blood from road side accident wounds. Alone or in combination with chlorhexidine, it is one of the most popular hospital antiseptic and disinfectant for surgical instruments, utensils, baths, etc.

CETAVLON CONCENTRATE: Cetrimide 20%

SAVLON LIQUID ANTISEPTIC: Chlorhexidine gluconate 1.5% + Cetrimide 3%.

SAVLON/CETAVLEX CREAM: Chlorhexidine HCl 0.1% + Cetrimide 0.5%.

SAVLON HOSPITAL CONCENTRATE: Chlorhexidine gluconate 7.5% + Cetrimide 15%.

Benzalkonium chloride (Zephiran) It is highly soluble in water and alcohol. A 1:1000 solution is used for sterile storage of instruments and 1 in 5000 to 1 in 10,000 for douches, irrigation, etc.

Dequalinium chloride Has been used in gum paints and lozenges.

DEQUADIN 0.25 mg lozenges.

6. SOAPS

Soaps are anionic detergents with weak antiseptic action. They affect only gram-positive bacteria. Their usefulness primarily resides in their cleansing action. Washing with soap and warm water is one of the most effective methods of preventing transmission of infection by removing or diluting pathogenic bacteria. Soaps can be medicated by other antiseptics.

7. ALCOHOLS

Ethanol It is an effective antiseptic and cleansing agent at 40–90% concentration. The rapidity of action increases with concentration upto 70% and decreases above 90%. It acts by precipitating bacterial proteins. A cotton swab soaked in 70% ethanol rubbed on the skin kills 90% bacteria in 2 min. This has been used before hypodermic injection and on minor cuts. Alcohol-based hand rubs are recommended for decontamination of hands in the health-care setting, as well as for personal hygiene. Low concentrations enhance the antiseptic activity of iodine and chlorhexidine when used as solvent for these. Alcohol is an irritant and should not be applied to mucous membranes or to delicate skin (scrotum), ulcers, etc. On open wounds it produces a burning sensation, injures the surface and forms a coagulum under which bacteria could grow. It is a poor disinfectant for instruments—does not kill spores and promotes rusting.

Isopropanol It is less volatile; can be used in place of ethanol.

8. ALDEHYDES

Formaldehyde It is a pungent gas—sometimes used for fumigation. A 37% aqueous solution called *Formalin* is diluted to 4% and used for hardening and preserving dead

tissues. Formaldehyde denatures proteins and is a general protoplasmic poison, but acts slowly. It is a broad-spectrum germicide, but use as antiseptic is restricted by its irritating nature and pungent odour. It is occasionally employed to disinfect instruments and excreta. Those who handle formalin can develop eczematoid reactions. The urinary antiseptic methenamine acts by releasing formaldehyde in acidic urine (*see* p. 810). Formaline is also used to precipitate *toxoids* from toxins.

Glutaraldehyde It is less volatile, less pungent, less irritating and better sterilizing agent than formalin, but needs to be activated by alkalinization of the solution. Glutaraldehyde exerts broad-spectrum activity against bacteria, fungi and viruses. Organic matter does not inactivate it. A 2% solution is used to disinfect surgical instruments and endoscopes, but prolonged contact is needed. Repeated application on skin can cause sensitization. The alkalinized solution has a short shelf life (2 weeks) unless stabilizing agents are added.

9. ACIDS

Boric acid It is only bacteriostatic and a very weak antiseptic. But being nonirritating even to delicate structures, saturated aqueous solutions (4%) have been used for irrigating eyes and as mouthwash, douche, etc. Boroglycerine paint (30%) is used for stomatitis and glossitis. A 10% ointment (BOROCIDE) is available for cuts and abrasion. Boric acid is included in prickly heat powders and ear drops. However, it is not innocuous; systemic absorption causes vomiting, abdominal pain, diarrhoea, visual disturbances and kidney damage. Hence its use for irrigating bladder, large wounds and as ointment on extensive burnt areas, liberal use of the powder for infants is not recommended.

10. METALLIC SALTS

Silver compounds These are astringent and caustic. They react with SH, COOH, PO_4 and NH_2 groups of proteins.

(i) Silver nitrate It rapidly kills microbes, action persisting for long periods because of slow release of Ag^+ ions from silver proteinate formed by interaction with tissue proteins. Tissues get stained black due to deposition of reduced silver. Silver nitrate touch is used for hypertrophied tonsillitis and aphthous ulcers. It is highly active against gonococci—1% solution is used for ophthalmia neonatorum.

(ii) Silver sulfadiazine (*see* p. 757) It is highly active against *Pseudomonas* and has been used on burns.

Zinc salts They are astringent and mild antiseptics.

(i) Zinc sulfate: It is highly water soluble, 0.1–1% is used for eyewash and in eye/ear drops (Zinc-boric acid drops—in ZINCO-SULFA 0.1% eye drop). Applied to skin, it decreases perspiration. *White lotion* containing 4% each of zinc sulfate and sulfurated potash has been used for acne and impetigo; (THIOSOL 2.5%, THIOSOL FORTE 4% lotion).

(ii) Calamine and zinc oxide: These are insoluble. In addition to being mildly antiseptic, they are popular dermal protectives and adsorbants.

11. DYES

Gentian violet (crystal violet) A rosaniline dye active against staphylococci, other gram-positive bacteria and fungi, but gram-negative organisms and mycobacteria are insensitive. Aqueous or alcoholic solution (0.5–1%) has been used on furunculosis, bedsores, chronic ulcers, infected eczema, thrush, Vincent's angina, ringworm, etc. However, it has become unpopular due to deep staining.

Acriflavine and Proflavine These are orange-yellow acridine dyes active against gram-positive bacteria and gonococci. Their efficacy is not reduced by organic matter and is enhanced in alkaline medium. Solutions lose efficacy on exposure to light; therefore needs to be stored in amber bottles. They are nonirritant, do not retard healing, and are particularly suitable for chronic ulcers and wounds. Bandage impregnated with acriflavine-vaseline is used for burn dressing;
ACRINOL 0.1% acriflavine cream.

The *triple dye lotion* containing gentian violet 0.25% + brilliant green 0.25% + acriflavine 0.1% (TRIPLE DY), has been used for burns and for dressing umbilical stump in neonates.

12. FURAN DERIVATIVES

Nitrofurazone (Nitrofural) It is cidal to both gram-positive and negative, aerobic and anaerobic bacteria, even in high dilutions, but activity is reduced in the presence of serum. Nitrofurazone acts by inhibiting enzymes necessary for carbohydrate metabolism in bacteria. It is highly efficacious in burns and for skin grafting. Its local toxicity is negligible—but sensitization occurs frequently.
FURACIN 0.2% cream, soluble ointment, powder.

Nitrofurantoin and Furazolidone are other furan derivatives used for urinary and intestinal infections respectively.

ECTOPARASITICIDES

These are drugs used to kill parasites that live on body surface. Lice (*Pediculus sp.*—wingless insects) and mites (*Sarcoptes/Acarus scabiei*—arachnids) are minute arthropods infesting human skin and hair.

Scabies It is highly contagious; the mite burrows through the epidermis, laying eggs which form papules that itch intensely. Lesions may get secondarily infected requiring systemic antimicrobial therapy. The finger webs are the preferred sites of entry, but may soon spread

to forearms, trunk, genitals and lower legs. Other members of the patient's family should be treated concurrently; garments and bed linen should be washed in hot water and put in the sun to prevent cross infection and re-infection.

Pediculosis The lice thrive on head (*P. capitis*), body (*P. corporis*) or pubic region (*P. pubis*). They cause itching, suck blood and transmit typhus and relapsing fever. The eggs called *nits* get attached to the hair and clothing by a chitin like cement.

Drugs used are:

Permethrin	Sulfur
Lindane (BHC)	Dicophane (DDT)
Benzyl benzoate	Ivermectin
Crotamiton	

1. Permethrin This broad-spectrum and potent pyrethoid insecticide is currently the most efficacious and most convenient drug for both scabies and lice. It causes neurological paralysis in insects, probably by delaying depolarization. Toxicity of permethrin in humans is very low; apparently 40–400 times lower than that of lindane. After application, permethrin persists on the skin for days; systemic absorption is minimal. Nearly 100% cure rates have been obtained in scabies and pediculosis. Some comparative studies have found it to be more effective than lindane, benzyl benzoate and crotamiton. Single application is needed in most cases. Resistance to permethrin is very rare and it is effective in lindane nonresponsive cases. Few patients may experience mild and transient burning, itching, tingling, erythema or rash.

For scabies: PERMITE, OMITE, NOMITE 5% cream; apply all over the body except face and head; wash after 8–12 hours. SCABERID 5% cream, 1% soap; SCABPER 5% lotion.

For head lice: PERLICE, KERALICE 1% cream rinse, ELICE 5% lotion, SCALTIX 1% lotion; massage about 30 g into the scalp, washoff after 10 min.

Thus, permethrin is now the 1st choice drug for scabies and pediculosis

2. Lindane (Gamma benzene hexachloride, BHC) Another broad-spectrum insecticide which kills lice and mites by penetrating through their chitinous cover and affecting the nervous system. Lindane is highly effective in treating headlice (67–92% cure) and scabies (84–92% cure) by single treatment. However, efficacy is lower than permethrin. Both lice and mites can develop resistance to lindane. Combining it with benzyl benzoate precludes resistance and improves cure rate to nearly 100%.

GAB 1% lotion, ointment; GAMADERM, SCABOMA 1% lotion; GAMASCAB 1% lotion, cream; ASCABIOL 1% emulsion with cetrimide 0.1%; BENZO 1% lotion, 1% soap.

For pediculosis: apply to scalp and hair (taking care not to enter eyes), leave for 12–24 hr. (a shower cap may be used for long hair) and then wash off. If lice are still present, repeat treatment after 1 week.

For scabies: the lotion/cream is rubbed over the body (below neck) and a scrub bath taken 12–24 hr later. Single treatment suffices in most patients; can be repeated only after a week, if the mite is still present.

The disadvantages of lindane are:

Being highly lipid soluble it can be absorbed through the skin (especially from oily vehicles and in small children). This can produce systemic toxicity—CNS stimulation, vertigo, convulsions (especially in children) and cardiac arrhythmias.

Absorbed lindane is widely distributed in the body, especially in fat; is metabolised and eliminated with a t½ ~24 hr. It can induce CYP isoenzymes in liver and affect metabolism of many drugs.

Though well tolerated by most patients if instructions are followed carefully, it is less favoured for treatment of scabies—because application over large body surface is required which increases possibility of systemic absorption. It should be avoided in infants, young children and during pregnancy. Skin irritation is not prominent.

3. Benzyl benzoate It is an oily liquid with faint aromatic smell. Benzyl benzoate has been popular for treatment of scabies. The emulsion is applied all over except face and neck after a cleansing bath. A second coat is applied next day which is washed after 24 hours. The treatment is convenient and does not interfere with routine activities. It has achieved 76–100% cure in scabies. Benzyl benzoate is minimally absorbed through the skin; systemic toxicity is low, but neurological symptoms have occurred in children, therefore contraindicated in them. Skin irritation is common, especially in children. Contact dermatitis is possible.

BENZYLBENZOATE APPLICATION 25% lotion; DERMIN 25% lotion; SCABINDON 25% oint with DDT 1% and benzocaine 2%

For pediculosis, it can be applied to the scalp, taking care not to enter eyes, and is washed off after 24 hours. Benzyl benzoate is now a 2nd line drug for scabies and is seldom used for pediculosis. Its combination with lindane is highly effective.

4. Crotamiton It is an effective scabicide, pediculocide and antipruritic, but has produced lower cure rates (60–88%) in scabies. Better results have been obtained by extended 5 day application in children. Crotamiton is less prone to cause skin irritation and has low systemic toxicity despite absorption through the skin—may be preferred for children. It is applied twice at 24 hr interval and washed off day after that.

CROTORAX, CROTON 10% cream, lotion

Because of lower efficacy and need for repeat application, it is a second choice drug for scabies and pediculosis.

5. Sulfur It is the oldest scabicide and weak pediculocide, antiseptic, fungicide and keratolytic. Applied to skin it is slowly reduced to H_2S and oxidized to SO_2 and *pentathionic acid*. These, especially the latter, dissolve the cuticle of itch mite and kill it. The reactions are carried out by epidermal cells and the arthropods themselves.

Sublimed sulfur or precipitated sulfur is used as a 10% ointment. After a warm scrubbing bath (to open the burrows) the ointment is massaged over the entire body (below the neck) for 3 consecutive days, followed by soap water bath on the fourth day. It is cheap but has disadvantages:

(a) Treatment is messy.
(b) Produces bad odour—socially unacceptable —may interfere with patient's vocation.
(c) Repeated applications are required.

Sulfur has been superseded by better drugs.

6. Dicophane (DDT) It has been a popular insecticide for mosquitoes, flies and other pests. For this purpose, it is used in the dust or watery suspension form, which is poorly absorbed through skin. For pediculosis and scabies a 1–2% lotion or ointment is applied and washed off after 12–24 hours. It penetrates through the exoskeleton and acts as a neurotoxin for the arthropods. When oily vehicles are used, significant amounts may be absorbed through the skin and cause rashes, muscle weakness, tremor. Very high doses produce BHC like convulsions. It gets stored in body fat and induces microsomal enzymes. Combination with benzyl benzoate (SCABINDON oint) is more effective. It is rarely used.

7. Ivermectin This anthelmintic drug (*see* p. 911–12) has been found highly effective in scabies and pediculosis as well. It is the only orally administered drug used for ectoparasitosis. A single 0.2 mg/kg (12 mg in adults) dose has cured upto 91–100% patients of scabies. AIDS patients with scabies also respond. Most cases of head/body lice have been successfully treated.

Ivermectin is very well tolerated by scabies/ pediculosis patients, with few if any side effects. However, it is not to be given to children < 5 yr, pregnant and lactating women. Only limited use of ivermectin has been made in scabies and pediculosis because of the availability of efficacious topical agents.

Chapter 68 Chelating Agents

These are drugs which complex metallic ions, forming ring structures within their molecule (Greek *Chele* = Crab; the compound holds the metal like a crab's claw). They are primarily used in heavy metal poisonings.

Those compounds which form stable, nontoxic and easily excreted complexes with toxic metals are valuable in poisonings. The useful agents contain two or more reactive groups (ligands) which can hold the metal from at least two sides so that a ring is formed. When the ring is 5–7 membered, it is most stable.

Ligand is a functional group capable of forming coordinate bond, i.e. a covalent bond in which both the shared electrons are donated by the ligand—generally O, N, or S atoms in hydroxyl, carboxyl, keto, sulfhydryl, disulfide, amino or phosphate groups.

Heavy metals exert their toxic effects by combining with and inactivating functional groups (ligands) of enzymes or other critical biomolecules. Chelating agents compete with body ligands for the heavy metal. They differ in their affinity for different metals. Clinically useful agents should have a higher affinity for the toxic metal than for calcium, because Ca^{2+} is readily available in plasma and extracellular fluid. They should also have higher affinity than the body ligands for the toxic metal. Moreover, to be effective in metal poisoning, their distribution in the body should correspond to that of the metal to be chelated, and they should be water soluble.

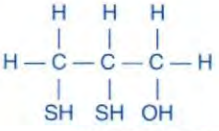
Efficacy of all chelating agents in promoting excretion of the toxic metal and in reversing toxic manifestations declines rapidly as the interval between entry of the metal in the body and the administration of the chelator increases.

Chelating agents useful as drugs are:

- Dimercaprol (BAL)
- Dimercaptosuccinic acid (Succimer)
- Disodium edetate
- Calcium disodium edetate
- Penicillamine
- Desferrioxamine
- Deferiprone
- Deferasirox

Dimercaprol (British antilewisite; BAL)

It is an oily, pungent smelling, viscous liquid, developed during World War II by Britishers as an antidote to the arsenical war gas *lewisite*. The two SH groups of dimercaprol bind those metals which produce their toxicity by interacting with sulfhydryl containing enzymes in the body, i.e. As, Hg, Au, Bi, Ni, Sb, Cu. The complex of 2 molecules of dimercaprol with one metal ion



DIMERCAPROL

is more stable than 1:1 complex. It is, therefore, desirable to maintain excess of dimercaprol in plasma to allow formation of 2: 1 complex. The dimercaprol-metal complex spontaneously dissociates releasing the metal at a slow rate; also dimercaprol is partly oxidized in the body: further emphasizing the necessity to have excess dimercaprol available. But due to dose dependent toxicity of dimercaprol, large amounts should not be given at a time.

Uses

1. Poisoning by As, Hg, Au, Bi, Ni, Sb: it is administered i.m., 5 mg/kg *stat*, followed by 2–3 mg/kg every 4–8 hours for 2 days, then once or twice a day for 10 days. It is partly oxidized and glucuronide conjugated, but mainly excreted as such in 4–6 hours. Earlier the treatment is instituted, the better it is. Because the dimercaprol-metal complex dissociates faster in acidic urine and the released metal can damage the kidney, urine is alkalinized during dimercaprol therapy.

2. As an adjuvant to Cal. disod. edetate in lead poisoning.

3. As an adjuvant to penicillamine in Cu poisoning and in Wilson's disease—300 mg/day i.m. for 10 days every second month.

BAL INJ 100 mg/2 ml (in arachis oil) inj.

It is contraindicated in iron and cadmium poisoning, because the dimercaprol-Fe and dimercaprol-Cd complex is itself toxic.

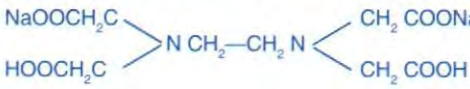
Adverse effects These are frequent, dose related and distressing, but generally not damaging.

Rise in BP, tachycardia, vomiting, tingling and burning sensations, inflammation of mucous membranes, sweating, cramps, headache and anxiety.

Antihistaminics given 30 min before dimercaprol injection, reduce the intensity of adverse effects.

Dimercaptosuccinic acid (Succimer) It is similar to dimercaprol in chelating properties, water soluble, less toxic and orally effective. Its efficacy has been demonstrated in As, Hg and Pb poisoning, but it may also chelate some essential metals like Cu and Zn. Side effects are nausea, anorexia and loose motions.

Disodium edetate (Na_2EDTA) It is the disodium salt of ethylene diamine tetraacetic acid (EDTA). It is a potent chelator of calcium—causes tetany on i.v. injection. When a slow infusion is given, tetany does not occur, because calcium is withdrawn from bones. It can be used for emergency control of hypercalcaemia: 50 mg/kg i.v. infusion over 2–4 hours, but bisphosphonates are preferred.



DISODIUM EDETATE

Calcium disodium edetate (Ca Na_2 EDTA)

It is the calcium chelate of Na_2 EDTA. Because this chelating agent has higher affinity for metals like Pb, Zn, Cd, Mn, Cu and some radioactive metals, it can remove them from the body by exchanging with Ca held by it. Along with the toxic metal, some essential Zn may also be removed. It is highly ionized, therefore distributed only extracellularly and rapidly excreted in urine by glomerular filtration ($t_{1/2} \leq 1$ hour) carrying the toxic metal along. It is not metabolized. Because of its ionic nature, Ca Na_2 EDTA is not absorbed from the g.i.t.—must be given parenterally. Since i.m. injection is painful, preferred route is i.v. It does not enter brain or CSF. Thus, it can remove toxic metals only from accessible sites.

Uses

1. *Lead poisoning* This is the most important indication for $CaNa_2$EDTA; 1 gm is diluted to 200–300 ml in saline or glucose solution and infused i.v. over 1 hour twice daily for 3–5 days. The urinary excretion of Pb is promptly increased, but declines quickly as the metal is removed from accessible sites (primarily bone). A second course of $CaNa_2$EDTA may be repeated after 5–7 days, allowing time for Pb to redistribute to extracellular sites.

2. It is also useful in Fe, Zn, Cu, Mn and radioactive metal, but not Hg poisoning, because Hg is more firmly bound to body constituents and is localized in areas not accessible to $CaNa_2$ EDTA.

Adverse effects $CaNa_2$ EDTA does not produce tetany and is relatively safe.

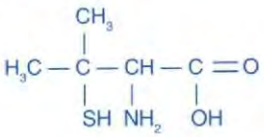
Kidney damage with proximal tubular necrosis is the most important problem. This is roughly dose-related and may be due to the toxic metal partly dissociating in the tubule. It can be minimized by maintaining high urine flow.

An acute febrile reaction with chills, bodyache, malaise, tiredness occurs in some individuals.

Anaphylactoid reaction with fall in BP and congestion of eyes and nose is also reported.

Penicillamine

It is dimethyl cysteine, obtained as a degradation product of penicillin. Penicillamine was found to have strong copper chelating property and was used in 1956 for Wilson's disease. It selectively chelates Cu, Hg, Pb and Zn. The d-isomer is used therapeutically, because the l-isomer and the racemate produce optic neuritis and are more toxic. It is adequately absorbed after oral administration, little metabolized in the body and excreted in urine and faeces. When given to patients with heavy metal toxicity, excretion of the metal is enhanced.



PENICILLAMINE

Uses

1. *Wilson's disease* (Hepatolenticular degeneration): This is due to genetic deficiency of ceruloplasmin, a protein which normally binds and disposes off Cu from the body. In its absence, plasma concentration of free Cu is high which gets deposited in liver, substantia nigra, basal ganglia of brain, and causes local degeneration. Life long therapy is needed to prevent progression of the disease.

Dose: 0.5–1 g daily in divided doses 1 hour before or 2 hour after meals to avoid chelation of dietary metals.

ARTAMIN, CILAMIN 250 mg cap, ARTIN 150, 250 mg cap.

Pot. sulfide 20–40 mg may be given with each meal to decrease the absorption of dietary copper.

2. *Copper or mercury poisoning:* 1–1.5 g/day is given for a few days. It is the drug of choice for Cu poisoning and alternative drug to dimercaprol/succimer for Hg poisoning.

3. *Chronic lead poisoning:* It may be used as an adjuvant to $CaNa_2$EDTA, but succimer is preferred.

4. *Cystinuria and cystine stones:* It promotes the excretion of cysteine and prevents its precipitation in the urinary tract, because penicillamine-cysteine complex is more soluble than dicysteine (cystine).

5. *Scleroderma:* Penicillamine benefits by increasing soluble collagen.

Adverse effects Short-term administration (as metal chelator) of penicillamine does not cause much problem. Various cutaneous reactions, itching and febrile episodes may occur. However, long-term use produces pronounced toxicity. Dermatological, renal, haematological and collagen tissue toxicities are prominent.

Desferrioxamine

Ferrioxamine is a long chain iron containing complex obtained from an actinomycete. Chemical removal of iron from it yields desferrioxamine which has very high affinity for iron: 1g is capable of chelating 85 mg of elemental iron. The straight chain desferrioxamine molecule winds round ferric iron and forms a stable nontoxic complex which is excreted in urine. Desferrioxamine removes loosely bound iron as well as that from haemosiderin and ferritin, but not from haemoglobin or cytochrome. Another desirable property is its low affinity for calcium.

Little of orally administered desferrioxamine is absorbed. Parenterally administered desferrioxamine is partly metabolized and rapidly excreted in urine.

Uses

1. Acute iron poisoning: mostly in children. This is the most important indication of desferrioxamine, which may be life saving (*see* p. 652).
2. Transfusion siderosis: occurs in thalassemia patients who receive repeated blood transfusion. Desferrioxamine 0.5–1 g/day i.m. helps to excrete the chronic iron overload. It may also be infused i.v. concurrently with blood transfusion—2 g per unit of blood.

Adverse effects Desferrioxamine can cause histamine release resulting in fall in BP, flushing, itching, urticaria and rashes. A variety of allergic reactions are reported. Changes in lens and retina can occur on repeated use.

Other side effects are abdominal pain, loose motions, muscle cramps, fever and dysuria.

DESFERAL 0.5 g/vial inj.

Deferiprone

It is an orally active iron chelator which has simplified the treatment of transfusion siderosis in thalassemia patients. Excessive haemolysis occurs in these patients, and they have to be given repeated blood transfusions. An iron chelator has to be used to clear the resulting iron overload. Oral deferiprone is a somewhat less effective alternative to injected desferrioxamine, but side-effects and cost of treatment are reduced. Deferiprone may also be used for acute iron poisoning, but is less effective than desferrioxamine. Facilitating removal of iron load in hepatic cirrhosis is another indication.

Dose: 50–100 mg/kg daily in 2–4 divided doses.

KELFER 250, 500 mg caps.

Side effects are anorexia, vomiting, altered taste, joint pain, reversible neutropenia, rarely agranulocytosis.

Deferasirox

Another oral iron chelator which lowers serum ferritin and hepatic iron concentration in patients with chronic iron overload due to repeated blood transfusion, as well as non-transfusion dependent thalassaemia syndromes. Deferasirox has high affinity for iron, but low affinity for other trace metals like Cu and Zn. It is well absorbed orally and needs once daily dosing. The deferasirox-iron complex is excreted in bile. Side effects are mostly nausea, epigastric pain, headache, pruritus, rashes and skin discolouration. Infrequently, g.i. ulceration and haemorrhages, proteinurea and renal failure are also reported.

Dose: 20 mg/kg once daily on empty stomach and no food for next 1 hr. The tab should be dispersed in water/orange juice before intake. Dose to be adjusted later according to serum ferritin level.

DESIROX, DEFRIJET 250 mg, 500 mg tab.

Chapter 69 | Vitamins

Vitamins are nonenergy yielding organic compounds, essential for normal human metabolism, that must be supplied in small quantities in the diet. This definition excludes the inorganic essential trace minerals and essential amino acids and fatty acids which are required in much larger quantities. Other substances needed for proper growth of microorganisms or cells in culture are called 'growth factors'. The different chemical forms and precursors of a vitamin can be called its *Vitamers* (analogy—isomers).

The importance of vitamins as drugs is primarily in the prevention and treatment of deficiency diseases. Some vitamins do have other empirical uses in pharmacological doses. Vitamin deficiencies occur due to inadequate intake, malabsorption, increased tissue needs, increased excretion, certain genetic abnormalities and drug-vitamin interactions.

Vitamins, as a class, are over-promoted, over-prescribed and over-used. Myths like 'vitamins energise the body', 'any physical illness is accompanied by vitamin deficiency', 'vitamin intake in normal diet is precariously marginal', 'vitamins are harmless', are rampant.

Vitamins are traditionally divided into two groups:

(a) *Fat-soluble* (A, D, E, K): These (except vit K) are stored in the body for prolonged periods and are liable to cause cumulative toxicity after regular ingestion of large amounts. Some of them interact with specific cellular receptors analogous to hormones.

(b) *Water-soluble* (B complex, C): These vitamins are meagerly stored: excess is excreted with little chance of toxicity. They act as cofactors for specific enzymes of intermediary metabolism. Chemical forms and preparations of vitamins are listed in Table 69.1.

FAT-SOLUBLE VITAMINS

VITAMIN A

Chemistry and source Vitamin A occurs in nature in several forms. *Retinol* (Vit. A_1) is an unsaturated alcohol containing an 'ionone' ring. Marine fish (cod, shark, halibut) liver oils are rich sources. Appreciable amounts are present in egg yolk, milk and butter.

Dehydroretinol (Vit A_2) is present in fresh water fishes. *Carotenoids* are pigments found in green plants (carrot, turnip, spinach) of which β *Carotene* is the most important carotenoid. It is inactive as such, one molecule splits to provide two molecules of retinol. Man on normal diet gets half of his vit A as retinol esters and half from carotenoids.

1 µg of retinol = 3.3 IU of vit. A activity

1 *Retinol Equivalent* = 6 µg of dietary carotene (because of incomplete utilization of the provitamin).

Absorption and fate Retinyl palmitate, the chief retinyl ester in diet, is hydrolysed in intestines to retinol which is absorbed by carrier transport and reesterified. Aided by bile, it passes into lacteals. Absorption is normally complete, but not in steatorrhoea, bile deficiency and from protein poor diet. Retinol ester circulates in chylomicrons and is stored in liver cells. Free retinol released by hepatocytes combines with *retinol binding protein* (*RBP* a plasma globulin) and is transported to the target cells. On entering them, it gets bound to the *cellular retinol*

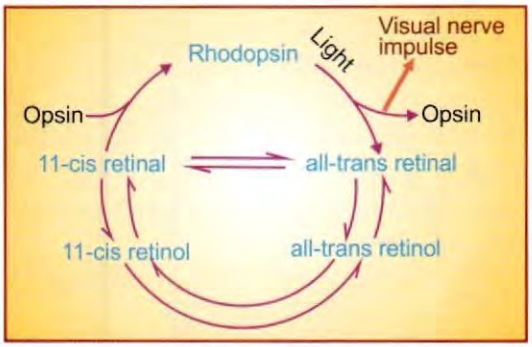


Fig. 69.1: The role of vit. A in visual cycle

binding protein (*CRBP*). Small amount is conjugated with glucuronic acid, excreted in bile, undergoes enterohepatic circulation. Minute quantities of water soluble metabolites are excreted in urine and faeces.

In contrast to retinol, only 30% of dietary β carotene is absorbed. It is split into two molecules of *retinal* in the intestinal wall; only half of this is reduced to retinol and utilized.

Physiological role and actions

(a) *Visual cycle* Retinal generated by reversible oxidation of retinol is a component of the light sensitive pigment *Rhodopsin* which is synthesized by rods during dark adaptation. This pigment gets bleached and split into its components by dim light and in the process generates a nerve impulse through a G-protein called *Transducin*. Retinal so released is reutilized. A similar pigment (Iodopsin) is synthesized in the cones—responsible for vision in bright light, colour vision and primary dark adaptation. In vit. A deficiency rods are affected more than cones; irreversible structural changes with permanent night blindness occur if the deprivation is long-term.

(b) *Epithelial tissue* Vit. A promotes differentiation and maintains structural integrity of epithelia all over the body. It also promotes mucus secretion, inhibits keratinization and improves resistance to infection. It appears to have the ability to retard development of malignancies of epithelial structures. Vit A is also required for bone growth.

(c) *Reproduction* Retinol is needed for maintenance of spermatogenesis and foetal development.

(d) *Immunity* Increased susceptibility to infection occurs in vit A deficiency. Physiological amount of vit A appears to be required for proper antibody response, normal lymphocyte proliferation and killer cell function.

Deficiency symptoms Since vit. A is stored in liver, deficiency symptoms appear only after long-term deprivation, but vit A deficiency is quite prevalent, especially among infants and children in developing countries. Manifestations are:

- Xerosis (dryness) of eye, 'Bitot's spots', keratomalacia (softening of cornea), corneal opacities, night blindness (nyctalopia) progressing to total blindness.
- Dry and rough skin with papules (phrynoderma), hyperkeratinization, atrophy of sweat glands.
- Keratinization of bronchopulmonary epithelium, increased susceptibility to infection.
- Unhealthy gastrointestinal mucosa, diarrhoea.
- Increased tendency to urinary stone formation due to shedding of ureteric epithelial lining which acts as a nidus.
- Sterility due to faulty spermatogenesis, abortions, foetal malformations.
- Growth retardation, impairment of special senses.

Therapeutic uses

1. Prophylaxis of vit A deficiency during infancy, pregnancy, lactation, hepatobiliary diseases, steatorrhoea: 3000–5000 IU/day.
2. Treatment of established vit A deficiency: 50,000–100,000 IU i.m or orally for 1–3 days followed by intermittent supplemental doses.
3. Skin diseases like acne, psoriasis, ichthyosis. Retinoic acid (*see* below) and 2nd or 3rd generation retinoids are used.

Interactions

- Vit E promotes storage and utilization of retinol and decreases its toxicity.
- Regular use of liquid paraffin by carrying through with it vit A can result in deficiency.
- Long-term oral neomycin induces steatorrhoea and interferes with vit A absorption.

Hypervitaminosis A Regular ingestion of gross excess of retinol (100,000 IU daily for

months) has produced toxicity—nausea, vomiting, itching, erythema, dermatitis, exfoliation, hair loss, bone and joint pains, loss of appetite, irritability, bleeding, increased intracranial tension and chronic liver disease. Excess retinol is also teratogenic in animals and man. Daily intake should not exceed 20,000 IU.

Acute poisoning has been described after consumption of polar bear liver which contains 30,000 IU/g vit A. Single massive ingestion (> 1 million IU) produces intense headache, drowsiness, irritability, rise in intracranial tension, vomiting, liver enlargement and shedding of skin. Due to saturation of RBP, excess retinol esters circulate in the free state or loosely associated with lipoprotein. These have surfactant property which damages tissues.

Treatment consists of stopping further ingestion, supportive measures, and vit E which promotes storage of retinol in tissues and speeds recovery. Most signs regress in a week, some persist for months. Excess intake of carotenoids does not produce hypervitaminosis A, because conversion to retinol has a ceiling.

Retinoic acid (vit A acid) Retinoic acid has vit A activity in epithelial tissues and promotes growth, but is inactive in eye and reproductive organs. All-trans retinoic acid (Tretinoin) is used topically, while 13-cis retinoic acid (Isotretinoin) is given orally for acne (*see* Ch. 66). Unlike retinol, it is not stored but rapidly metabolized and excreted in bile and urine.

The *cellular retinoic acid binding protein* (*CRABP*) is different from CRBP, is present in skin and other tissues but not in retina—this may be the reason for the inability of retinoic acid to participate in visual cycle.

Retinoid receptors Retinol and retinoic acid act through *nuclear retinoid receptors* which function in a manner analogous to the steroid receptors. Their activation results in modulation of protein synthesis. In the target cells (epithelial, gonadal, fibroblast) synthesis of certain proteins is enhanced while that of other proteins is depressed—accounting for the structural and functional changes. Two distinct families of retinoid receptors, *viz. Retinoic acid receptors (RARs)* and *Retinoid X receptors (RXRs)* have been identified with differing affinities for different retinoids.

VITAMIN E

Chemistry and source A number of tocopherols, of which α tocopherol is the most abundant and potent, have vit E activity. The *d*-isomer is more potent than *l*-isomer. Wheat germ oil is the richest source, others are cereals, nuts, spinach and egg yolk.

1 mg of *d* α-tocopherol is called α-tocopherol equivalent = 1.49 IU of vit E.

The daily requirement of vit. E is estimated at 10 mg. It is increased by high intake of polyunsaturated fats.

Absorption and fate Vit. E is absorbed from intestine through lymph with the help of bile; it circulates in plasma in association with β-lipoprotein, is stored in tissues and excreted slowly in bile and urine as metabolites.

Physiological role and actions Vit E acts as *antioxidant*, protecting unsaturated lipids in cell membranes, coenzyme Q, etc. from free radical oxidation damage and curbing generation of toxic peroxidation products. Feeding animals with polyunsaturated fats increases vit E requirement, while antioxidants like cystein, methionine, selenium, chromenols prevent some vit E deficiency symptoms in animals. However, vit E might be having some more specific action or a structural role in biological membranes, because other deficiency symptoms are not relieved by these unrelated antioxidants.

Deficiency symptoms Experimental vit E deficiency in animals produces recurrent abortion, degenerative changes in spinal cord, skeletal muscles and heart, and haemolytic anaemia. No clear-cut vit E deficiency syndrome has been described in humans, but vit E deficiency has been implicated in certain neuromuscular diseases in children, neurological defects in hepatobiliary disease and some cases of haemolytic anaemia.

Therapeutic uses

1. Primary vit E deficiency does not occur clinically. Supplemental doses (10–30 mg/day) may be given to patients at risk (*see* above).
2. G-6-PD deficiency—prolonged treatment with 100 mg/day increases survival time of erythrocytes.

3. Acanthocytosis—100 mg /week i.m: normalizes oxidative fragility of erythrocytes.
4. The risk of *retrolental fibroplasia* in premature infants exposed to high oxygen concentrations can be reduced by 100 mg/kg/day oral vitamin E.
5. Alongwith vit A to enhance its absorption and storage, and in hypervitaminosis A to reduce its toxicity.
6. Large doses (400–600 mg/day) have been reported to afford symptomatic improvement in intermittent claudication, fibrocystic breast disease and nocturnal muscle cramps.

For its antioxidant property, vit E has been promoted for recurrent abortion, sterility, menopausal syndrome, toxaemia of pregnancy, atherosclerosis, ischaemic heart disease, cancer prevention, several skin diseases, prevention of neurodegenerative disorders, postherpetic neuralgia, scleroderma and many other conditions, but without convincing evidence of benefit.

Toxicity Even large doses of vit E for long periods have not produced any significant toxicity, but creatinuria and impaired wound healing have been reported; abdominal cramps, loose motions and lethargy have been described as side effects of vit. E.

Vit E can interfere with iron therapy.

Antioxidant vitamins (vit E, β carotene, vit C) in prevention of cardiovascular disease and cancer

Antioxidants are believed to quench free radicals. Free radicals are atoms or molecules with 'singlet', i.e. unpaired electron which makes them highly reactive. Oxidative free radicals are generated by metabolic reactions, and create a chain reaction leading to membrane lipid peroxidation, DNA damage, etc. Free radical oxidation has been implicated in atherosclerosis (oxidized LDL is more atherogenic), cancers, neurodegenerative diseases and inflammatory bowel diseases. Many endogenous and dietary compounds like superoxide dismutase, ferritin, transferrin, ceruloplasmin, α tocopherol, β carotene and ascorbic acid have antioxidant and free radical scavenging properties. On this theoretical basis supported by some epidemiological observations, cohort studies and prospective trials β carotene, vit C and especially vit E have been claimed to protect against atherosclerosis leading to coronary artery disease as well as many types of cancers (lung, breast, mouth, skin, esophagus, stomach, etc.). As a result, vit E and others are being aggressively promoted and many physicians are prescribing them for prophylaxis of these conditions. Learning from mass media, people on their own also are consuming antioxidants on a large scale. However, the evidence of a beneficial effect is highly equivocal.

Several large observational studies (involving tens of thousands of subjects) and their metaanalysis have failed to demonstrate any benefit of antioxidant vitamins in terms of cardiovascular event/cancer prevention in well nourished population. On the other hand, there is some indication of increased risk of CHF with >400 mg/day α tocopherol and increased risk of hip fracture among postmenopausal women with high dose of vit A. Therefore, it would be well advised to adopt a healthy lifestyle, *viz.* eating sufficient fruits and vegetables, doing regular exercise, avoiding overweight and smoking, rather than consuming antioxidant medications.

A large number of antioxidant proprietary preparations (ANTOXID, CAROFIT, GLACE, VITOXID, REVOX, CARNITOR, CARNIVIT-E, etc.) containing widely variable amounts of β-carotene, vit A acetate, vit E, vit C, selenium, zinc, copper, manganese, carnitine (a substance synthesized in liver and kidney, and involved in intracellular transport of long-chain fatty acids) are briskly promoted and consumed, but with no credible evidence of benefit, and may be some potential harm.

WATER-SOLUBLE VITAMINS

THE VITAMIN B COMPLEX GROUP

Thiamine (Aneurine, vit B_1)

Chemistry and source A colourless, crystalline compound containing a pyrimidine and a

Table 69.1: Chemical forms, stability, daily allowance and non-combination preparations of vitamins

Vitamin	*Chemical forms*	*Thermostability*	*Daily allowance (adult males)*	*Preparations*
		Fat-Soluble Vitamins		
A	Retinol (A_1) Dehydroretinol (A_2) β-Carotene (provit)	Stable in absence of air	1000 µg (4000 IU)	AQUASOL-A 25,000 IU cap, 100,000 IU in 2 ml inj. AROVIT 10,000 IU tab, 150,000 IU/ml drops, 100,000 IU/ 2 ml inj. CAROFRAL 50,000 IU tab, 100,000 IU/2 ml inj.
D	Calciferol (D_2) Cholecalciferol (D_3) Calcitriol	Stable	5 µg (200 IU) 1 µg	ACRACHITOL, OSTELIN FORTE 300,000 IU/ml & 600,000 IU/ml inj (1 ml amp.), CALCIROL 60,000 IU in 1 g granules. CALTROL, ROCALTROL 0.25 µg cap, CALCIBEST 1 µg/ml inj.
E	α-Tocopherol	Stable; air and UV light decompose	10 mg	EVION 100, 200, 400, 600 mg pearls, 50 mg/ml paed. drops. VITEOLIN, ECAP 200, 400 mg pearls, cap., EROVIT, ETOPLEX, EPHYNA 200, 400 mg caps.
K	Phytonadione (K_1) (Phylloquinone) Menaquinones (K_2) Menadione (K_3) Acetomenaphthone	Stable, decomposed by light	50–100 µg	VITAMIN-K, KENADIONE 10 mg/ml inj. KAPILIN 10 mg tab., ACETOMENADIONE 5, 10 mg tab.
		Water-Soluble Vitamins		
B_1	Thiamine	Relatively labile	1.5 mg	BERIN 50, 100 mg tab, 100 mg/ml inj. (10 ml vial) BENEURON 5 mg cap., BETABION 100 mg tab.
B_2	Riboflavin	Relatively stable	1.7 mg	LIPABOL 20 mg tab. RIBOFLAVIN 10 mg/ml inj.
B_3	Nicotinic acid, Nicotinamide } Niacin Tryptophan (provit.)	Stable	20 mg	NICOTINIC ACID 25, 50 mg tab., NIALIP 250, 375, 500 mg tab NICOTINAMIDE 25, 50 mg tab.
B_6	Pyridoxine Pyridoxal Pyridoxamine	Stable in absence of air	2 mg	PYRIDOXINE HCl 50 mg/2 ml inj., 10 mg tab. BENADON 40 mg tab, PYRICONTIN 100 mg tab
	Pantothenic acid	Labile	4–7 mg	CALCIUM PANTOTHENATE 50 mg tab., 50 mg/2 ml inj.
	Biotin	Stable	0.1–0.2 mg	
	Folic acid Folinic acid	Labile	0.2 mg	FOLVITE, FACITAB 5 mg tab. CALCIUM LEUCOVORIN 3 mg/ml inj.
B_{12}	Cyanocobalamin Hydroxocobalamin Methylcobalamin	Stable	2 µg	MACRABIN 35 µg/ml liq: 100, 500, 1000 µg inj., REDISOL-H, MACRABIN-H 500, 1000 µg inj. VITAMIN B_{12} 500, 1000 µg in 10 ml vial. METHYLCOBAL, BIOCOBAL, DIACOBAL, 500 µg cap
C	Ascorbic acid	Labile in solution	60 mg	CECON 500 mg tab, 100 mg/ml drops. CELIN 50, 100, 500 mg tab., CHEWCEE 500 mg tab REDOXON 200, 500 mg tab, 500 mg/5 ml inj.

thiazole ring. It is present in the outer layers of cereals (rice polishing), pulses, nuts, green vegetables, yeasts, egg and meat.

Absorption and fate Physiological amounts are absorbed by active transport. When large doses are given orally, some passive diffusion also occurs. Limited amounts are stored in tissues. About 1 mg/day is degraded in the body, excess is rapidly excreted in urine.

Physiological role After conversion in the body to *Thiamine pyrophosphate*, it acts as a coenzyme in carbohydrate metabolism, catalysing decarboxylation of ketoacids and in hexose monophosphate shunt. Requirement of thiamine is dependent upon carbohydrate intake—about 0.3 mg/ 1000 K cal. It also appears to play some role in neuromuscular transmission.

Pyrithiamine and *oxythiamine* are synthetic thiamine antagonists. Tea also contains a thiamine antagonist.

Deficiency symptoms The syndrome of thiamine deficiency called beriberi is seen in *dry* and *wet* forms:

Dry beriberi: Neurological symptoms are prominent—polyneuritis with numbness, tingling, hyperesthesia, muscular weakness and atrophy resulting in 'wrist drop', 'foot drop', paralysis of whole limb, mental changes, sluggishness, poor memory, loss of appetite and constipation.

Wet beriberi: Cardiovascular system is primarily affected—palpitation, breathlessness, high output cardiac failure and ECG changes. Protein deficiency is commonly associated and adds to the generalised anasarka due to CHF.

Therapeutic uses

1. Prophylactically (2–10 mg daily) in infants, pregnant women, chronic diarrhoeas, patients on parenteral alimentation. Glucose infusion unmasks marginal thiamine deficiency.

2. Beriberi—100 mg/day i.m. or i.v. till symptoms regress—then maintenance doses orally.

3. Acute alcoholic intoxication: thiamine 100 mg is added to each vac of glucose solution infused. Most neurological symptoms in chronic alcoholics are due to thiamine deficiency—peripheral neuritis, Wernick's encephalopathy, Korsakoff's psychosis: give 100 mg/day parenterally.

4. In neurological and cardiovascular disorders, hyperemesis gravidarum, chronic anorexia and obstinate constipation—thiamine has been used even without definite proof of its deficiency—symptoms improve dramatically if thiamine deficiency has been causative.

Adverse effects Thiamine is nontoxic. Sensitivity reactions sometimes occur on parenteral injection.

Riboflavin (vit B_2)

Chemistry and source A yellow flavone compound found in milk, egg, liver, green leafy vegetables, grains.

Absorption and fate Well absorbed by active transport and phosphorylated in the intestine. Riboflavin phosphate (Flavin mononucleotide: FMN) is formed in other tissues as well. Body does not significantly store riboflavin; larger doses are excreted unchanged in urine. Thiamine and riboflavin are both synthesized by colonic bacteria but this does not become available to the host.

Actions and physiological role Flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) are coenzymes for flavoproteins involved in many oxidation-reduction reactions. Thiamine and riboflavin are devoid of pharmacological actions.

Deficiency symptoms Riboflavin deficiency generally occurs in association with other deficiencies. Characteristic lesions are angular stomatitis; sore and raw tongue, lips, throat, ulcers in mouth; vascularization of cornea. Dry scaly skin, loss of hair; anaemia and neuropathy develop later.

Therapeutic uses To prevent and treat ariboflavinosis (2–20 mg/day oral or parenteral), generally along with other B complex members. There is no proof of benefit in any other condition.

Niacin (vit B_3)

Chemistry and source Niacin refers to *Nicotinic acid* as well as *Nicotinamide*—pyridine compounds that were initially termed 'pellagra preventing factor'. Sources are liver, fish, meat, cereal husk, nuts and pulses.

The amino acid *tryptophan* (mainly from animal protein) can be regarded as a provitamin, because it is partially converted in the body to nicotinic acid (60 mg tryptophan = 1 mg

nicotinic acid). Maize eaters have suffered from pellagra because corn flour is poor in tryptophan and it is believed to contain a niacin antagonist. Thus, daily requirement of niacin is dependent on the amount of tryptophan in diet.

Absorption and fate Niacin is completely absorbed from gastrointestinal tract. Physiological amounts are metabolized in the body, while large doses are excreted unchanged in urine. Modest amounts are stored in liver.

Physiological role and actions Nicotinic acid is readily converted to its amide which is a component of the coenzyme *Nicotinamide-adenine-dinucleotide* (NAD) and its *phosphate* (NADP) involved in oxidation-reduction reactions. These pyridine nucleotides act as hydrogen acceptors in the electron transport chain in tissue respiration, glycolysis and fat synthesis. Flavoproteins regenerate them by oxidizing NADH and NADPH.

Nicotinic acid (but not nicotinamide) in large doses is a vasodilator, particularly of cutaneous vessels. It also lowers plasma lipids (*see* Ch. 46).

Deficiency symptoms Niacin deficiency produces 'Pellagra', cardinal manifestations of which are:

Dermatitis—sunburn like dermal rash on hands, legs and face which later turn black, crack and peal.

Diarrhoea—with enteritis, stomatitis, glossitis, salivation, nausea and vomiting.

Dementia—with hallucinations preceded by headache, insomnia, poor memory, motor and sensory disturbances.

Anaemia and hypoproteinaemia are common in pellagra. Chronic alcoholics are particularly at risk of developing pellagra, because in addition to dietary deficiency, niacin absorption is impaired in them. Other B vitamin deficiencies are often associated.

Therapeutic uses

1. Prophylactically (20–50 mg/day oral) in people at risk of developing pellagra.
2. Treatment of pellagra—200 to 500 mg/day in divided doses orally or parenterally. Striking improvement occurs in 1–2 days, but skin lesions take weeks to months. Nicotinamide is preferred, especially for injection, because it does not cause flushing and other side effects seen with nicotinic acid.
3. Hartnup's disease: in which tryptophan transport is impaired, and in carcinoid tumours which use up tryptophan for manufacturing 5-HT, need niacin supplementation.
4. Nicotinic acid (not nicotinamide) has been used in peripheral vascular disease and as hypolipidaemic (Ch. 46).

Adverse effects Nicotinic acid, in pharmacological doses, has many side effects and toxicities (*see* p. 688–89). Nicotinamide is innocuous.

Pyridoxine (vit B_6)

Chemistry and source *Pyridoxine, Pyriodoxal* and *Pyridoxamine* are related naturally occurring pyridine compounds that have vit B_6 activity. Dietary sources are—liver, meat, egg, soybean, vegetables and whole grain.

Absorption and fate All three forms of the vitamin are well absorbed from the intestine. They are oxidized in the body and excreted as pyridoxic acid. Little is stored.

Physiological role and actions Pyridoxine and pyridoxamine are readily oxidized to pyridoxal, which is then phosphorylated to *pyridoxal phosphate*—the coenzyme form. Pyridoxal dependent enzymes include transaminases and decarboxylases involved in synthesis of nonessential amino acids, sulfur containing amino acid and tryptophan metabolism, formation of 5-HT, dopamine, histamine, GABA and aminolevulinic acid (first step in the synthesis of haeme). High protein diet increases pyridoxine requirement.

Prolonged intake of large doses of pyridoxine can give rise to pyridoxine-dependence. Mega doses (0.2–2.0 g/day) have been linked with sensory neuropathy. Otherwise, pyridoxine is free from pharmacological actions and side effects. However, suppression of lactation has been noted in nonsuckling postpartal women given high doses of pyridoxine, which may be due to increased dopamine synthesis and action on pituitary lactotropes.

Drug interactions

1. Isoniazid reacts with pyridoxal to form a hydrazone, and thus inhibits generation of pyridoxal phosphate. Isoniazid also combines with pyridoxal phosphate to interfere with its coenzyme function. Due to formation of hydrazones, the renal excretion of pyridoxine

compounds is increased. Thus, isoniazid therapy produces a pyridoxine deficiency state.

2. Hydralazine, cycloserine and penicillamine also interfere with pyridoxine utilization and action.

3. Oral contraceptives reduce pyridoxal phosphate levels in some women.

4. Pyridoxine, by promoting formation of dopamine from levodopa in peripheral tissues, reduces its availability in the brain, abolishing the therapeutic effect in parkinsonism, but not when a peripheral decarboxylase inhibitor is combined with levodopa.

5. 4-deoxypyridoxine is a vit B_6 antagonist.

Deficiency symptoms Deficiency of vit B_6 usually occurs in association with that of other B vitamins. Symptoms ascribed to pyridoxine deficiency are—seborrheic dermatitis, glossitis, growth retardation, mental confusion, lowered seizure threshold or convulsions (due to fall in brain GABA levels), peripheral neuritis and anaemia.

Therapeutic uses

1. Prophylactically (2–5 mg daily) in alcoholics, infants and patients with deficiency of other B vitamins.

2. To prevent and treat (10–100 mg/day) isoniazid, hydralazine and cycloserine induced neurological disturbances. Acute isoniazid poisoning has been successfully treated with massive doses (in grams) of parenteral pyridoxine. Pyridoxine is routinely given along with anti-MDR-TB regimens (*see* p. 826).

3. To treat mental symptoms in women on oral contraceptives (50 mg daily).

4. Pyridoxine has been combined with doxylamine for treating morning sickness (*see* p. 712).

5. Pyridoxine responsive anaemia (due to defective haeme synthesis) and homocystinuria are rare genetic disorders that are benefited by large doses of pyridoxine (50–200 mg/day).

6. Convulsions in infants and children.

Pantothenic acid

Pantothenic acid is an organic acid, widely distributed in food sources, especially liver, mutton, egg yolk and vegetables. It is quickly absorbed and excreted unchanged in urine with little storage.

Pantothenic acid is a component of coenzyme-A which functions in carbohydrate, fat, steroid and porphyrin metabolism by catalysing acetate transfer reactions. Clinical deficiency of pantothenic acid is not known. Experimental deficiency in man causes insomnia, intermittent diarrhoea, flatulence, vomiting, leg cramps and paresthesias. Calcium/sodium pantothenate is included in B complex and multivitamin preparations. Intravenous calcium pantothenate has been tried in paralytic ileus.

Biotin

Biotin is a sulfur containing organic acid found in egg yolk, liver, nuts and many other articles of food. Some of the biotin synthesized by intestinal bacteria is also absorbed. Dietary biotin is well absorbed from intestine and excreted mainly unchanged in urine. Not much is stored in the body. *Avidin*, a heat labile protein in egg white, binds to and prevents the absorption of biotin. Some other biotin antagonists are also known.

Biotin is a coenzyme for several carboxylases involved in carbohydrate and fat metabolism. Deficiency symptoms include seborrheic dermatitis, alopecia, anorexia, glossitis and muscular pain. Spontaneous deficiency of biotin has been noted only in subjects consuming only raw egg white and in patients on total parenteral nutrition. Except for these unusual instances and rare genetic abnormalities of biotin dependent enzymes, there are no clearly defined therapeutic uses of biotin. It is present in some multivitamin preparations.

VITAMIN C (ASCORBIC ACID)

Chemistry and source Ascorbic acid is a 6 carbon organic acid with structural similarity to glucose. It is a potent reducing agent and the *l*-form is biologically active. Citrus fruits (lemons, oranges) and black currants are the richest sources; others are tomato, potato, green chillies, cabbage and other vegetables. Human milk is richer in vit C (25–50 mg/L) than cow's milk.

Absorption and fate Ascorbic acid is nearly completely absorbed from g.i.t. and widely distributed extra- and intracellularly. Plasma concentration and total body store of vit C is related to daily intake. The usual 60 mg/day intake results in about 0.8 mg/dl in plasma and 1.5 g in the body as a whole. Increasing proportions are excreted in urine with higher intakes. Body is not able to store more than 2.5 g. It is partly oxidized to active (dehydroascorbic acid) and inactive (oxalic acid) metabolites.

Physiological role and actions Vit C plays a role in many oxidative and other metabolic reactions, e.g. hydroxylation of proline and lysine residues of

Table 69.2: Combination preparations of vitamins

Proprietary name		*Dose unit*	*Vit. A*	*Vit. D*	*Vit. E*	*Thiamine*	*Riboflavin*	*Niacin*	*Pyridoxine*	*Pantothenic*	*Biotin*	*Folic acid*	*B_{12}*	*Vit. C*
			(IU)	(IU)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(µg)	(mg)
ABDEC DROPS		per 0.6 ml	5,000	400	–	1	1	10	0.6	3	–	–	–	50
ADEXOLIN	cap	per cap.	5,000	400	–	–	–	–	–	–	–	–	–	–
AQUASOL-A-D	drops	per ml	24,000	1,000	–	–	–	–	–	–	–	–	–	–
AQUASOL-A-E	cap	per cap.	30,000	–	50	–	–	–	–	–	–	–	–	–
BECOSULES	cap	per cap.	–	–	–	10	10	50	3	12.5	–	1	5	150
"	syrup	per 5 ml	–	–	–	2	2.5	20	2	6	–	–	–	75
BECOZYME C FORTE	tab.	per tab.	–	–	–	15	15	50	3	16.3	0.15	–	10	150
BEJECTAL	inj.	per ml	–	–	–	10	2	75	5	5	–	–	–	–
EDINOL	cap	per cap.	10,000	1,000	15	10	10	50	3	10	–	1	5	150
MULTIVITAPLEX	elixir	per 5 ml	2,500	200	–	2	2.5	20	1	5	–	–	–	50
" FORTE	cap.	per cap.	10,000	400	15	5	5	50	1.5	5	–	1	5	75
COBADEX FORTE	cap.	per cap	–	–	–	10	10	100	3	50	–	1.5	15	–
COBADEX SYRUP	syr	per 5 ml	–	–	–	5	2.5	50	1.5	5	–	–	–	–
KINETONE	liq.	per 15 ml	2,000	200	7.5	2	3	–	1.5	–	–	–	1	–
OPTINEURON	inj.	per 3 ml	–	–	–	100	5	100	100	50	–	–	1000	–
STRESS CAPS	cap.	per cap	–	–	–	10	10	100	2	20	–	–	5	150
NEUROXIN-12	inj.	per 10 ml	–	–	–	30	–	–	14	–	–	–	500	–
" FORTE	inj.	per 3 ml	–	–	–	100	5	100	100	50	–	–	1000	–
NEUROBION	tab.	per tab	–	–	–	10	10	45	3	50	–	–	15	–
POLYBION	cap.	per cap.	–	–	–	10	10	100	3	50	–	1.5	15	150
"	inj.	per 2 ml	–	–	–	10	4	40	4	6	–	–	8	–
ZEVIT	cap.	per cap.	–	–	20	1	10	75	2	25	–	–	–	150
SCLEROBION	tab.	per tab.	10,000	–	25	–	–	–	3	–	–	–	–	–
VIMAGNA	drops	per ml	2,000	200	–	0.8	0.8	13	0.8	1.7	–	–	–	20

Combined formulations of vitamins with analgesics, antiinflammatory drugs, tranquilizers and antitubercular drugs (except isoniazid + pyridoxine) are banned in India.

protocollagen which is essential for formation and stabilization of collagen triple helix; hydroxylation of carnitine, conversion of folic acid to folinic acid, biosynthesis of adrenal steroids, catecholamines, oxytocin and vasopressin and metabolism of cyclic nucleotides and prostaglandins. It directly stimulates collagen synthesis and is very important for maintenance of intercellular connective tissue. A number of ill-defined actions have been ascribed to ascorbic acid in mega doses, but none is proven.

Deficiency symptoms Severe vit C deficiency called *Scurvy*, once prevalent among sailors is now seen only in malnourished infants, children, elderly, alcoholics and drug addicts. Symptoms stem primarily from connective tissue defect, *viz* increased capillary fragility causing swollen and bleeding gums, petechial and subperiosteal haemorrhages, deformed teeth, brittle bones, impaired wound healing, anaemia and growth retardation.

Therapeutic uses

1. Prevention of ascorbic acid deficiency in individuals at risk (*see* above) and in infants: 50–100 mg/ day. Vit C or orange juice can be routinely included in infant diet.
2. Treatment of scurvy—0.5–1.5 g/day.
3. Postoperatively (500 mg daily): though vit C does not enhance normal healing, suboptimal healing can be guarded against. It has also been found to accelerate healing of bedsores and chronic leg ulcers. Requirement of ascorbic acid is increased in postinjury periods.
4. Anaemia: Ascorbic acid enhances iron absorption and is frequently combined with ferrous salts (maintains them in reduced state). Anaemia of scurvy is corrected by ascorbic acid, but it has no adjuvant value in other anaemias.
5. To acidify urine (1 g TDS–QID) in urinary tract infections (*see* Ch. 55).
6. Large doses (2–6 g/day) of ascorbic acid have been tried for a variety of purposes (common cold to cancer) with inconsistent results. No definite beneficial effect has been noted in asthma, cataract, cancer, atherosclerosis, psychological symptoms, infertility, etc. However, severity of common cold symptoms may be somewhat reduced, but not the duration of illness or its incidence. Improved working capacity at submaximal workloads has been found in athletes but endurance is not increased.

Adverse effects Ascorbic acid is well tolerated in usual doses. Mega doses given for long periods can cause 'rebound scurvy' on stoppage—probably due to enhancement of its own metabolism or tissue acclimatization. The risk of urinary oxalate stones may be increased. High doses may also be cytotoxic when added to iron preparations.

Vitamin D (Ch. 24), vit K (Ch. 45), folic acid and vit B_{12} (Ch. 44) have been considered in earlier chapters.

Chapter 70 Vaccines, Antisera and Immunoglobulins

Vaccines, sera and immunoglobulins are biological products which act by reinforcing the immunological defence of the body against foreign agencies (mostly infecting organisms or their toxins).

Vaccines impart *active immunity:* they act as antigens which induce production of specific antibodies and/or cell mediated immunity by the recipient himself.

Antisera and *immunoglobulins:* they impart passive *immunity*—readymade antibodies (produced by another person or animal who has been actively immunized) are transferred to the recipient.

Active immunization is more efficacious and longer lasting than passive immunization, but the former needs a latent period of one to many weeks, whereas the latter affords immediate protection. Antisera are, therefore, curative also, whereas vaccines are only prophylactic. Acutely ill, debilitated or immunocompromised individuals may not be able to generate an adequate antibody response and require passive protection.

Vaccines and sera are potentially dangerous products and mostly used in public health programmes. Their manufacture, quality control, distribution and sale is strictly supervised by State health authorities. These biologicals are standardized by bioassay and need storage in cold to maintain potency.

VACCINES

Vaccines are antigenic materials consisting of the whole microorganism or one of its products. Vaccines are of 3 types:

(i) *Killed (Inactivated) vaccines*: They consist of microorganisms killed by heat or chemicals. They generally require to be given by a series of injections for primary immunization. The immunity is relatively shorter-lasting; booster doses are mostly needed at intervals of months or years.

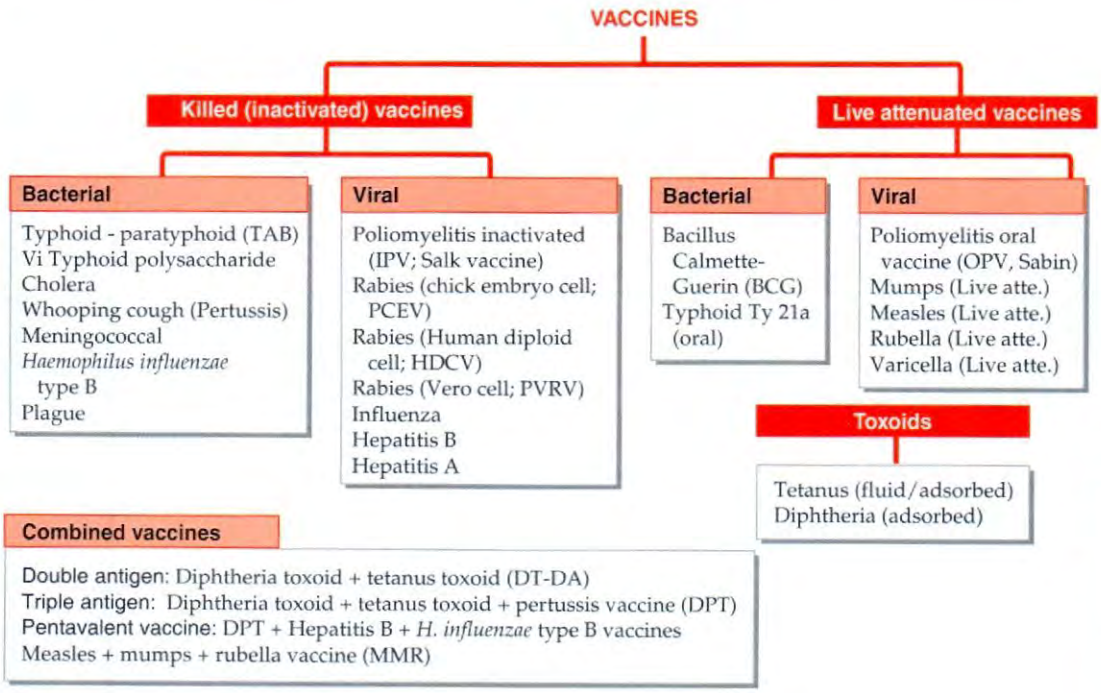
(ii) *Live attenuated vaccines*: They consist of live bacteria or viruses which have been rendered avirulent. They nevertheless grow and multiply in the body of the host to a limited extent. Live vaccines usually produce long-lasting immunity. In individuals with impaired host defence, e.g.

(a) Leukaemia or other malignancies, especially those receiving cytotoxic chemotherapy.
(b) Systemic lupus erythematosus.
(c) Corticosteroid recipients.
(d) AIDS and other immune deficiency states, the limited virulence of organisms in the live vaccine may be sufficient to cause a disease; live vaccines are contraindicated in them.

Two live vaccines, if not given together, should preferably be administered with a gap of 1 month.

(iii) *Toxoids*: These are modified bacterial exotoxins so that toxicity is lost but antigenicity is retained. The term 'vaccine' is sometimes restricted to preparations of whole microorganisms and toxoids are enumerated separately.

Active immunization with vaccines may fail to 'take' during corticosteroid or immunosuppressant medication and should be avoided. Vaccination should be deferred in the presence of any acute (especially respiratory) infection



and during pregnancy. Antibiotics added during production of vaccines and present in trace amounts in viral vaccines may cause reaction in individuals sensitive to these. Egg proteins (in vaccines prepared on chick embryo) and other materials used for vaccine culture may be responsible for allergic reactions. Adrenaline injection (1 in 1000) should be available to control allergic reaction to the vaccine, if it occurs.

The antibodies developed in response to live or killed vaccines inactivate the bacteria/virus when it subsequently enters the body, while those induced by toxoids neutralize the elaborated exotoxin. The latent period between vaccination and development of immunity and the period for which it lasts depends primarily on the organism, but varies somewhat in different individuals. Viral vaccines and toxoids generally afford more prolonged protection than bacterial vaccines. The important vaccines are described briefly.

BACTERIAL VACCINES

1. Typhoid-Paratyphoid A, B (TAB vaccine) It is a sterile suspension, 1 ml containing 1×10^9 *S. typhi* and 7.5×10^8 each of *S. paratyphi* A and B organisms in 5, 10 ml vials. *Dose*—0.5 ml s.c., 2–3 injections at 2–4 weeks intervals. Local tenderness, fever and malaise lasting 1–2 days are common after the first dose. It is estimated to be 70% effective in preventing enteric fever for 1 year. Booster doses may be given every 2–3 years.

2. Vi Typhoid polysaccharide vaccine It contains purified Vi capsular antigen of *S. typhi*. A single 0.5 ml s.c./i.m. dose affords 72% protection at 18 months and 60% protection at 3 years. It produces much less local and systemic side effects than TAB and induces longer lasting immunity, but does not protect against paratyphoid A and B. Thus, it is an improvement over the whole cell TAB vaccine. However, it is not approved for use in children below 2 years and in pregnant women.
VACTYPH, TYPHIM Vi, TYPHIVAX 0.025 mg in 0.5 ml inj; repeat after 3 years.

3. 'Typhoid-Ty21a' oral vaccine This is a newer live oral typhoid vaccine prepared from Ty21a attenuated strain of *S. typhi* which lacks the Vi polysaccharide and is nonpathogenic. It is avirulent. By lodging in the

intestinal mucosa it protects against *S. typhi* invasion of the gut in addition to imparting systemic immunity. High cell mediated and modest antibody mediated immunity is produced. Administered as 3 doses on alternate days in the form of enteric coated capsules it affords protection for 3 years. Efficacy is better than TAB. Trials in India and other countries have reported 67–90% protection at 3 years. Side effects are negligible: only 2% cases have reported diarrhoea, abdominal pain or rashes. It is much more convenient, safer and longer acting. It is not approved for use in ~~children below 5 years~~ and in ~~pregnant women~~.

TYPHORAL *S. typhi* strain Ty21A 10^9 organism per cap; 3 caps taken in 3 doses on alternate days in between meals.

4. Cholera vaccine It is a suspension of phenol/formalin killed Inaba and Ogawa strains of *V. cholerae*, each ml containing 8×10^9 organisms in 5, 10, 30 ml vials. *Dose:* 0.5 ml s.c. or i.m. followed by 1 ml 1–4 weeks later, or a single dose of 1 ml for mass inoculation. Immunity, sufficient to prevent clinical disease, is produced only in < 50% of those inoculated, and lasts 6 months or so. It is infrequently used now.

Two new oral cholera vaccines have been produced: killed whole cell/recombinant B subunit (WC/r BS) and live CVD-103 HgR vaccine. Both these vaccines are highly immunogenic, safer than the present cholera vaccine and provide immunity upto 3 years. Cumulative protective efficacy of 86% at 3 weeks and 50% at 3 years have been estimated. They have been made available in Europe, but not yet in India.

5. Whooping cough (pertussis) vaccine It is killed 2×10^{10} organisms/ml suspension of *B. pertussis* organisms. *Dose* 0.25–0.5 ml s.c. or i.m. thrice at 4 week intervals in infants and children below 5 years (whooping cough is very rare after 5 years age).

It also induces a state of diminished β adrenergic reactivity and aids sensitization to other antigens.

In addition to local pain and induration, severe systemic (even fatal) reactions have been reported, but extremely rarely—high fever with hypotonic hyporesponsive child, convulsions, alterations of consciousness and focal neurological signs. Once any such reaction has occurred, further doses are contraindicated. Pertussis vaccine is also contraindicated in children with history of convulsions or other neurological disease.

It is a component of triple antigen: seldom used separately.

6. Meningococcal A&C vaccine It contains purified capsular polysaccharide of *N. meningitidis* group A and C, 50 µg of each per unit in single dose and 10 dose vials. One dose (0.5 ml s.c. or i.m.) is indicated for prophylaxis of meningitis during an epidemic caused by group A or C meningococci.

MENINGOCOCCAL A & C, MENCEVAX A & C 0.5 ml amp, 5 ml vial.

7. Haemophilus influenzae type b (Hib) vaccine It contains medium oligosaccharide of *H. influenzae* type b (10 µg) conjugated with nontoxic protein (25 µg) of CRM_{197} mutant *C. diphtheriae* toxin along with alum. hydrox. adjuvant. It is indicated for protection of infants and children against *H. influenzae* meningitis, pneumonia, etc. Infants 2–6 months are given 3 doses (0.5 ml i.m.) at 8 week gaps, 7–11 months 2 doses, while those older than 1 yr require only 1 dose. Good antibody response and protection has been obtained in > 90% recipients.

VAXEM-HIB, HIB-TITER 0.5 ml and 5 ml vials.

8. Antiplague vaccine formalized It contains 2×10^9 *Y. pestis* organisms per ml, killed by formaline, in 10 ml vial. *Dose*—1 ml i.m. twice 1–2 weeks apart or 2 ml single dose. Local and systemic reactions are relatively frequent and increase with the number of booster doses. Immunity lasts 6–8 months—sufficient to cover an epidemic. Plague is now rare, so is the need for this vaccine.

9. Bacillus Calmette-Guérin (BCG) vaccine It is a live vaccine bearing an attenuated bovine strain of *M. tuberculosis*, developed in 1921 by Calmette and Guérin in France. It is supplied as 0.5–1 mg dry powder ($1–2.5 \times 10^7$ colony forming units) in ampules to be suspended in 1 ml of sterile water; 0.05 ml (in neonate) 0.1 ml (older individuals) is injected intracutaneously in the left deltoid region at birth. In children and adults tuberculine testing is done beforehand and BCG is given only to negative responders.

A red painless papule appears after 7–10 days; reaches about 8 mm diameter in 5 weeks with swelling of axillary lymph node. The papule may ulcerate, but later scales and dries in 3 months; totally heals in 6 months. The protection afforded by BCG is partial and neither permanent nor

entirely predictable. BCG has been widely used to enhance resistance to tubercular infection, but doubt has been cast about its utility in adults, though children appear to be benefited.

BCG has also been used to enhance immunity nonspecifically by stimulating the reticuloendothelial system, e.g. as adjuvant in immunotherapy of cancer and some other conditions. It is contraindicated in tuberculine positive individuals, in those with compromised host defence including HIV positive children, and during pregnancy.

VIRAL VACCINES

1. Poliomyelitis The virus (type 1, 2, 3) is grown in monkey kidney cell culture and two vaccines are prepared from it.

(a) *Oral poliovirus vaccine (OPV; Sabin vaccine)* It is the live vaccine virus available in 10 ml and 50 ml vials; each dose is 2 drops, dropped directly in the mouth. The virus multiplies in the intestines and produces active immunity, simulating natural infection, without producing symptoms of the disease. For primary immunization OPV is now generally given at birth and then at 6, 10 and 14 weeks. Booster doses are given between 15–18 months and at school entry. OPV is the vaccine of choice for active immunization of children because it is simple to administer, is well accepted, induces systemic as well as intestinal immunity (the portal of entry of disease virus) and is highly efficacious. The intestinal immunity also eliminates carrier state and thus limits spread of the disease. It is advised to postpone the vaccine in presence of vomiting and diarrhoea. Vaccine associated paralysis occurs extremely rarely.

Simultaneous vaccination of all infants and children upto 5 years age (pulse polio programme) has eradicated the wild virus in many countries by colonizing all susceptible intestines by the vaccine virus. This programme is underway in India.

(b) *Inactivated poliomyelitis vaccine (IPV, Salk vaccine)* It is inactivated suspension of the virus which is preferred over OPV only for:

(i) primary immunization in adults (risk of vaccine associated paralysis following OPV is higher in adults).
(ii) in persons with compromized immune system.

Three doses of 1 ml each are injected s.c. in the deltoid region at 4–6 week intervals and a fourth is given 6–12 months later. Booster doses are given every 5 years. Fever and local pain are common. Allergic reactions sometimes occur, probably to the animal protein present in the vaccine.

2. Rabies Four rabies vaccines have been produced. The neural tissue vaccine is no longer used.

a. *Purified chick embryo cell vaccine (PCEV)* It consists of Flury-LEP strain of rabies virus grown on chick fibroblasts and inactivated by β-propiolactone; available as 2.5 IU in 1 ml amp (RABIPUR). The efficacy of this vaccine is nearly equal to HDCV, and it produces local reactions in ~5% cases. However, neuroparalytic complications have been reported rarely. Local pain, erythema, swelling and lymph node enlargement can occur.

b. *Human diploid cell vaccine (HDCV)* It is lyophilized inactivated rabies virus grown in human diploid cell culture. The vial containing 2.5 IU is freshly suspended in 1 ml of diluent. MERIEUX HDC 2.5 IU inj.

A local reaction in the form of redness and slight induration lasting 1–2 days occurs in 10% cases. Fever and arthralgia is reported in 1%. HDCV is ~100% effective and well tolerated. Vaccine associated encephalitis does not occur.

c. *Purified vero cell rabies vaccine (PVRV)* This contains inactivated wistar rabies PM/WI38-1-503-3M strain grown on vero continuous cell line (VERORAB 1 ml; VEROVAX-R 0.5 ml).

Post-exposure prophylaxis: This is given to all nonimmunised animal-bite cases suspected to have been exposed to the rabies virus. The intradermal (i.d.) regimen for all tissue culture rabies vaccines called the 'Thai regimen' that has been recommended by the WHO since 1992, has been approved and notified by the Government of India in 2006. This regimen requires only 1/5 dose of the earlier used i.m. regimen, is less expensive, more convenient and equally efficacious. In this regimen 0.1 ml of PCEV or PVRV or 0.2 ml of HDCV

is injected i.d. at 2 sites (over deltoid of both arms) on days 0, 3 and 7 followed by 1 site injection on day 28 (or 30) and day 90, (2 + 2 + 2 + 1 + 1 = 8 injections). Thus, no injection is given on day 14 as in earlier i.m. regimen which employed 1 ml PCEV/HDCV or 0.5 ml PVRV per injection on days 0, 3, 7, 14, 30, 90.

Because rabies vaccines take 10–14 days to develop protective antibodies, concurrent administration of rabies immunoglobulin (RIG) is recommended in category III bites, where risk of contacting rabies is high.

An alternative 8 site i.d. regimen (Oxford regimen) is advocated for an earlier antibody response, particularly when RIG is not available for postexposure treatment. In this regimen 0.1 ml of PCEV or HDCV (but not PVRV) is injected at 8 sites (over both deltoids, suprascapular region, thighs and abdomen) on day 0. On 7th day 4 sites are injected followed by one site injection on day 28 and 90 (total 14 injections).

Pre-exposure prophylaxis (Primary vaccination): This is usually recommended for veterinary workers and animal handlers, who are at high risk of animal bites. Three i.d. injections of 0.1 ml each of PCEV/HDCV/PVRV are given on days 0, 7 and 28. Booster doses are recommended every 2 years so long as the person remains at risk.

Post-exposure prophylaxis in already vaccinated subjects: This is given when an immunized person is bitten by a suspected animal. Three 0.1 ml i.d. injections are given on days 0, 3 and 7.

Local treatment of bite wound: Early local treatment of bite wound is essential in addition to the vaccine ± RIG. The wound should be thoroughly washed with soap under running water for at least 5 min, followed by application of an antiseptic (alcohol/povidone iodine/cetrimide). Cauterization with carbolic acid is contraindicated. In category III bites, RIG should be infiltrated locally in the depth and around the wound to inactivate the locally present virus. Suturing of the wound should be avoided, at least for 2 days.

3. Influenza virus vaccine It contains inactivated influenza virus A and B. Immunization may be done annually or during an epidemic: 2 injections of 0.5–1 ml i.m. 1–2 months apart. Influenza virus undergoes frequent antigenic changes; hence the efficacy of the vaccine is inconsistent. It is indicated only in high risk cases.

VAXIGRIP 0.5 ml prefilled syringe.

Adverse reactions are commoner in children—local tenderness and induration occurs in 30%. Fever, malaise and myalgia lasting 1–2 days is less frequent. Allergic reactions to the egg protein present in the vaccine occur rarely.

4. Hepatitis B vaccine The new hepatitis B vaccine is prepared in yeast cells by recombinant DNA technique and contains aluminium hydroxide adsorbed hepatitis B virus surface antigen 20 µg in 1 ml suspension. Three 1 ml injections in the deltoid muscle given at 0, 1 and 6 months produce protective antibody titers in 99% subjects. Children <10 yr are given 0.5 ml doses in the thigh. Hepatitis B vaccine is now included in universal immunization for all, but is especially indicated in persons who come in contact with blood, blood products and other body fluids (surgeons, dentists, blood bank personnel, laboratory technicians and other health care workers, haemophilics, haemodialysis patients, drug addicts, etc). Induration and soreness at injection site and occasional fever and malaise are the adverse effects.

ENGERIX-B, ENVIVAC-HB 1 ml (single dose) and 10 ml (multi dose) vials.

5. Hepatitis A vaccine It is prepared by inactivating with formaldehyde hepatitis A virus grown in human diploid cell culture. A single 0.5 ml i.m. injection in deltoid muscle affords protection, but a booster dose ater 6 months is recommended.

AVAXIM 0.5 ml prefilled syringe, HAVRIX 0.5 ml inj.

6. Mumps virus vaccine live attenuated It is prepared from mumps virus grown in cell culture of chick embryo. A single dose of 5000 $TCID_{50}$ (tissue culture infectious dose 50%) affords protection for 10 years; revaccination is not required. Clinical disease may occur if the vaccine is given *after exposure* to natural mumps. It is generally combined with measles and rubella vaccine (MMR), and is not recommended below 1 year of age. A mild febrile reaction occurs occasionally.

7. Measles vaccine live attenuated This is also a vaccine grown on chick embryo; available in single dose vials containing 1000 $TCID_{50}$ of *Edmonston Schwarz* strain (ROUVAX, RIMEVAX) or *Edmonston zagreb* strain (M-VAC) for s.c. injection over right deltoid region. It produces a modified infection—fever, rash and coryza may appear after 5–10 days; immunity lasts 8 years and no booster doses are required. It is recommended in children 9 months or older. Ordinarily, adults need not be immunized.

Malnourished, chronically ill and tuberculous children must be protected to minimize the risk of serious complications of natural measles. Some protection is afforded even if given after exposure. It should be given with caution to children with history of febrile convulsions or parental history of epilepsy.

8. Rubella vaccine (R-VAC) It contains live attenuated rubella virus Wistar RA27/3 strain 1000 $TCID_{50}$ per 0.5 ml inj. for deep s.c. or i.m. injection in upper arm. It is used especially in girls from 1 yr age to puberty—for immunization against German measles; mostly as combined MMR vaccine. It is contraindicated during pregnancy, febrile illness and in untreated tuberculosis patients. Reactions are fever, malaise, sore throat, joint pain and lymphadenopathy.

9. Measles-Mumps-Rubella (MMR) vaccine Two preparations of this combined live vaccine are available. Both have similar efficacy.

TRIMOVAX lyophilized measles 1000 $TCID_{50}$ of Schwarz strain, mumps 5000 $TCID_{50}$ and rubella 1000 $TCID_{50}$ per unit dose (0.5 ml) vial.

TRESIVAC lyophilized measles 5000 $TCID_{50}$ of Edmonston Zagreb strain, mumps 5000 $TCID_{50}$ and rubella 4000 $TCID_{50}$ per unit dose (0.5 ml) vial.

A single dose injected s.c. over right deltoid is indicated in children older than 12 months for protection against these 3 diseases. Mild fever, rash, enlargement of cervical/occipital lymph nodes, parotid glands and local induration may occur after ~5 days. This vaccine is absolutely contraindicated during pregnancy; adult female vaccinees should not conceive for at least 2 months.

10. Varicella vaccine It is lyophilised live attenuated OKa strain of varicella-zoster virus grown in human diploid cell culture, containing $10^{3.3}$ PFU (plaque forming units) of the virus. A single dose induces antibody response in > 98% children and affords protection for 10 years.

Dose: 0.5 ml s.c. single dose for children 1–12 years, and 2 doses 6–10 weeks apart in those >12 years.

VARILRIX, OKAVAX 0.5 ml inj.

Varicella vaccine is contraindicated during pregnancy, in those with lymphocytopenia and within 1 month of measles vaccination. Mild local reaction, papular eruption and short-lasting fever occurs in 4–5% children.

TOXOIDS

1. Tetanus toxoid It is formaline treated exotoxin of tetanus bacilli; indicated for routine immunization in all children and adults. Two types of preparations—*fluid* toxoid and *adsorbed* toxoid are available. The adsorbed toxoid is superior. It induces higher antibody titers and more prolonged immunity. *Dose:* 0.5 ml, preferable route is i.m., can also be given s.c.

For primary immunization—Tetanus toxoid adsorbed (0.5 ml amp. 10 ml vial), 2 doses are given 4–6 weeks apart, or Tetanus toxoid fluid (1 ml amp, 10 ml vial) 3 doses at interval of 3–4 weeks. Booster dose should be given after 1 year and then every 10 years. In non-immunized or inadequately immunized individuals the toxoid should be given after any injury likely to introduce tetanus bacilli. Concomitant administration of chloramphenicol is avoided, as it may interfere with antibody response.

TETANUS TOXOID ADSORBED 0.5 ml amp, 5.0 ml vial.

Reactions—Local erythema, pain and induration is not uncommon. Axillary lymph nodes may enlarge. Fever, chills, malaise, aches and pains occur occasionally, especially in adults. Paresis and other neurological complications are rare.

2. Diphtheria toxoid adsorbed It is modified diphtheria exotoxin adsorbed onto aluminium hydroxide. It is indicated in infants and children below 6 years of age. Older individuals seldom require protection against diphtheria. For primary immunization 2–3 injections of 0.5 ml i.m. are given 4–6 weeks apart, booster dose after 1 year and then at school entry. Reactions are similar to those caused by tetanus toxoid.

MIXED ANTIGENS

1. Double antigen (DT-DA) It consists of alum precipitated toxoids of tetanus and diphtheria, available in 0.5 ml ampule and 5 ml vial (DUAL ANTIGEN). It is used in children above 5 years and in younger children in place of triple antigen when pertussis vaccine is contraindicated.

Dose: 0.5 ml i.m.

2. Triple antigen (DPT) It is a mixture of toxoids of tetanus and diphtheria with pertussis vaccine (TRIPVAC: Diphtheria toxoid 25 Lf, tetanus toxoid 5 Lf, *B. pertussis* 20,000 million in 0.5 ml amp; also 10 ml multidose vial).

DPT is the preparation of choice for primary active immunization against the 3 diseases in children below 5 years age. *Dose*–0.5 ml i.m. in the anterolateral aspect of midthigh or right deltoid, 2–3 injections 4–8 weeks apart, between 3–9 months age and one at 18 months. Reactions, precautions and contraindications mentioned under the individual vaccines apply to triple antigen as well.

3. Pentavalent vaccine It contains toxoids of tetanus and diphtheria along with pertussis vaccine, hepatitis B vaccine and *Haemophilus influenzae* type b (Hib) vaccine. It is indicated in place to triple antigen for primary immunization of infants, and affords protection against two additional common infections. It also reduces the total number of injections that the infant receives for protection against these 5 infections. Pentavalent vaccine has been used in many countries, and now Government of India has included it in the Essential Medicines List (2015). It is to be used in the universal immunization programme for infants and children. Few infant deaths have been reported, though the relationship between the deaths and the vaccine is not clear. Nevertheless, some experts have raised concern about its safety.

A routine immunization schedule for infants and children is given in the box.

Routine immunization schedule for infants and children

At birth	BCG + OPV (first dose) + Hepatitis B (after 12–24 hours)
At 6 weeks	DPT + OPV + Hepatitis B
At 10, 14 weeks	DPT + OPV
At 6 months	Hepatitis B
At 9 months	Measles
At 15–18 months	DPT + MMR + OPV (booster dose)
At 4–5 years	DT-DA + OPV (booster dose)
(School entry)	Typhoid (TAB 2 doses/Vi 1 dose/ Ty 21a 3 doses) optional
At 10 years	TT + TAB/Vi/Ty 21a (optional)
At 16 years	TT
For pregnant women	
16–24 weeks	TT (1st dose)
24–34 weeks	TT (2nd dose)

ANTISERA AND IMMUNE GLOBULINS

Antisera These are purified and concentrated preparations of serum of horses/rabbits actively immunized against a specific antigen.

Immediate type of allergic reactions (urticaria, angioedema, respiratory distress, anaphylaxis) can occur with any antiserum; adrenaline (1:1000 amp.) should be at hand while injecting them. Prior to each administration, history of reaction to any 'serum' preparation should be elicited and an intracutaneous/scratch test should be performed. A positive test contraindicates administration but a negative test does not completely rule out systemic sensitivity.

Serum sickness with fever, rash, joint pain, lymphadenopathy appearing 7–12 days later is more frequent after large doses and repeated administration. An overall incidence of 5–10% is reported.

Local pain, erythema and arthus type reaction without constitutional symptoms may also occur 7–10 days after i.m. injection.

Immune globulins (IGs) These are separated human gamma globulins which carry the antibodies. The IGs may be nonspecific (normal) or specific (hyperimmune) against a particular antigen. IGs are *more efficacious* than the corresponding antisera, and have a longer t½. Hypersensitivity reactions are very rare with IGs. Skin tests may be misleading and are not needed. However, large doses and repeated injections do increase the risk; adrenaline should be available. Transient local tenderness and stiffness of injected muscle is occasional. Serum sickness does not occur with human IGs.

1. Normal human gamma globulin It is concentrated IG obtained by fractionation in cold from pooled human plasma. Indications for its use are—viral hepatitis A and B (prophylaxis), measles, mumps, poliomyelitis and chickenpox (prophylaxis and modification of course of

Antisera (from horse)

- Tetanus antitoxin (ATS)
- Gas gangrene antitoxin (AGS)
- Diphtheria antitoxin (ADS)
- Antirabies serum (ARS)
- Antisnake venom polyvalent

Immune globulins (human)

- Normal human gamma globulin
- Anti-D immune globulin
- Tetanus immune globulin
- Rabies immune globulin
- Hepatitis-B immune globulin

illness), and has some beneficial action in burns. It is especially valuable in agammaglobulinemia, premature infants and in patients of leukemia or those undergoing immunosuppression. It can augment the response to antibiotics against bacterial infections in debilitated patients.

Dose: 0.02–1 ml/kg i.m. for different indications.

GAMMALIN, GLOBUNAL, Sii GAMMA GLOBULIN, GAMAFINE 10%, 16.5% injection in 1, 2 ml amps.

An intravenous preparation (Sii I.V.GG 0.1–0.4 g/kg/day) has been made available for conditions requiring high doses which cannot be injected i.m.

2. Anti-D immune globulin (see p. 944).

3. Tetanus

(a) *Tetanus immune globulin (human)* It is indicated for prophylaxis in non-immunized persons getting a contaminated wound who are at high risk of developing tetanus. The t½ of this antitoxin is 4 weeks and significant blood levels are maintained for upto 14 weeks. It is more efficacious and longer acting than the equine antitoxin (ATS). If tetanus toxoid is given at the same time (but at a different site), development of primary immune response to the toxoid is not interfered with. It has also been used for the treatment of clinical tetanus, but the efficacy is variable. Intrathecal administration has also been tried.

Dose: prophylactic 250–500 IU, therapeutic 3000–6000 IU i.m. and/or 250-500 IU intrathecal.

Sii TIG 250 IU (liquid), 500 IU (lyophilized), TETNAL 250 IU/2 ml inj., TETAGAM 250 IU/ml inj.

(b) *Tetanus antitoxin (antitetanic serum, ATS)* It is obtained from horse, and is inferior to human antitoxin. It should be used for the above indications only when tetanus immune globulin is not available.

Dose: prophylactic 1500–3000 IU, i.m. or s.c.; therapeutic 50,000–100,000 IU part i.v. and rest i.m.

TETANUS ANTITOXIN 750 IU, 1500 IU, 5000 IU, 10,000 IU, 20,000 IU, and 50,000 IU in 1–10 ml ampoules.

TETANUS IMMUNE SERUM (enzyme refined, equine) 10,000 and 20,000 IU vials.

4. Rabies

(a) *Antirabies serum (ARS)* Also called 'equine rabies immune globulin' (ERIG) is refined, concentrated and lyophilized serum from horses hyperimmunized by repeated injections of fixed rabies virus. It is indicated promptly after suspected exposure and is given simultaneously with rabies vaccine to nonimmunized individuals.

Dose—40 IU/kg infiltrated round the wound and excess is injected i.m.; single dose at the initiation of antirabic therapy along with rabies vaccine. It is inferior to HRIG and should be used only when HRIG is not available.

IMORAB 1000 IU/5 ml inj.

(b) *Rabies immune globulin human (HRIG)* It is used in the same manner as ARS and is superior to it with longer t½. *Dose*—20 IU/kg, on day 0 only, infiltrated round the bite; excess may be injected i.m. elsewhere. Passive protection with HRIG or ARS is needed because active immunity takes 2 or more weeks to develop.

BERIRAB-P 300 IU/2 ml and 750 IU/5 ml inj; RABGLOB 300 IU/2 ml inj.

5. Hepatitis B immune globulin

It is 10–18% solution of human IG containing a high titer of antibody to hepatitis B surface antigen. It is a better prophylactic than normal human gamma globulin and is indicated in individuals accidentally exposed to HBsAg positive blood or blood products. Hepatitis B vaccine should be given concurrently.

Dose: 1000–2000 IU (adults), 32–48 IU/kg (children) to be administered within 7 days of exposure.

HEPAGLOB 100 IU (0.5 ml) 200 IU (1 ml) per vial for i.m. inj.

6. Diphtheria antitoxin (Antidiphtheritic serum ADS)

It is obtained from horse and is used therapeutically in clinical diphtheria without waiting for bacteriological report, because each hour's delay increases the dose requirement and decreases beneficial effects. Moreover, damage already caused by the toxin is not reversed. The

antitoxin neutralizes the exotoxin released at the site of infection and that circulating in blood but not that fixed to tissues.

Dose: 20,000–40,000 IU i.m. or i.v. for pharyngeal/laryngeal disease of upto 48 hour duration. Higher dose (upto 100,000 IU may be needed).

DIPHTHERIA ANTITOXIN 10,000 IU in 10 ml amp.

Appropriate antimicrobials should also be given. Unprotected child contacts should be given ADS (1000 IU) along with diphtheria toxoid for prophylaxis.

7. Gas gangrene antitoxin (Anti gas gangrene serum, AGS) It is enzyme refined equine antitoxin against *Cl. edematiens, Cl. perfringens* and *Cl. septicum.*

Dose: prophylactic 10,000 IU; therapeutic 30,000–75,000 IU s.c./i.m./i.v.

AGGS 10,000 IU amp.

8. Antisnake venom (ASV) serum polyvalent It is available as purified, enzyme refined and concentrated equine globulins in lyophilized vials with 10 ml ampoule of distilled water. After reconstitution, each ml neutralizes:

0.6 mg of standard Cobra (*Naja naja*) venom.

0.6 mg of standard Russel's viper (*Vipera russelli*) venom.

0.45 mg of standard Sawscaled viper (*Echis carinatus*) venom.

0.45 mg of standard Krait (*Bungarus caeruleus*) venom.

ANTISNAKE VENOM SERUM POLYVALENT, ASVS

Dose: 20 ml i.v. (1 ml/min injection) repeated at 1–6 hourly intervals till symptoms of envenomation disappear; upto 300 ml may be required in viper bites, while still larger amounts (upto 900 ml) have been used in cobra bites, but it is important to continue ASV treatment till evidence of envenomation persists. In case of viper bite some serum should also be infiltrated around the site to prevent venom induced gangrene.

Allergic reactions, including anaphylactic shock, to the serum are possible. When time permits, sensitivity test should be done; otherwise adrenaline may be injected s.c. concurrently. An antihistaminic and a glucocorticoid may also be given prophylactically.

Chapter 71 Drug Interactions

Drug interaction (more precisely 'drug-drug interaction') refers to modification of response to one drug by another when they are administered simultaneously or in quick succession. The modification is mostly quantitative, i.e. the response is either increased or decreased in intensity, but sometimes, it is qualitative, i.e. an abnormal or a different type of response is produced. The possibility of drug interaction arises whenever a patient concurrently receives more than one drug, and the chances increase with the number of drugs taken.

Many medical conditions are treated with a combination of drugs. The components of the combination are so selected that they complement each other's action, e.g. an antibiotic is used along with an analgesic to treat a painful infective condition; adrenaline is added to lidocaine for local anaesthesia; antitubercular drugs are combined to prevent drug resistance; mixed aerobic-anaerobic bacterial infections are treated with a combination of antimicrobials. More commonly, multiple drugs are used to treat a patient who is suffering from two or more diseases at the same time, e.g. hypertension and diabetes. The chances of unintended or adverse drug interactions are greater in this later situation, because an assortment of different drugs may be administered to a patient depending on his/her diseases/symptoms.

Several drug interactions are desirable and deliberately employed in therapeutics, e.g. the synergistic action of ACE inhibitors + diuretics to treat hypertension or sulfamethoxazole + trimethoprim to treat bacterial infection or furosemide + amiloride to prevent hypokalaemia. These are well-designed interactions and do not pose any undue risk to the patient. The focus of attention in this chapter are drug interactions which may interfere with the therapeutic outcome or be responsible for adverse effects, or may even be fatal (bleeding due to excessive anticoagulant action).

The severity of drug interactions in most cases is highly unpredictable. However the doctor must know which drugs are not to be prescribed concurrently. More importantly, a large section

Regular medication drugs
(Likely to be involved in drug interactions)

1. Antidiabetics
2. Antihypertensives
3. Antianginal drugs
4. Antiarthritic drugs
5. Antiepileptic drugs
6. Antiparkinsonian drugs
7. Oral contraceptives
8. Anticoagulants
9. Antiasthmatic drugs
10. Psychopharmacological agents
11. Antipeptic ulcer/reflux drugs
12. Corticosteroids
13. Antitubercular drugs
14. Anti-HIV drugs

of patients may be receiving one or several drugs for their chronic medical conditions like hypertension, diabetes, arthritis, etc. (*see* box for regular medication drug classes employed commonly). The physician may prescribe certain drugs for an intercurrent illness which may interact with those already being taken by the patient and result in adverse consequences. It is, therefore, imperative for the doctor to elicit a detailed drug history of the patient and record all the medication that he/she is currently on. The list of potential adverse drug interactions is already quite long and constantly growing. It is practically impossible for anyone to know/remember all possible drug interactions. Fortunately, the clinically important and common drug interactions that may be encountered in routine practice are relatively few. Some of these are listed in Table 71.1. More exhaustive compilations and documentation are available in specialized books, monographs, review articles and computer database on the subject, but these also need constant updating.

Certain types of drugs (*see* box) can be identified that are most likely to be involved in clinically important drug interactions. The physician may take special care and pay attention to the possibility of drug interactions when the patient is receiving one or more of such medications, or when the doctor intends to prescribe any of such drugs.

Types of drugs most likely to be involved in clinically important drug interactions

- Drugs with narrow safety margin, e.g. aminoglycoside antibiotics, digoxin, lithium
- Drugs affecting closely regulated body functions, e.g. antihypertensives, antidiabetics, anticoagulants
- Highly plasma protein bound drugs like NSAIDs, oral anticoagulants, sulfonylureas
- Drugs metabolized by saturation kinetics, e.g. phenytoin, theophylline

MECHANISM OF DRUG INTERACTIONS

Drug interactions can be broadly divided into *pharmacokinetic* and *pharmacodynamic* interactions. In certain cases, however, the mechanisms are complex and may not be well understood. Few interactions take place even outside the body when drug solutions are mixed before administration.

Pharmacokinetic interactions

These interactions alter the concentration of the object drug at its site of action (and consequently the intensity of response) by affecting its absorption, distribution, metabolism or excretion.

Pharmacokinetic interactions

- Alteration of absorption or first-pass metabolism
- Displacement of plasma protein bound drug
- Alteration of drug binding to tissues affecting volume of distribution and clearance
- Inhibition/induction of metabolism
- Alteration of excretion

Absorption Absorption of an orally administered drug can be affected by other concurrently ingested drugs. This is mostly due to formation of insoluble and poorly absorbed complexes in the gut lumen, as occurs between tetracyclines and calcium/iron salts, antacids or sucralfate. Phenytoin absorption is decreased by sucralfate due to binding in the g.i. lumen. Such interactions can be minimized by administering the two drugs with a gap of 2–3 hours so that they do not come in contact with each other in the g.i.t. Ketoconazole absorption is reduced by H_2 blockers and proton pump inhibitors because they decrease gastric acidity which promotes dissolution and absorption of ketoconazole. Antibiotics like ampicillin, tetracyclines, cotrimoxazole markedly reduce gut flora that normally deconjugates oral contraceptive steroids secreted in the bile as glucuronides and permits their enterohepatic circulation. Several instances of contraceptive failure have been reported with concurrent use of these antibiotics due to lowering of the contraceptive blood levels. Alteration of gut motility by atropinic drugs, tricyclic antidepressants, opioids and prokinetic drugs like metoclopramide can also affect drug absorption.

Distribution Interactions involving drug distribution are primarily due to displacement of one drug from its binding sites on plasma proteins by another drug. Drugs highly bound to plasma proteins that have a relatively small volume of distribution like coumarine anticoagulants, sulfonylureas, certain NSAIDs and antiepileptics are particularly liable to displacement interactions. Another requirement is that the displacing drug should bind to the same sites on the plasma proteins with higher affinity. Displacement of bound drug will initially raise the concentration of the free and active form of the drug in plasma that may result in toxicity. However, such effects are usually brief, because the free form rapidly gets distributed, metabolized and excreted, so that steady-state levels are only marginally elevated. The clinical outcome of displacement interactions is generally significant only when displacement extends to tissue binding sites as well, or is accompanied by inhibition of metabolism and/or excretion. Quinidine has been shown to reduce the binding of digoxin to tissue proteins as well as its renal and biliary clearance by inhibing the efflux transporter P-glycoprotein, resulting in nearly doubling of digoxin blood levels and toxicity.

Metabolism Certain drugs reduce or enhance the rate of metabolism of other drugs. They may thus affect the bioavailability (if the drug undergoes extensive first pass metabolism in liver) and the plasma half-life of the drug (if the drug is primarily eliminated by metabolism). Inhibition of drug metabolism may be due to competition for the same CYP450 isoenzyme or cofactor, and attains clinical significance mostly for drugs that are metabolized by saturation kinetics. Macrolide antibiotics, azole antifungals, chloramphenicol, omeprazole, SSRIs, HIV-protease inhibitors, cimetidine, ciprofloxacin and metronidazole are some important inhibitors of metabolism of multiple drugs. Risk of statin induced myopathy is increased by fibrates, niacin, erythromycin, azole antifungals and HIV-protease inhibitors, probably due to inhibition of statin metabolism. Because lidocaine metabolism is dependent on hepatic blood flow, propranolol has been found to prolong its t½ by reducing blood flow to the liver.

A number of drugs induce microsomal drug metabolizing enzymes and enhance biotransformation of several drugs (including their own in many cases). Induction involves gene mediated increased synthesis of certain CYP450 isoenzymes. It takes 1–2 weeks of medication with the inducer to produce maximal effect (contrast inhibition of metabolism which develops quickly) and regresses gradually over 1–3 weeks after discontinuation of the inducer. Barbiturates, phenytoin, carbamazepine, rifampin, cigarette smoking, chronic alcoholism and certain pollutants are important microsomal enzyme inducers. Contraceptive failure and loss of therapeutic effect of many other drugs have occurred due to enzyme induction. On the other hand, the toxic dose of paracetamol is lower in chronic alcoholics and in those on enzyme inducing medication, because one of the metabolites of paracetamol is responsible for its overdose hepatotoxicity.

Excretion Interaction involving excretion are important mostly in case of drugs actively secreted by tubular transport mechanisms, e.g. probenecid inhibits tubular secretion of penicillins and cephalosporins and prolongs their plasma t½. This is particularly utilized in the single dose treatment of gonorrhoea. Aspirin blocks the uricosuric action of probenecid and decreases tubular secretion of methotrexate. Change in the pH of urine can also affect excretion of weakly acidic or weakly basic drugs. This has been utilized in the treatment of poisonings. Diuretics and to some extent tetracyclines, ACE inhibitors and certain NSAIDs have been found to raise steady-state blood levels of lithium by promoting its tubular reabsorption.

Pharmacodynamic interactions

These interactions derive from modification of the action of one drug at the target site by another drug, independent of a change in its concentration. This may result in an enhanced

Table 71.1: Selected clinically important drug interactions

*Precipitant drug**	*Object drug£*	*Likely interaction and comments*
1. Ampicillin, Amoxicillin	Oral contraceptives	Interruption of enterohepatic circulation of the estrogen → failure of contraception; Advise alternative contraception.
	Warfarin	Inhibition of gut flora → decreased vit K production in gut → risk of bleeding; Monitor INR and reduce anticoagulant dose if needed.
2. Probenecid	Penicillin, Ampicillin, Cephalosporins	Inhibition of tubular secretion → prolongation of antibiotic action; Desirable interaction utilized for single dose therapy.
3. Allopurinol	Ampicillin	Increased incidence of rashes; Avoid concurrent use.
	6-Mercaptopurine, Azathioprine	Inhibition of metabolism; Reduce dose of 6-MP/ azathioprine to 1/3.
	Warfarin, Theophylline	Inhibition of metabolism; Monitor and reduce dose of object drug.
4. Carbenicillin, Ticarcillin	Aspirin and other antiplatelet drugs	Perturbation of surface receptors on platelets → additive platelet inhibition → risk of bleeding; Avoid concurrent use.
5. Ceftriaxone, Cefoperazone	Warfarin	Additive hypoprothrombinaemia → bleeding; Monitor INR and reduce dose of anticoagulant.
6. Sulfonamides, Cotrimoxazole	Phenytoin	Displacement$ + inhibition of metabolism → phenytoin toxicity; Avoid concurrent use.
	Warfarin	Displacement + inhibition of metabolism + decreased production of vit K in gut → risk of bleeding; Monitor INR and reduce dose of warfarin.
	Sulfonylureas	Displacement + inhibition of metabolism → hypoglycaemia; Avoid concurrent use.
7. Metronidazole, Tinidazole, Cefoperazone	Alcohol	Possibly accumulation of acetaldehyde → disulfiram-like or bizarre reactions; Warn the patient not to drink alcohol.
8. Metronidazole, Tinidazole	Lithium salts	Decreased excretion → Li^+ toxicity; Monitor Li^+ level and reduce lithium dose.
	Warfarin	Inhibition of metabolism → risk of bleeding; Avoid concurrent use
9. Ciprofloxacin, Norfloxacin, Pefloxacin	Theophylline, Warfarin	Inhibition of metabolism → toxicity of object drug; Monitor and reduce dose of object drug.
10. Erythromycin, Clarithromycin, Ketoconazole, Itraconazole, Fluconazole, Protease inhibitors	Phenytoin, Carbamazepine, Warfarin, Sulfonylureas, Diazepam, Theophylline, Cyclosporine, HIV protease inhibitors	Inhibition of metabolism by CYP3A4 → toxicity of object drug; Avoid concurrent use or readjust dose of object drug.
	Statins	Inhibition of metabolism, higher risk of myopathy; Avoid concurrent use.

* Precipitant drug is the drug, which alters the action/pharmacokinetics of the other drug.
£ Object drug is the drug whose action/pharmacokinetics is altered.
$ Displacement of plasma protein bound drug.

Contd...

Table 71.1: Selected clinically important drug interactions. *Contd...*

*Precipitant drug**	*Object drug£*	*Likely interaction and comments*
11. Gemfibrozil, Nicotinic acid	Statins	Increased risk of myopathy; Caution in concurrent use.
12. Tetracyclines	Oral contraceptives	Interruption of enterohepatic circulation of the estrogen → failure of contraception; Advise alternative contraception.
	Lithium salts	Rise in plasma Li^+ level due to decreased excretion; Avoid use of tetracycline or monitor and reduce dose of lithium.
13. Iron salts, Calcium salts, Antacids, Sucralfate	Tetracyclines, Fluoroquinolones	Decreased absorption due to formation of complexes in g.i.t. → failure of antibiotic therapy; Stager drug administration by 2–3 hours.
14. Furosemide	Minocycline, Aminoglycoside antibiotics	Enhanced vestibular toxicity; Avoid concurrent use. Additive ototoxicity and nephrotoxicity; Avoid concurrent use.
15. Diuretics	Lithium	Decreased excretion—rise in Li^+ level—toxicity; Reduce dose of lithium and monitor level.
	Digoxin	Hypokalaemia caused by diuretic increases digoxin toxicity; Give K^+ sparing diuretic/K^+ supplements.
16. Tetracyclines, Chloramphenicol, Macrolide antibiotics	Penicillins, Cephalosporins	Bactericidal action of penicillins and cephalosporins may be antagonized by the bacteriostatic antibiotics; Avoid concurrent use.
17. Clindamycin	Erythromycin, Clarithromycin, Azithromycin, Chloramphenicol	Mutual antagonism of antibacterial action due to proximal binding sites on bacterial ribosomes; Avoid concurrent use.
18. Phenobarbitone, Phenytoin, Carbamazepine, Rifampin	Metronidazole, Doxycycline, Chloramphenicol, Protease inhibitors, Warfarin, Corticosteroids, Oral contraceptives, Sulfonylureas, Antidepressants	Induction of metabolism → loss of efficacy of object drug; Avoid concurrent use or increase dose of object drug with monitoring.
19. Chloramphenicol	Warfarin, Phenytoin, Sulfonylureas	Inhibition of metabolism → toxicity of the object drug. Avoid concurrent use or monitor and reduce dose of object drug.
20. NSAIDs	Ciprofloxacin and other fluoroquinolones	Enhanced CNS toxicity, seizures; Avoid concurrent use.
21. Aspirin and other NSAIDs	Sulfonylureas, Phenytoin, Valproate, Methotrexate	Displacement and/or reduced elimination → toxicity of object drug; Avoid concurrent use/substitute NSAID with paracetamol.
	Warfarin, Heparin	Enhanced risk of bleeding due to antiplatelet action and gastric mucosal damage; Caution in concurrent use.
	ACE inhibitors, β blockers, Thiazide diuretics	Reduced antihypertensive effect due to inhibition of renal PG synthesis; Avoid concurrent use.
	Furosemide	Reduced diuretic action due to PG synthesis inhibition in kidney; Avoid concurrent use.
	Alcohol, Corticosteroids	Increased risk of gastric mucosal damage and gastric bleeding; Concurrent use contraindicated.

Contd...

Table 71.1: Selected clinically important drug interactions. *Contd...*

*Precipitant drug**	*Object drug\$*	*Likely interaction and comments*
22. Aspirin	Spironolactone	Reduced K^+ conserving action due to decreased tubular secretion of canrenone (active metabolite of spironolactone); Avoid concurrent use.
23. Chronic alcoholism	Paracetamol	Hepatotoxic dose of paracetamol is reduced; doses < 3 g/day are safe.
24. Chlorpromazine, Imipramine and other TCAs	Morphine, Pethidine, Codeine	Enhanced CNS and respiratory depression; Avoid concurrent use.
25. Chlorpromazine, Haloperidol, Metoclopramide	Levodopa-carbidopa	Antagonism of antiparkinsonian effect; Concurrent use contraindicated.
26. Levodopa-carbidopa	ACE inhibitors, Vasodilators, Prazosin	Excessive postural hypotension; Reduce dose of antihypertensives.
27. TCAs	Adrenaline (added to local anaesthetic)	Potentiation due to neuronal uptake inhibition → rise in BP; Use plain local anaesthetic solution.
28. Promethazine, Alcohol, Opioids, Antipsychotics	Diazepam and other benzodiazepines	Additive CNS and respiratory depression, motor impairment; Avoid concurrent use.
29. Cimetidine, Isoniazid	Diazepam and other benzodiazepines	Inhibition of metabolism → exaggerated CNS depression; Avoid concurrent use or reduce benzodiazepine dose.
30. Sildenafil, Tadalafil	Nitrates	Marked potentiation → precipitous fall in BP; Concurrent use contraindicated.
31. Propranolol	Lidocaine	Reduced hepatic clearance of lidocaine; Ceiling amount used in local anaesthesia is reduced.
32. Lidocaine	β-blockers	Enhanced bradycardia and hypotension; Avoid concurrent use.
	Quinidine and other antiarrhythmic drugs	Exaggerated cardiac depression, precipitation of arrhythmias; Avoid concurrent use.

NSAIDs: Nonsteroidal antiinflammatory drugs
TCAs: Tricyclic antidepressants

response (synergism), an attenuated response (antagonism) or an abnormal response. The phenomena of synergism and antagonism are described in Chapter 4, and are deliberately utilized in therapeutics for various purposes. Of clinical significance are the inadvertent concurrent administration of synergistic or antagonistic pair of drugs with adverse consequences. Some examples are:

1. Excessive sedation, respiratory depression, motor incoordination due to concurrent administration of a benzodiazepine (diazepam), a sedating antihistaminic (promethazine), a neuroleptic (chlorpromazine), an opioid (morphine) or drinking alcoholic beverage while taking any of the above drugs.
2. Excessive fall in BP and fainting due to concurrent administration of α_1 adrenergic blockers, vasodilators, ACE inhibitors, high ceiling diuretics and cardiac depressants.
3. Pronounced and asymptomatic hypoglycaemia can occur when propranolol is administered to diabetics receiving insulin/sulfonylureas, due to blockade of β adrenoceptors which contribute to recovery from hypoglycaemia as well as some hypoglycaemic symptoms.

4. Additive prolongation of prothrombin time and bleeding by administration of ceftriaxone or cefoperazone to a patient on warfarin.
5. Excessive platelet inhibition resulting in bleeding due to simultaneous use of aspirin/clopidogrel and carbenicillin.
6. Increased risk of bleeding due to concurrent use of antiplatelet drugs (aspirin, clopidogrel) with anticoagulants (warfarin).
7. Marked bradycardia due to administration of propranolol in digitalized patients.
8. Precipitous fall in BP and myocardial ischaemia due to use of sildenafil by patients receiving organic nitrates, because nitrates increase generation of cGMP, while sildenafil prevents its degradation by inhibiting PDE 5.
9. Severe hyperkalaemia by concurrent use of ACE inhibitors and K^+ sparing diuretics.
10. Antagonism of bactericidal action of β-lactam antibiotic by combining it with a bacteriostatic drug like tetracycline.
11. Mutual antagonism of antibacterial action of macrolides, clindamycin and chloramphenicol due to interference with each other's binding to the bacterial 50S ribosome.
12. Attenuation of antihypertensive effect of ACE inhibitors/β blockers/diuretics by NSAIDs due to inhibition of renal PG synthesis.
13. Blunting of K^+ conserving action of spironolactone by aspirin, because it inhibits the tubular secretion of canrenone (an active metabolite of spironolactone).
14. Blockade of antiparkinsonian action of levodopa by neuroleptics and metoclopramide having antidopaminergic action.

Abnormal responses sometimes result from pharmacodynamic interaction between certain drugs, e.g. bizarre somewhat disulfiram-like distressing symptoms are experienced by certain subjects when they drink alcoholic beverages while taking metronidazole or cefoperazone. It is not known whether this is due to inhibition of aldehyde dehydrogenase. The basis of certain interactions is not explained, e.g. ampicillin has produced high incidence of skin rashes in patients treated with allopurinol.

Drug interactions before administration

Certain drugs react with each other and get inactivated if their solutions are mixed before administration. In combined oral or parenteral formulations, the manufacturers take care that such incompatibilities do not take place. In practice situations, these *in vitro* interactions occur when injectable drugs are mixed in the same syringe or infusion bottle. Some examples are:

- Penicillin G or ampicillin mixed with gentamicin or another aminoglycoside antibiotic
- Thiopentone sodium when mixed with succinylcholine or morphine
- Heparin when mixed with penicillin/gentamicin/hydrocortisone
- Noradrenaline when added to sodium bicarbonate solution.

In general, it is advisable to avoid mixing of any two or more parenteral drugs before injecting.

Comment Not all patients taking interacting drugs experience adverse consequences, but it is advisable to take due precautions to avoid mishaps in all cases where interactions are possible. That two drugs have the potential to interact does not necessarily contraindicate their concurrent use. In many cases, knowledge of the nature and mechanism of the possible interaction may permit their concurrent use provided appropriate dose adjustments are made or other corrective measures are taken. A list of significant and common drug interactions that may be encountered in clinical practice is given in Table 71.1, along with the suggested corrective measure. However, it is prudent to consider the possibility of drug interaction whenever two or more drugs are prescribed to a patient, or any drug is added to what the patient is already taking.

APPENDICES

Appendix 1 Solution to Problem Directed Study

SOLUTION 1.1

a. Since the child is seriously ill, a fast and more predictable action of the antibiotic is needed; a parenteral route of administration is appropriate. Moreover, oral dosing may be difficult in this case as the child is dull and irritable. Entering a vein for i.v. injection is relatively difficult in children, particularly in the presence of dehydration. Therefore, the antibiotic may be injected i.m. However, if an i.v. line is set up for rehydration, the antibiotic may be administered through the i.v. line.
b. In this case the provisionally selected antibiotic should be started as early as possible, because the child is seriously ill. Waiting for the lab. reports to confirm the diagnosis/select the definitive antibiotic may compromise the prognosis.

SOLUTION 2.1

a. Gastric acid is required for the absorption of oral iron salts. Concurrent ingestion of antacid tablets could have interfered with iron absorption. Hence, the anaemia failed to improve.

SOLUTION 2.2

a. Aspirin displaces sulfonylureas from plasma protein binding sites. Therefore, plasma concentration of unbound (and active) glibenclamide could have risen after aspirin ingestion causing hypoglycaemia. Moreover, aspirin enhances cellular metabolism in skeletal muscles, and this could have accentuated the hypoglycaemia producing the symptoms. As such, glucose ingestion relieved the symptoms.
b. Paracetamol and ibuprofen are analgesics equally effective in toothache as aspirin, and do not displace or otherwise interact with sulfonylureas. As such, these analgesics are more suitable for the given patient.

SOLUTION 3.1

a. Rifampin is known to induce the metabolism of contraceptive steroids. Thus, after regular intake of rifampin for more than 2 weeks (needed for enzyme induction) the steady-state blood level of levonorgestrel and ethinylestradiol could have fallen below the threshold for inhibition of ovulation/contraception. As such, fertility was restored and the woman conceived.
b. In view of the essentiality of rifampin (and other antitubercular drugs) in this patient and the likelihood of failure of the oral contraceptive, the couple should have been advised to take additional/alternative contraceptive measure such as condom or intrauterine contraceptive device.

SOLUTION 3.2

The total volume of distribution and total body clearance for this patients has to be calculated first.

Total V = 1.4 L/kg × 60 kg = 84 L

Total body clearance (CL) = 80 ml/hr/kg × 60 kg
= 4.8 L/hr

Fractional bioavailability (F) $= \frac{70}{100} = 0.7$

Applying the formula:

Loading dose $= \frac{\text{target Cp} \times V}{F}$

Or $\frac{6 \text{ mg/L} \times 84 \text{ L}}{0.7} = 720 \text{ mg}$

Maintenance dose rate $= \frac{\text{Cpss} \times CL}{F}$

Or $\frac{6 \text{ mg/L} \times 4.8 \text{ L/hr}}{0.7} = 41 \text{ mg/hr}$

Or 41 mg/hr × 24 hr = 984 mg/day

For this patient: Loading dose 720 mg initially; or practically 3½ tablets of 200 mg each.

Maintenance dose: 984 mg/day.

To be practical, the maintenance dose could be one 400 mg tab. in the morning and 1½ tab. (600 mg) in the evening.

SOLUTION 4.1

a. Since Mtx binds to the same site of DHFRase as the endogenous metabolite DHFA, it will act as a competitive inhibitor. However, because the binding affinity of Mtx for the enzyme is 50,000 times greater, even excess DHFA will not be able to displace it from the enzyme and nonequilibrium type of inhibition will be produced.

b. Folic acid administered as a drug will not be able to counteract Mtx toxicity because it will not be converted to the active coenzyme form THFA. On the other hand, folinic acid will supply readymade active coenzyme THFA and will be able to overcome Mtx toxicity.

SOLUTION 5.1

a. The most likely pathogenesis of the symptoms on the 3rd day of brisk diuretic therapy in this patient is occurrence of hypokalaemic alkalosis, which precipitated hepatic encephalopathy. In cirrhotics with moderate to severe hepatic dysfunction, ammonia (NH_3) produced by gut bacteria is not completely detoxified (by conversion to urea) in the liver. Blood NH_3 tends to rise. This ionizes partly to NH_4^+ and is excreted in urine as NH_4Cl. The NH_4^+ ions do not cross the blood-brain barrier. During alkalosis, NH_3 ionizes to a lesser extent, raising blood NH_3 level which enters brain to cause encephalopathy. Weakness and postural hypotension are the other manifestations of hypokalaemic alkalosis.

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b. The diuretic should be withheld till the fluid electrolyte and acid-base balance is restored. Intravenous infusion of KCl along with normal saline can hasten recovery from hypokalaemia and alkalosis. Oral lactulose (a nonabsorbable disaccharide) helps in reducing blood NH_3 level by producing acidic degradation products in the gut which convert NH_3 into poorly absorbed NH_4^+ ions. Moreover, lowering of stool pH by lactulose has a suppressant effect on NH_3 producing gut bacteria.

SOLUTION 6.1

a. The patient has a serious disease for which many effective drugs are available. As such, antitubercular treatment should be continued, albeit with nonhepatotoxic drugs.

b. The criteria for causality assessment, *viz.* temporal relationship, previous knowledge, dechallenge and rechallenge should be applied to identify the causative drug. In this case, the reaction occurred in the 4th week of drug therapy which is consistent with the time-sequencing of drug-induced hepatitis. The reaction can be confirmed and the actual causative drug identified by dechallenge and rechallenge.
   - Stop all suspected drugs (H, R and Z); treat the patient with E and two other nonhepatotoxic drugs, preferably streptomycin (i.m.) and a fluoroquinolone (e.g. levofloxacin). If the jaundice clears in the subsequent weeks, dechallenge is positive (one or more of the 3 stopped drugs had caused hepatitis).
   - Rechallenge by reintroducing the stopped drugs, one at a time, and repeatedly monitor liver function tests.
   - Generally, R is started first followed by H after 7–10 days. If both are tolerated, Z could have been the causative drug and is not restarted, but the 3 drug combination R + H + E is extended to 9 months.
   - If R is implicated, it should be stopped as soon as the liver function tests become abnormal. Start H and continue H+E+S for 2 months followed by H+E for 10 months.
   - If H is implicated, it should be stopped immediately, and R+E+Z may be given for 9 months.

   In this way, the implicated drug can be identified and antitubercular therapy completed with minimal use of parenteral/2nd line drugs.

SOLUTION 7.1

a. The diagnosis of myasthenia gravis can be confirmed by the *'edrophonium test'*. Edrophonium is injected i.v. (2 mg initially which if tolerated; followed by 8 mg after 30–60 sec). Reversal of ptosis, diplopia and increase in the strength of affected muscles lasting 5–10 min constitutes a positive result.

   In case edrophonium is not available, the test can be performed with neostigmine 1.5 mg i.v. Atropine 0.6 mg may be given i.m./i.v. to block the muscarinic side effects of edrophonium/neostigmine.

b. Myasthenia gravis is an autoimmune disorder due to production of antibodies against the nicotinic receptor at the muscle end-plate. No drug is curative. Both anticholinesterases (neostigmine, etc.) and corticosteroids (other immunosuppressants as well) afford only symptomatic relief till administered. The former preserve ACh and improve neuromuscular transmission, while the latter inhibit the immunological reaction, without removing the cause of the illness.

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c. In many cases (especially older men), thymus is the source of the nicotinic receptor antigen. As such, thymectomy has been found to lower disease activity and even induce long-lasting remission.

SOLUTION 8.1

a. Dimenhydrinate is a H_1 antihistaminic-antivertigo drug with potent antimuscarinic action. Since muscarinic cholinoceptors mediate neurogenic contraction of the detrusor muscle, antimuscarinic drugs interfere with vesical contractions needed for urination. Elderly men with benign hypertrophy of prostate have bladder neck obstruction and are prone to develop urinary retention as a side effect of antimuscarinic drugs. This patient has history indicative of prostatic hypertrophy. As such, all drugs having antimuscarinic activity must be given cautiously to elderly males.

SOLUTION 9.1

a. The symptoms and intraocular pressure (i.o.p.) of this patient indicate that she is having gluaucoma in both eyes. Phenylephrine (10%) eyedrop would be the suitable mydriatic for her. Phenylephrine is an α_1 adrenergic agonist that dilates the pupil by increasing the tone of radial muscles of iris, which are adrenergically innervated. It does not produce cycloplegia because the ciliary muscles lack adrenergic motor innervation. Cycloplegia causes blurring of near vision and is not required in this patient. Phenylephrine is not likely to raise i.o.p. in glaucoma patients. On the other hand, antimuscarinic mydriatics like tropicamide, cyclopentolate, etc. produce both mydriasis and cycloplegia, and tend to raise i.o.p. in glaucoma patients. Therefore, antimuscarinics are to be avoided in glaucoma patients.

SOLUTION 10.1

a. The smooth muscles of the bladder neck and prostatic urethra are constricted by sympathetic innervation via α_1 adrenergic receptors. Terazosin being α_1 receptor blocker reduces the dynamic component of urinary obstruction in benign hypertrophy of prostate, improves urinary flow and affords symptomatic relief.

b. The α_1 adrenergic receptors also mediate reflex vasoconstriction in the lower extremity and trunk which occurs on standing up from a reclining position to maintain cerebral blood flow. Terazosin blocked these α_1 receptors as well; reflex vasoconstriction failed to occur when this patient got up from bed to pass urine; blood supply to brain suffered and the patient fainted. That is why he soon regained consciousness on being laid flat on the bed. Such an event is especially likely to occur after the first dose when compensatory haemodynamic adjustments have not taken effect.

c. The patient should have been advised not to spring up from the bed. He should first sit on the bed for few minutes and then slowly assume the erect posture. This would allow time for the reflex adjustments.

The 5 mg terazosin dose is a high starting dose. Therapy should have been initiated at 1 mg daily dose, with upward titration every 1–2 weeks according to the symptomatic relief obtained and the haemodynamic tolerance by the patient.

SOLUTION 10.2

a. Timolol is a potent lipophilic, nonselective ($\beta_1 + \beta_2$) adrenergic blocker. In this patient of mild episodic asthma, the drug in the eyedrops appears to have been absorbed systemically during drainage

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through the nasolacrimal ducts and precipitated severe bronchospasm by blocking bronchodilator adrenergic β_2 receptors. Since timolol is a competitive antagonist, its action could be overcome by higher concentration of salbutamol in the nebulized aerosol supplemented with the anticholinergic ipratropium bromide to block the reflex vagal bronchoconstriction.

b. This complication could have been prevented by eliciting the history of episodic asthma and avoiding β-blocker ocular hypotensive drug. Latanoprost (a prostaglandin analogue) would be a more suitable antiglaucoma drug for this patient. In case, it was imperative to use an ocular β-blocker, the β_1 selective antagonist betaxolol would be a safer alternative. It is also prudent to start with 0.25% timolol drops and change to 0.5% drops only when needed. In any case, the patient should be advised to apply mild pressure by fingertip for few minutes at the inner canthus of the eye after each eyedrop instillation to prevent passage of the drug into the nasolacrimal duct.

SOLUTION 11.1

a. Since histamine is an important mediator of allergic rhinitis, the H_1 antihistaminics afford rapid symptomatic relief and ameliorate the allergic rhinitis within 2–3 days. A non-sedating second generation antihistaminic like loratadine, des-loratadine or fexofenadine would be suitable for this patient, who is a taxi driver. These drugs are least likely to impair alertness and driving. Moreover, the duration of action of these antihistamines is long enough to make them suitable for once daily dosing. The first generation sedating antihistamines like promethazine, hydroxyzine, chlorpheniramine, clemastine, etc. are contraindicated if the recipient has to drive. Even the second generation antihistaminic cetirizine impairs psychomotor performance and should be avoided in this patient.

b. Antihistaminics are only symptomatic remedies; they have no prophylactic effect. Because the patient has recurrent episodes during spring, he should in addition be prescribed a topical corticosteroid like budesonide or fluticasone nasal spray, starting just before and continuing all through the season to prevent further attacks of rhinitis.

SOLUTION 12.1

a. From the description it is clear that the patient is suffering from common migraine, and the condition can be graded as moderate-to-severe. Simple and combination analgesics have become ineffective at this stage. As such, this patient should be treated with a specific antimigraine drug, preferably a triptan. She may be treated with sumatriptan 50–100 mg orally at the first sign of migraine attack. If the patient vomits, sumatriptan 6 mg can be injected s.c. Only one similar dose (oral/parenteral) can be repeated if the pain recurs within 24 hours. An antiemetic, such as metoclopramide 10 mg oral or i.m. (if the patient is vomiting), or domperidone 10 mg oral should be given along with sumatriptan.

b. Before prescribing a triptan, it is important to rule out ischaemic heart disease, hypertension, hepatic or renal impairment, epilepsy and pregnancy. As such, appropriate medical history should be elicited, physical examination including BP measurement should be performed and ECG, kidney function test, liver function test should be carried out. If appropriate, pregnancy test should be performed and patient advised to avoid pregnancy till she is going to take sumatriptan.

c. Because the migraine episodes are frequent and incapacitating in this case, the patient can be counselled about prophylactic medication. If agreed, she may be put on β blocker prophylaxis,

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such as Tab. propranolol 40 mg twice a day to start with, and dose increments later, if needed. Alternative prophylactic drugs are amitriptyline 25–50 mg at bed time or flunarizine 10–20 mg once a day. Third line prophylatic drugs are topiramate/gabapentin/valproic acid, and many others.

SOLUTION 13.1

a. Prostaglandin E_2 (Dinoprostone) has the property to soften the cervix and make it more compliant at term. Applied to the cervix or inserted into vagina, low doses of dinoprostone act within a few hours and help to ripen the cervix so that it is 'taken up' and dilates to allow passage of the presenting part. Side effects are minimal with these routes of administration. The preferred formulation for this purpose is the cervical gel containing 0.5 mg of dinoprostone in 2.5 ml gel. It should be inserted into the cervical canal. Alternatively, the vaginal gel containing 1.0 mg in 2.5 ml should be deposited at the posterior fornix of vagina. These doses of PGE_2 only affect the cervix and do not significantly augment uterine contractions.
b. Since the patient has no anaemia or toxaemia of pregnancy or cephalopelvic disproportion, presentation is correct and head is engaged, there are no contraindications to the use of PGE_2.

SOLUTION 14.1

a. Paracetamol taken in adequate doses (upto 2.6 g per day) is the most suitable analgesic for relieving knee pain in the given patient. Unlike many NSAIDs, it does not increase the risk of myocardial infarction/stroke. Paracetamol does not inhibit endothelial PGI_2 synthesis, does not affect platelet function and does not nullify the cardioprotective effect of low dose aspirin. Moreover, it is a first-line drug for osteoarthritic pain, and is well tolerated with minimal gastric side effects.
b. The selective COX-2 inhibitors (celecoxib, etoricoxib) are not suitable for this patient, because they increase the risk of heart attack and stroke by inhibiting endothelial PGI_2 synthesis. Diclofenac is also not free of such risk. Though propionic acid NSAIDs (ibuprofen, etc.) are nonselective COX inhibitors which do not increase thrombotic risk, they block the cardioprotective effect of low dose aspirin that this patient is taking.
c. Topical NSAIDs, e.g. diclofenac/ketoprofen gel can afford adjuvant symptomatic relief in this patient. Since blood levels of NSAIDs after local application are low, they are well tolerated and do not increase cardiovascular risk.

SOLUTION 15.1

a. This patient is taking 150 mg/day diclofenac, which is an adequate dose. The reason for only partial relief of symptoms now is progression of the rheumatoid disease and not inadequacy of NSAID dose or drug. As such, changing over to another NSAID or escalation of diclofenac dose is not likely to afford better relief or to adequately treat her disorder.
b. Since this is a confirmed patient of rheumatoid arthritis, and clinical findings as well as test reports indicate active disease, she must be treated with a disease modifying antirheumatic drug (DMARD) in addition to the NSAID. Methotrexate (Mtx), an antifolate immunosuppressant drug, is the standard first line DMARD which should be prescribed to this patient at an initiating dose of 7.5 mg once a week orally. If a DMARD is not added, the disease will progress despite use of NSAIDs, causing articular cartilage damage and bony erosions leading to pain, loss of function and deformity.

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c. Before prescribing Mtx, liver function tests should be performed to exclude liver disease. Peptic ulcer should be ruled out, preferably by endoscopy. Although normal WBC count indicates absence of any acute infection, tuberculosis or any focus of infection should be excluded. It should be ensured that the patient is not pregnant, and that she does not conceive till she takes Mtx. Symptomatic relief in pain, swelling and joint function is expected to begin after 3–4 weeks of initiating Mtx therapy. Complete relief may take 2–4 months. If not, the dose may be increased to 15 mg/week. When Mtx takes effect, requirement of NSAID may decrease, and finally it may be possible to stop it. Mtx is expected to suppress the rheumatoid process and retard its progression. Joint damage is expected to be delayed, function maintained and deformity prevented.
d. Pantoprazole, a proton pump inhibitor, has been prescribed to reduce the risk of developing NSAID induced peptic ulcer, because she has been put on regular NSAID treatment. It should be continued, at least, till the patient is taking an NSAID.

SOLUTION 16.1

a. Since this is a patient of moderate severity bronchial asthma with >1 episode per day, he must be put on regular prophylactic antiinflammatory drug therapy. His present treatment with short acting β_2 agonist (salbutamol) inhalation alone is not adequate for his condition. The first line treatment of this patient would be a low-dose inhaled corticosteroid + a long acting β_2 agonist on a regular twice daily schedule. For example, he may be prescribed— Fluticasone 125 μg + salmeterol 25 μg per puff inhaler, one puff to be taken twice daily. A medium dose of the inhaled corticosteroid (Fluticasone 125 μg per puff, 2 puffs twice daily) alone may also be tried if prolonged use of long-acting β_2 agonist is to be avoided.
b. The patient should continue to use the short acting β_2 agonist (salbutamol) inhalation to abort/terminate each episode of asthma when it occurs despite instituting prophylactic therapy.
c. Since no other drug is as effective prophylactic as a corticosteroid, it should not be replaced in this case of medium severity bronchial asthma. However, the long acting β_2 agonist can be replaced by a leukotriene antagonist, like Montelukast 10 mg 1 tab daily in the evening. However, some patients may not benefit from it. As a third option, sustained release theophylline 400 mg tab OD may be tried, with dose titration over time, as add on drug to the low dose inhaled corticosteroid.

SOLUTION 16.2

a. The recently developed symptoms of the patient are indicative of early stage theophylline toxicity. Erythromycin is an inhibitor of several hepatic microsomal enzymes, including those that metabolize theophylline. As such, when the patient took erythromycin, metabolism of theophylline appears to have been retarded, causing rise in its plasma concentration over the next 2 days and producing overdose symptoms.
b. This complication could have been prevented in *two* ways, *viz.*
   i. When erythromycin was prescribed, the daily dose of theophylline should have been reduced from 800 mg to 500 mg, and maintained at this level till the patient was taking erythromycin.

   Or

   ii. An alternative antibiotic (e.g. a β-lactam like amoxicillin or cephalexin) which does not inhibit theophylline metabolism but is effective in sore throat, could have been selected for this patient.

SOLUTION 18.1

a. Since carbimazole inhibits further synthesis of thyroid hormones (T_3, T_4) without affecting their release or action, the hormone stored in the gland continues to be released and produce effects. Moreover, thyroxine has a long plasma t½ of 6–7 days. Thus, the effect of carbimazole starts manifesting only after 2–3 weeks and peaks after 2–3 months.
Many of the symptoms of thyrotoxicosis are due to sympathetic overactivity. Blockade of β adrenergic receptors (β_1 and β_2) by propranolol or similar drug affords rapid symptomatic relief, without affecting thyroid status. A nonselective β-blocker given to her along with carbimazole could have controlled palpitation, tremor, etc. within a few days. This drug could be withdrawn when carbimazole had taken effect.

b. The reappearance of neck swelling without any symptom of thyrotoxicosis indicates that it is due to deficient feedback inhibition of TSH by a suboptimal thyroid hormone level as a result of higher maintenance dose of carbimazole. This is supported by the mild hypothyroid symptoms experienced by the patient and the raised TSH level alongwith low normal FT_4 level. The raised TSH is stimulating the thyroid so that despite its low functional status, deficiency is not marked. Since the disease activity in Graves' disease may decline after some time, the maintenance dose of carbimazole needs to be adjusted from time-to-time according to the assessed clinical and laboratory thyroid status of the patient. This patient requires temporary discontinuation of carbimazole followed by a lower maintenance dose as assessed later.

SOLUTION 19.1

a. According to the current recommendation of professional guidelines, the patient should be prescribed metformin therapy concurrently with dietary and lifestyle measures. This is based on the finding that metformin can delay progression of diabetes and prevent microvascular as well as macrovascular (heart attack, stroke) complications. Metformin does not increase circulating insulin, reduces insulin resistance, is unlikely to induce hypoglycaemia and may have a positive influence on pancreatic β cell health. Lack of serious toxicity over several decades of use of metformin is well established. No other antidiabetic drug has all these favourable features, and therefore, it is considered the first-choice drug. Metformin is particularly suitable for this patient who is overweight, because it can help weight reduction. A combination of antidiabetic drugs is not indicated at this stage. Another drug needs to be added only when the target blood glucose and HbA_{1c} levels are not attained by metformin alone.

SOLUTION 20.1

a. The patient has received supraphysiological doses of a corticosteroid for more than 3 weeks, and is likely to have developed hypothalamo-pituitary-adrenal (HPA) suppression. The injury and surgery are a stress which need excess corticoid activity. The depressed HRA axis may not be able to cope up with increased demand, and there is risk of developing acute adrenal insufficiency. As such, hydrocortisone hemisuccinate 100 mg should be infused i.v. during surgery and repeated 8 hourly till the patient is stable.

b. Prednisolone therapy must not be stopped in the postoperative period apprehending spread of infection and delayed healing. Effective antibiotic medication to prevent wound infection should be given and prednisolone dose should be increased temporarily (for a week or so) to 20 mg/day, till the stress of the trauma and surgery subsides.

SOLUTION 21.1

a. This is a case of advanced metastatic prostate carcinoma, for which only palliative therapy with androgen deprivation (tumour cells remain androgen dependent) is possible. When orchidectomy has been refused, the most effective method of androgen deprivation is to give a long acting GnRH agonist. Thus, the choice of triptorelin is correct. The GnRH agonists initially increase LH (also FSH) release for 1–2 weeks, followed by receptor desensitization and nearly total blockade of LH secretion by 3–4 weeks. The raised LH levels in the beginning stimulate testis to secrete more testosterone which activates tumour cells resulting in increased bone pain and bladder obstruction noticed after 1 week of therapy in this patient.

b. The initial flaring of symptoms can be avoided by pretreating with an antiandrogen bicalutamide 50 mg orally daily for 3 days before starting triptorelin injection and then continuing both drugs together. The stimulatory effect of excess testosterone on tumour cells would be blocked by bicalutamide so that no flaring of symptoms would occur. The combined androgen blockade with GnRH agonist + androgen antagonist is the favoured approach.

c. The patient can be given an antiresorptive drug in addition to relieve bone pain. A potent parenteral bisphosphonate like zoledronate infused i.v. over 15 min every 1–4 weeks is the most effective drug for this purpose. It may also retard growth of the bony metastasis for some time.

SOLUTION 22.1

a. The most likely cause of endometrial thickening in this patient is tamoxifen therapy. Tamoxifen is a selective estrogen receptor modulator (SERM) which has estrogen antagonistic action in the breast (basis of its use in breast carcinoma), but agonistic action on the endometrium which stimulates proliferation. Such unopposed (by progestin) hyperproliferation can produce thickening and predisposes to endometrial carcinoma.

b. For the reason stated above, tamoxifen should not be continued in this patient. Total stoppage of adjuvant therapy is not advisable, because estrogen suppression therapy has been shown to exert protective effect for at least 5 years. Aromatase inhibitors, which block synthesis of estrogens in the body, have been clearly demonstrated to prevent recurrence of breast cancer, without stimulating endometrial proliferation or predisposing to endometrial carcinoma. Therefore, in this case, tamoxifen should be replaced by letrozole 2.5 mg /day or anastrozole 1.0 mg/day for the next 5 years. Due precautions to prevent osteoporosis and measures to address arthritic symptoms, if they develop, should be taken concurrently.

SOLUTION 22.2

a. All diseases and conditions which contraindicate use of oral contraceptives or need caution in their use have to be ruled out before prescribing one to this subject. Full medical history, including menstrual history and past pregnancy details should be elicited. Any thromboembolic episode, jaundice or toxaemia of pregnancy should be ascertained. History of smoking, diabetes, hypertension, migraine, tuberculosis and gallbladder disease should be specifically asked. Any medication that she is taking and the reason for it should be taken into account to foresee possible interactions with the contraceptive. Whether she is obese or very lean also matters in selecting the contraceptive preparation. General physical examination, including palpation of breast, for any lump and a per vaginum examination for fibroid/other tumour, should be done. Blood pressure should be recorded to rule out hypertension. Fasting and postprandial blood glucose,

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lipid profile should be ordered to detect diabetes and dyslipidaemia. Ultrasound examination of pelvic organs should be performed for uterus size, fibroid, ovarian cyst or malignancy.
Only after all the above findings are favourable that an oral contraceptive be selected and prescribed.

SOLUTION 23.1

a. Though the progress of labour in this case is tardy and uterine contractions are relatively weak, there are signs of foetal distress (passage of meconium stained liquor, rapid foetal heart becoming irregular during uterine contraction). Moreover, the mother is dehydrated and exhausted. As such, the best course of action is to deliver the baby by caesarean section.
b. The mother should not be administered an oxytocic drug, because stronger uterine contractions are likely to worsen foetal distress and pose risk to the baby. The mother is also not in a fit condition to endure the stress of a difficult labour.

SOLUTION 25.1

a. Rocuronium is the preferred muscle relaxant for tracheal intubation and short lasting muscle relaxation in this patient. Succinylcholine (SCh), the fastest and shortest acting muscle relaxant which is most commonly used for aiding tracheal intubation, is not suitable for this patient, because it is a depolarizing blocker and releases K^+ from skeletal muscles. Since this patient has extensive burns and tissue injury, which itself causes hyperkalemia due to leakage of K^+ from injured cells, the K^+ released by SCh will accentuate the hyperkalemia and expose the patient to risk of cardiac arrhythmias and other complications.
Rocuronium, on the other hand, is a nondepolarizing blocker which does not trigger loss of intracellular K^+. It is the fastest acting nondepolarizing blocker with speed of action approaching that of SCh. Intubating conditions can be obtained in 60–90 sec. It also provides surgical grade relaxation for 25–40 min, along with good cardiovascular stability.

SOLUTION 26.1

a. Labour pain as well as that due to stretching of the birth canal can be largely relieved by spinal as well as epidural anaesthesia. It is desirable, at the same time, not to produce motor block so that the mother can actively participate in the process of labour. Since motor fibres are less sensitive to local anaesthetics (LAs) than sensory fibres, motor block of a lower level is usually produced during spinal anaesthesia. Such separation is more pronounced with epidural anaesthesia. Lidocaine and bupivacaine are the two LAs commonly used for epidural anaesthesia. Out of these, bupivacaine is more suitable for this purpose for the following reasons:
   - It provides greater separation of sensory from motor block. Separation is still larger when lower concentration (0.25% bupivacaine) is used.
   - Because of higher lipid solubility, its tissue distribution is large and maternal blood levels are lower. Less drug is likely to cross to the foetus, reducing chances of neonatal depression.
   - It is longer acting.

Thus, epidural anaesthesia with 0.25% bupivacaine is most suitable for this patient.

SOLUTION 28.1

a. Alcohol exerts anticonvulsant action while its concentration in the brain is rising or is maintained. This is followed by lowering of seizure threshold when the concentration falls and becomes zero. Thus, recurrence of seizures in this patient could most likely be due to the temporarily increased susceptibility to seizures caused by withdrawal of alcohol from the brain.
b. Since this lowering of seizure threshold is a short-term problem, no abrupt change in antiepileptic medication or alteration of dose is warranted at this stage. The patient should be kept under observation for few days/weeks and decision about further antiepileptic therapy taken only on the basis of the subsequent course of events. The patient also must be advised to strictly avoid alcoholic drinks in future.

SOLUTION 29.1

a. Since this patient does not require a hypnotic on regular basis, there is no identifiable cause of occasional sleep onset difficulty and he has tried non-drug measures, he can be prescribed a hypnotic to be kept handy for use when required. Because there is only sleep onset difficulty, and he will take the drug only later at night (after going to bed as usual), he needs a short acting hypnotic which would be free of residual effect next morning. Zaleplon would be suitable for this patient, as it has a short t½ (1 hour), does not cause next morning drowsiness, day time anxiety or rebound insomnia. Tolerance is unlikely to develop, because use is going to be occasional.

SOLUTION 30.1

a. The husband of the patient should be instructed that at the first sign of a seizure attack the patient should be laid on bed or ground in the prone or lateral position with neck extended to ensure free airway. No emergency medicine is required during or just after the fit. Only reassurance and moral support are needed. These instructions should be shared will other family members, so that anyone who is closeby may do the needful.
b. Because the patient has a history of head trauma and two seizure attacks have occurred within one week, the probability of developing epilepsy is high. As such, antiepileptic medication should be started rightaway without waiting for test reports or further fits to occur.
c. Therapy should be initiated with a single antiepileptic drug. Antiepileptics with proven efficacy in post-head injury tonic-clonic seizures are phenobarbitone, phenytoin, carbamazepine and valproate. Since the patient is a young active lady, phenobarbitone with sedative/cognitive side effects, phenytoin with gum hyperplasia, hirsutism and other cosmetic side effects as well as problems related to maintaining optimum blood levels of the drug, and valproate with tremor and weight gain would be less suitable. Carbamazepine appears to be the most appropriate initial drug in this case.

SOLUTION 31.1

a. The Parkinson's disease of this patient appears to have advanced over the last 5 years and he is now experiencing 'wearing off effect' of levodopa-carbidopa. He is also developing dyskinesia, a late adverse effect of the drug. At this stage, antiparkinsonian medication cannot be withdrawn, because he will develop marked rigidity, immobility and tremor hampering life activities. He is

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already experiencing an adverse effect of his medication; therefore, the dose should not be increased further.

Since levodopa-carbidopa is the most efficacious and cheapest medication for parkinsonism, it may be prudent to continue it at a reduced dose and supplement it with another longer acting drug to smoothen the therapeutic effect. The options available as supplementary medication are:

- A direct dopamine agonist like ropinirole/pramipexole can be gradually added to levodopa-carbidopa whose dose should be reduced in steps. Both drugs can be taken concurrently 3 times a day. Ropinirole/pramipexole being longer acting will smoothen symptom control. They also produce less dyskinesia.
- A MAO-B inhibitor like selegiline 5 mg twice a day or rasagiline 1 mg once a day in the morning will prevent degradation of dopamine in the brain, prolonging and smoothening effect of levodopa-carbidopa.
- Entacapone 200 mg with each dose of levodopa-carbidopa can also potentiate and prolong levodopa action by inhibiting another metabolizing enzyme COMT. It can also be an additional third drug to levodopa-carbidopa + selegiline for greater symptomatic relief.

SOLUTION 32.1

a. The most likely cause of the motor restlessness exhibited by the patient after 4 weeks of haloperidol therapy is appearance of a common extrapyramidal side effect of the antipsychotic drug called 'akathisia'. The symptom does not appear to be due to inadequate dose of haloperidol, because the psychotic symptoms have been relieved and the initial psychomotor restlessness had been controlled. There is no return of anxiety, hallucinations, etc. As such, there is no need to increase the dose of haloperidol. Dose reduction may be tried but return of psychotic symptoms is a risk. One of the atypical antipsychotic drugs may be substituted for haloperidol. Quetiapine with its sleep promoting effect will be more suitable in this case. The atypical antipsychotics have a low propensity to cause extrapyramidal motor side effects, including akathisia.

b. For early resolution of motor restlessness, a benzodiazepine, e.g. clonazepam 1 mg or diazepam (5 mg) 2–3 times a day may be given. This may be supplemented by trihexyphenidyl 2 mg 3 times/day. In case the akathisia persists, propranolol 40 mg 2–3 times a day may be added.

SOLUTION 33.1

a. Sertraline is a selective serotonin reuptake inhibitor (SSRI) and a first-line drug for major depression. The choice of drug is correct and the 50 mg twice daily an average dose for initiation of therapy. However, since antidepressant action of any drug (including sertraline) takes 2–4 weeks to manifest, it is too early at 1 week to expect any improvement in depressive symptoms. The dose is not subtherapeutic as indicated by appearance of mild side effects, which nevertheless are quick to appear, but to whom gradual tolerance usually develops. Restlessness, nausea, dyspepsia, epigastric distress and anorexia are expected side effects of SSRIs. The patient and his family members should be counselled to continue the medication for another 3–4 weeks by which time symptoms should start improving. The choice of drug is appropriate, and at this stage, there is no reason to change the medicine or its dose. No additional drug needs to be added at this stage.

SOLUTION 34.1

a. Symptoms and signs indicate that the patient is going into neurogenic shock due to the excruciating pain of the crush injury. As such, the first priority is to relieve the acute pain. Morphine 5 mg should be injected i.v. immediately. It will not only lessen the pain and suffering of the patient, but also allay apprehension and counteract neurogenic shock. It will facilitate proper examination and first aid measures as well. Supplemental doses may be given every 2–3 hours. An i.v. infusion of saline should be started at the earliest to restore blood pressure and maintain tissue perfusion.

SOLUTION 35.1

a. The primary reason for no improvement in the state of the patient is that all medicines, including donepezil, take weeks and months before any perceptible improvement in Alzheimer's symptoms become apparent. Moreover, donepezil (or any other drug) is not effective in a significant number of patients. However, one week is too short a time to know whether this patient is going to benefit or not. Since this patient has developed intolerable cholinergic side effects, they are due to donepezil which should be discontinued.
No other anticholinesterase drug is likely to be tolerated by this patient. Therefore, a drug which acts by a different mechanism could be used in this patient. Memantine is the only other drug, with documented efficacy in moderate to severe Alzheimer's disease, which is not a cholinergic drug, and which probably acts by blocking glutamate excitotoxicity. It is better tolerated and does not produce cholinergic side effects. However, improvement in memory and cognitive function is less likely, and it may only serve to slow the functional decline.

SOLUTION 36.1

a. The weakness, nausea, sweating and fainting suffered by the patient is due to the marked and rapid fall in BP caused by captopril (and augmented by furosemide). Congestive heart failure patients have an overactive renin-angiotensin system (RAS) which helps in maintaining haemodynamics in the face of low cardiac output. Captopril is a rapidly acting ACE inhibitor, which, given in doses used for hypertension, removes the RAS support (angiotensin II is not formed) and causes marked fall in BP. This is aggravated by Na^+ loss caused by the diuretic.
b. Though, a slower acting ACE inhibitor, e.g. enalapril, would be less likely to cause rapid fall in BP, captopril cannot be considered a wrong choice of drug, provided it is initiated at $1/4^{th}$ dose. In CHF, captopril therapy should be initiated at 6.25 mg dose, which can be gradually increased as haemodynamic adjustments take place.
c. The reaction could have been avoided by initiating captopril at 6.25 mg twice daily dose. A slower acting ACE inhibitor (at low starting dose) could be still less likely to produce acute hypotension.
d. The first measure to be taken in this case is to put the patient in 15° head low position. This could be supplemented by short-term fluid and electrolyte infusion. A pressor agent is rarely needed.

SOLUTION 38.1

a. This patient of moderate CHF is in a decompensated state with dilated heart. Though the diuretic (furosemide) and ACE inhibitor (enalapril) will relieve symptoms slowly, they may not be sufficient to restore a compensated cardiac status. Digoxin should be prescribed concurrently as it is the

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most effective drug for restoring compensation by increasing cardiac contractility. The features of this patient do not indicate any urgency. Therefore, the patient may be started with an average maintenance dose 0.25 mg/day of digoxin. It is expected to produce peak effect after 5–7 days. Dosage adjustment may be done after that depending on the response.

b. Enalapril dose of 5 mg twice a day should be increased by 5 mg/day at 1–2 week intervals till hypotension or other side effects appear or 40 mg/day dose is reached. For maximum prognostic benefit, ACE inhibitors have to be used at or near the highest permissible dosage. Enalapril should not be stopped unless compelled by an adverse effect, because it continues to retard worsening of CHF and avoid complications.

c. Since the patient is in a decompensated state, a β blocker cannot be added at this stage, because chances of deterioration of cardiac status are high. However, after compensation has been restored by digoxin, diuretic and enalapril and the patient is in a stable condition, a suitable β blocker may be started at a very low dose, to be upward titrated later, because β blockers afford further morbidity and mortality benefits.

SOLUTION 39.1

a. The patient has been having atrial fibrillation (AF) for at least the past one month. He is likely to have developed thrombi in the fibrillating atria, and is at risk of embolic stroke when sinus rhythm (SR) is restored. Therefore, he has been put on anticoagulant medication with warfarin to prevent thromboembolism.

b. His heart (ventricular) rate can be controlled by a drug which depresses A-V conduction. For this purpose verapamil or diltiazem or propranolol should be given orally and dose adjusted to maintain a heart rate between 60–70/min. Digoxin (0.25 mg/day) may be prescribed in addition if the target heart rate is not achieved by monotherapy.

c. If electrical cardioversion does not succeed, amiodarone 200 mg injected i.v. over 60 min may be tried for reversal to SR.

d. After restoration of SR, the same may be maintained by continued treatment with one of the following drugs, *viz.* sotalol/propafenone/amiodarone/dronedarone or disopyramide.

SOLUTION 40.1

a. This patient is having one or more episodes of angina practically every day; therefore, he should be prescribed regular medication to prevent the episodes. The first line drugs for this purpose which can be given to this patient are:

   1. A long-acting nitrate *viz.* oral sustained release isosorbide mononitrate or similar drug morning and afternoon or transdermal glyceryl trinitrate patch applied in the morning and taken off at night.
   2. A long-acting calcium channel blocker, like amlodipine once a day.

   Alternative second line or add-on drugs are:
   Nicorandil (K^+ channel opener), or ranolazine (I_{Na} current inhibitor), or trimetazidine (LC3-KAT inhibitor) or ivabradine (I_f current inhibitor).
   Since he is also suffering from COPD, he cannot be given a β blocker which is likely to precipitate severe breathlessness.

b. This patient is having coronary artery disease (CAD). None of the above drugs can alter the course of CAD or prevent complications like MI or death. He should in addition be put on

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long-term treatment with the following to arrest/delay the progression of CAD and to afford cardioprotection:

1. An antiplatelet drug, such as low-dose aspirin or clopidogrel.
2. A hypolipidaemic statin, such as atorvastatin.
3. An angiotensin converting enzyme (ACE) inhibitor, such as enalapril.

SOLUTION 41.1

a. Since the systolic BP is above 140 mm Hg and diastolic BP is below 90 mm Hg, this patient has 'isolated systolic hypertension'. Repeated measurements have confirmed the raised BP, therefore, antihypertensive medication is indicated. Therapy should be initiated with a single drug because he is stage I hypertensive (systolic BP <160, and diastolic BP <100 mm Hg). Considering the age of the patient (>55 years), diagnosis of isolated systolic hypertension, history of stroke in the past, absence of diabetes/heart failure/ischaemic heart disease/chronic kidney disease, the most suitable antihypertensive drug for this patient is a long-acting dihydropyridine calcium channel blocker (like amlodipine). Alternatively, a thiazide diuretic, like hydrochlorothiazide or chlorthalidone or indapamide may be prescribed.
Therapy may be initiated with either of these classes of drugs and later if BP is not normalized, an ACE inhibitor or angiotensin receptor blocker may be added.

SOLUTION 42.1

a. Induction of brisk diuresis with furosemide alone is not the appropriate treatment of cirrhotic edema and ascites. Hepatic cirrhosis is associated with raised aldosterone and low plasma K^+ levels. Therefore, the aldosterone antagonist spironolactone is the drug of choice. It can be supplemented by furosemide, because spironolactone alone is a weak diuretic. In this patient, use of furosemide alone resulted in further hypokalaemia and alkalosis. This indirectly raised blood NH_3 levels which crosses to the brain resulting in deterioration of mental status and neurological symptoms. Because of secondary hyperaldosteronism, the response to furosemide decreased within few days.

b. At this stage, the patient should be managed by temporarily stopping furosemide and instituting spironolactone (50 mg 6 hourly) therapy along with appropriate i.v. fluid and electrolyte infusion to correct the imbalance, guided by repeated serum electrolyte monitoring. After restoration of the fluid/electrolyte balance and his mental status, the patient should be put on maintenance therapy with spironolactone (100–400 mg/day) and furosemide (40–160 mg/day) with dose adjustment according to response. If hormonal side effects of spironolactone occur, it may be substituted by the other aldosterone antagonist eplerenone.

SOLUTION 44.1

a. There are several reasons which could account for failure of this patient of iron deficiency anaemia to improve with the oral iron medication she has been taking:
   - Ferric ammonium citrate 160 mg (iron content 20%) would provide just 32 mg of elemental iron/day. This is grossly inadequate to treat iron deficiency, for which 200 mg of elemental iron/day is required to yield optimum response.
   - Iron in ferric ammonium citrate needs to be reduced to ferrous form before absorption. Therefore, its bioavailability is lower compared to ferrous salts.

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- Gastric acid is required to reduce ferric iron to ferrous iron and to facilitate iron absorption. This patient is taking acid suppressant medication (rabeprazole, a proton pump inhibitor).

As such absorption of iron from the medicine that she took could be very low.

b. Since there are obvious factors in this case which can be tackled, it would be inappropriate to abandon oral iron therapy at this stage and jump on to injectable iron. Proper selection of oral iron preparation and its dose, and careful management of therapy may yield a response in this patient. A ferrous salt with high iron content like ferrous sulphate or ferrous fumarate (both having ~33% iron) should be prescribed in a dose of 200 mg 3 times a day (total 600 mg or 200 mg elemental iron/day). However, therapy should be initiated with a low dose to be gradually increased as the gastrointestinal tract adjusts to the medication and tolerance to side effects develops. The doses should preferably be taken in empty stomach, but if gastric discomfort occurs, it may be given with food. Selection of ferrous salt would reduce dependence on gastric acid for absorption of iron. However, if tolerated, an effort should be made to discontinue rabeprazole.

SOLUTION 45.1

a. Passage of dark urine indicates bleeding in the kidney. This along with blood loss per vaginum has resulted in acute fall in Hb level. The rise in INR value is indicative of excessive deficiency of clotting factors, especially of prothrombin, factor X and factor VII due to relative warfarin overdose. The obvious cause in this patient is the additive hypoprothrombinaemic action of inj ceftriaxone given for treatment of pelvic infection.

This complication could have been prevented either by selecting an antibiotic that does not cause hypoprothrombinaemia/interact with warfarin or by reducing the dose of warfarin when ceftriaxone was started. The new warfarin dose should have been arrived at by repeated determination of INR value till ceftriaxone was being given.

b. Further warfarin dose must be stopped immediately and vit K 10 mg injected i.m. at the earliest. The patient must be put on bed rest to reduce bleeding. Because Hb level is 9 g/dl, blood transfusion is not required at this stage, but must be kept handy in case she bleeds further. Repeat doses of vit K (5.0 mg i.m.) should be guided by frequent INR measurement and the severity of bleeding, avoiding too much vit K that would interfere with the protective effect of warfarin subsequently. Changing the antibiotic to one which does not cause hypoprothrombinaemia or bleeding may be considered on the basis of bacteriological sensitivity of the organism causing pelvic infection.

SOLUTION 46.1

a. This subject appears to be a nondiabetic with no evidence of atherosclerotic cardiovascular disease (ASCVD), but is a case of primary hypercholesterolemia with borderline high plasma triglyceride (TG) and marginally low plasma HDL-cholesterol (CH). As such, apart from lifestyle modification to regulate diet, reduce body weight and increase physical exercise, he requires CH lowering therapy with a statin.

b. Since his plasma LDL-CH is >190 mg/dL, according to current treatment guidelines, he stands to benefit in terms of ASCVD risk reduction by the institution of high intensity statin therapy. He may be started on atorvastatin 20 mg/day or rosuvastatin 10 mg/day aiming at achieving ~50% reduction in LDL-CH. If this goal is not achieved after 3 months, titrate dose upward till either ~50% reduction in LDL-CH is obtained, or ceiling dose (atorvastatin 80 mg/day or rosuvastatin

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40 mg/day) is reached, or further increase in dose is not tolerated. Statin therapy at this dose is to be maintained for long-term.

With the statin therapy, the borderline high TG level is also expected to decrease and normalize. The present TG level does not pose risk of acute pancreatitis, and no specific therapy to reduce TG level is indicated. Similarly, the marginally low HDL-CH is expected to rise and normalise. In any case, no specific drug to raise HDL-CH, is advised.

SOLUTION 47.1

a. This patient is suffering from recurrent peptic ulcer disease. The earlier episode of similar symptoms had responded to proton pump inhibitor (PPI) therapy. Therefore, it was also most likely due to peptic ulcer. Fast symptom relief and ulcer healing can be achieved this time as well with the use of a PPI given for 4–8 weeks depending on endoscopic confirmation of ulcer healing. However, this alone cannot prevent recurrences, which most commonly are caused by persistent colonization of upper gastrointestinal tract by *H. pylori.* Since the same cannot be confirmed in the absence of testing facility, he should be given the benefit of *H. pylori* eradication therapy which largely prevents ulcer recurrences. A 3 drug, one week regimen would be the most suitable option. Because he has a history of metronidazole use in the recent past, chances of nitroimidazole resistance are high, and he should be treated with a PPI (omeprazole 20 mg or esomeprazole 20 mg or lansoprazole 30 mg or pantoprazole 40 mg or rabeprazole 20 mg) + amoxicillin 1.0 g + clarithromycin 500 mg, all given twice daily. The PPI should then be continued till endoscopic confirmation of healing is obtained, because the ulcer was larger than 10 mm in diameter.

SOLUTION 48.1

a. This child has developed acute muscular dystonia, an extrapyramidal motor reaction that can be caused by drugs with dopaminergic D2 receptor blocking action. Antiemetics with D2 blocking action are chlorpromazine and related neuroleptics like triflupromazine, prochlorperazine, etc. and prokinetic drug metoclopramide. It is likely that the girl was given injection of one of these drugs by the local doctor, following which the vomiting had subsided and the dystonia had developed within 2–3 hours.

b. Though the dystonic reaction usually passes off within a few hours, it can be rapidly reversed by a parenterally administered centrally acting anticholinergic drug. Since the parents are alarmed and to afford quick relief, she may be given a deep intramuscular injection of 10–15 mg of promethazine or hydroxyzine, which have anticholinergic, antihistaminergic, sedative and antiemetic properties. This can reverse the dystonia within 15–30 min.

SOLUTION 49.1

a. This patient of diarrhoea seems to have lost only small amount of fluid and there are no signs of dehydration. Moreover, he is a young adult. Thus, there is no need of rehydration therapy, but normal fluid intake and nutrition should be continued.

b. The features of this patient including fever are indicative of moderately severe enteroinvasive infection. As such, antibiotic therapy is indicated. A well absorbed fluoroquinolone like ciprofloxacin or ofloxacin would be suitable first line antibiotic for empiric therapy.

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c. Antimotility-antidiarrhoeal drug is contraindicated in this patient, because in all likelyhood there is enteroinvasive infection; restriction of bowel clearance can favour further bowel wall invasion and systemic spread of the pathogen.
d. Symptomatic relief of fever can be afforded by paracetamol 500 mg 6 hourly. Abdominal pain and urgency can be dampened by an antispasmodic drug like dicyclomine 20 mg 6–8 hourly.

SOLUTION 50.1

a. Since this is an elective surgery with no indication of any infection in the operative area, but where the biliary tract is going to be cut, with no/minimal spillage or contact with infected material expected, it may be categorized as 'clean-contaminated' surgery. As such, she requires to be given antimicrobial prophylaxis.
b. The surgery involves cutting the biliary tract. Therefore, prophylaxis covering aerobic as well as anaerobic organisms and both gram-negative as well as gram-positive bacteria would be appropriate. Drugs recommended are:

Cefuroxime 1.5 g i.v.
or gentamicin 160 mg i.v. } + metronidazole 0.5 g i.v.

Single dose injected i.v. within 30 min before surgery. Normally, there is no need to repeat the injection, but if the surgery lasts more than 2 hours, a repeat injection after surgery may be given.

SOLUTION 51.1

a. Moxifloxacin is a 2nd generation fluoroquinolone (FQ) antibiotic with high activity against gram positive cocci which is primarily involved in acute sinusitis. Moreover, it has a convenient once a day oral dosing schedule and is generally well tolerated. It has been used in sinusitis with high success rates. These could be the considerations on the basis of which the doctor has decided to use moxifloxacin. However, moxifloxacin is *not* appropirate for this patient because she is receiving amitryptyline, a tricyclic antidepressant which has proarrhythmic potential. Moxifloxacin can prolong Q-T interval and increase the risk of serious cardiac arrhythmias such as *Torsades de pointes* when given along with amitryptyline.

Other antibiotics which are active against gram-positive cocci and suitable for treating sinusitis are amoxicillin alone or with clavulanic acid, a first generation cephalosporin or azithromycin. These antibiotics donot carry the risk of precipitating arrhythmias.

SOLUTION 52.1

a. In this patient antibiotic therapy should be started on the basis of clinical diagnosis, because the patient is quite sick. Rapid relief of symptoms and cure should be the aim. Moreover, blood culture is not necessarily positive in all cases of typhoid fever. Treatment cannot be withheld for want of confirmation by culture.
b. The most appropriate antibiotic is ceftriaxone (or a similar 3rd generation cephalosporin like cefoperazone, cefotaxime), becuase it produces the fastest and surest response. Moreover, being bactericidal it prevents relapse and the risk of carrier state. Being long acting, ceftriaxone can be given as a once daily injection. The daily dose for this boy would be (75 mg/kg x 25 kg) = 1875 mg or rounded off to 2.0 g per day, given as slow i.v. injection once daily. The dose may be halved after 2 days or when fever subsides. It should be given till 2 days after the fever subsides totally.

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c. In case of typhoid fever, a single antibiotic is sufficient, since addition of another antibiotic has not been found to hasten or improve the response.

SOLUTION 53.1

a. The most appropriate drugs and regimens for treating chlamydial endocervicitis are: Azithromycin 1.0 g (2 tabs of 500 mg) single dose, or Doxycycline 100 mg twice daily for 7 days. Both these regimens are adequate to treat uncomplicated gonococcal infection as well as concurrent chlamydial and gonococcal infection. Both these antibiotics are oral and well tolerated. While azithromycin has the advantage of single dose treatment, doxycycline needs twice daily dosing for one week, but is cheaper.
   Other first choice antibiotics like amoxicillin and ceftriaxone for gonorrhoea are not effective against chlamydia.
b. Both these infections are sexually transmitted diseases. Her husband is also likely to be infected. She must be counselled to get her husband examined and treated concurrently.

SOLUTION 54.1

a. The recommended dose range of gentamicin for a person with normal renal function is 3–5 mg/kg/day (or 4 mg/kg/day on average). For a patient with creatinine clearance value of 50 ml/min, the dose has to be reduced to about 50%, or 2 mg/kg/day. In this patient weighing 60 kg, it would be 120 mg/day. With renal impairment, this patient is not suitable for once daily dosing regimen, and he should be treated with the conventional 8 hourly regimen. As such, he may be injected with gentamicin 40 mg every 8 hours making it 120 mg/24 hours. Since the patient is unconscious and in ICU, an i.v. line must have been maintained. Gentamicin may be injected through the i.v. line taking 30 min to complete the injection. Alternatively, it may be injected i.m.
   The usual dose-range of cefotaxime for an adult is 1–2 g every 6–12 hours (2–8 g/day). This patient has renal impairment, half life of cefotaxime is likely to be prolonged. Therefore, a dose near the lower end the range would be appropriate for him. As such, a dose of 1 g every 8 hours (3 g/day) may be selected. This may be slowly injected in the i.v. line or given by i.m. route.

SOLUTION 55.1

a. Since the patient has distressing urinary symptoms and is febrile, empirical antimicrobial treatment should be started after urine has been collected for bacteriological testing. Moreover, in a sexually active woman, lower urinary tract infections (UTI) are moslty treated empirically. The first line antimicrobials for this purpose are fluoroquinolones, cotrimoxazole, amoxicillin-clavulanate, an oral 1st or 2nd generation cephalosporin, or nitrofurantoin. Any of these may be selected and prescribed for 3–5 days depending on symptom resolution. She should be avised to abstain from sexual intercourse in this period. Nitrofurantoin is usually not preferred because it needs at least 7 days treatment, and often causes nausea and gastric pain.
b. Phenazopyridine is a urinary analgesic with no antimicrobial activity. It relieves symptoms of bladder and urethral irritation and can be given with the selected antimicrobial drug.
c. Because this patient has suffered >3 episodes of cystitis within one year, she should be advised long term prophylactic therapy. The suitable prophylactic drug for her is cephalexin 250 mg

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once daily at bed time, because it is not contraindicated in pregnant women. Though this patient is not presently pregnant, she may conceive during use of the prophylactic drug. The other recommended prophylactic drugs, *viz.* cotrimoxazole, nitrofurantoin and norfloxacin are all contraindicated during pregnancy.

SOLUTION 56.1

a. Since the patient is a previously treated case of pulmonary TB, it is important to find out the drug resistance status of the bacilli infecting him. Because the rapid genotypic drug-sensitivity tests are not available, liquid-culture and drug-sensitivity test (LC-DST) on the patient's sputum should be initiated as the first step. However, chemotherapy should be started immediately, because the LC-DST takes 6 weeks or more and defering treatment for such a long time may jeopardise outcome.

b. As per current guidelines, this previously treated patient of pulmonary TB should be treated with the 8 month regimen of 1st line drugs. For the initial 2 months, he should be given all 5 first line drugs, *viz.* isoniazid 300 mg + rifampin 600 mg + pyrazinamide 1.5 g + ethambutol 1.0 g all orally and streptomycin 1.0 g i.m. daily. Streptomycin should be stopped after 2 months and the 4 oral drugs given for another 1 month. Pyrazinamide should be discontinued and 3 drugs rifampin, isoniazid and ethambutol should be continued for the next 5 months. This is a retreatment case, who must be given drugs daily under supervision. The above regimen may be modified when the culture and sensitivity test report becomes available.

SOLUTION 57.1

a. Since the patient had taken the standard multidrug therapy of multibacillary leprosy for the prescribed one year, and had responded clinically, the most likely cause of relapse is reactivation of dormant (persister) bacilli. Development of resistance to the multidrug regimen is very rare. The reactivated persisters remain sensitive to the same regimen. As such, he should be treated with the standard regimen, *viz.* rifampin 600 mg + clofazimine 300 mg once a month alongwith dapsone 100 mg + clofazimine 50 mg daily for one year.

SOLUTION 58.1

a. The treatment of choice for *Candida* esophagitis is oral fluconazole 100 mg/day for 3 weeks, because it is highly effective and well tolerated. However, some cases do not respond due to fluconazole resistance. These may be treated with itraconazole 200/day or voriconazole 200 mg twice daily.

b. Uncontrolled diabetes is an important predisposing factor in the causation of esophageal candidiasis, and appears to have played a role in this patient. Therefore, measures to achieve quick glycaemia control are needed. Since the patient already had a complication of diabetes (*Candida* infection) it is desirable to shift her to insulin therapy (at least till the esophagitis is fully cured). The dose and frequency of insulin injections should be guided by repeated blood glucose monitoring. Fluconazole (other azoles as well) inhibit CYP450 isoenzymes and raise the blood levels of sulfonylureas. The intensity of action of glibenclamide (if continued in this case) is likely to be affected unpredictably. Thus, even if this drug is continued, close monitoring of blood glucose level and dose adjustment of the sulfonylurea is required.

SOLUTION 60.1

a. Considering the facts of injury and exposure in this case, the risk of contacting HIV infection by the dental surgeon is low. However, HIV disease can only be prevented, but not cured, and has serious life-long implications. Moreover, even a few virions entering the body can set up an infection. Therefore, it would be prudent to give prophylactic medication to further cut down chances of acquiring the infection.

b. According to current WHO guidelines, a 3 antiretroviral (ARV) drug regimen, *viz.* 2 nucleoside reverse transcriptase inhibitors (NRTIs) + 1 boosted protease inhibitor (PI) post-exposure prophylactic (PEP) regimen is considered superior to the 2NRTIs regimen. As such, the dental surgeon should be advised to immediately start taking: Tenofovir 300 mg + Emtricitabine 200 mg + Lopinavir-ritonavir (400 mg + 100 mg) or Atazanavir-ritonavir (300 mg + 100 mg) each once daily for 4 weeks.

SOLUTION 61.1

a. Recurrence of fever after being afebrile for 7 days indicates 'recrudescence' due to incomplete parasitaemia clearance by the treatment given for the 1st episode of fever. This occurs due to low grade chloroquine-resistance. While majority of asexual schizonts are killed by chloroquine and the fever subsides, some survive and multiply to cause fever again. The second episode of fever is not due to 'relapse' which is caused by *vivax* hypnozoites reinvading RBCs. Relapse generally occurs after 3 weeks to few months. Moreover, the patient is taking primaquine which kills hypnozoites.

b. As broughtout above, recrudescence indicates low-grade chloroquine-resistance, which is particularly likely in this case, because the infection appears to be contacted from an area where chloroquine-resistance among *P. vivax* has been detected. As such, she should be treated with an alternative drug effective against chloroquine-resistant *P. vivax*. These are:
   1. Quinine 600 mg three times a day for 7 days along with doxycycline 100 mg once daily for 7 days or
   2. Artemether 80 mg + Lumefantrine 480 mg twice daily x 3 days.

c. The primaquine therapy should be continued to complete the 14-day course, so as to totally eradicate the *P. vivax* hypnozoites from the liver.

SOLUTION 62.1

a. Metronidazole is the drug of choice for amoebic liver abscess. Tinidazole is an equivalent, but not necessarily better alternative. Since the patient was seriously ill and was vomiting, the initial choice of i.v. route of administration was appropriate. It was correctly changed to oral route once the patient improved, because oral bioavailability of metronidazole is nearly complete.

b. Experience has shown that a single 10-day course of metronidazole is generally enough to kill all viable amoebae in the liver abscess, though the abscess cavity may persist for few weeks and heal spontaneously. Since the patient has improved clinically, visualization of persisting abscess cavity on ultrasound is not in itself an indication to extend/repeat metronidazole therapy.

c. Since amoebic liver abscess is always secondary to colonization of colon by amoebae (which may be asymptomatic) and because metronidazole does not effectively eradicate cyst forming trophozoites from the colon (it is completely absorbed in the upper intestine, and very little reaches the colonic lumen), a luminal amoebicide should be given along with or after metronidazole.

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Absence of cysts in stools does not ruleout colonization of colon by amoebae. The first choice luminal amoebicide that should have been given in addition is:
Diloxanide furoate 500 mg 3 times a day for 5–10 days alongwith or after metronidazole.

SOLUTION 63.1

a. This patient of neurocysticercosis is suitable for treatment with anthelmintic drug, because there are multiple active parenchymal cysticerci in the cerebral cortex which in addition to seizures can cause other focal reactions in the brain. Planned killing of the cysticerci under corticosteroid cover may prevent future episodes of the reaction and may abolish the cause of seizures, so that long term antiseizure therapy can be avoided.
b. The seizures must be controlled first before starting anthelmintic treatment. The preferred drug is carbamazepine; start with 200 mg 3 times a day, increase by 200 mg/day if the seizures recur till they are fully suppressed or a maximum of 1200 mg/day dose is reached. A second antiseizure drug may be added in nonresponsive cases. However, most cases respond to carbamazepine alone. It should be continued during the course of anthelmintic medication and for about 6 months thereafter, followed by gradual withdrawal over another 2–3 months.
c. Albendazole is the anthelmintic of choice in neurocysticercosis. To this patient, it should be given in a dose of 400 mg twice daily with milk or fat-rich food (to enhance absorption) for 15 days. It is better than the alternative drug praziquantel, because cure rate with albendazole is higher and praziquantel needs to be given for longer period (15–30 days). Carbamazepine induces praziquantel metabolism and lowers its blood level, but not that of albendazole. Dexamethasone (which has to be given) also lowers praziquantel blood levels, but increases albendazole absorption.
d. Dexamethasone in a dose of 8–12 mg once daily in the morning should be started 2 days before initiating albendazole, continued throughout the course and till 15 days thereafter, followed by gradual tapering of dose and final withdrawal. This is essential to suppress the inflammatory reaction to the dying cysticerci killed by albendazole therapy.

Appendix 2 Prescribing in Pregnancy

There are major concerns of permanent harm [teratogenesis in the 1st trimester (*see* p. 100) and effect on growth and development of foetus in the 2nd and 3rd trimester] to the baby whenever any drug is administered to pregnant women. Maternal medication can also increase the incidence of abortion, foetal death, premature or delayed labour, or create perinatal problems. Moreover, there are pronounced and progressive physiological changes during pregnancy which can affect drug disposition (*see* p. 75). As such, prescribing for the pregnant woman requires consideration of several factors and application of restraint. Possible harm to the foetus by the administered drug has to be weighed against harm to both mother and the baby due to untreated disease. There is paucity of data about safety of majority of drugs during pregnancy; largely because prospective drug trials in pregnant women are fraught with ethical, legal, emotional and practical difficulties. Information is mostly derived from anecdotal reports and retrospective studies. The validity of the US-FDA categorization of drugs into 5 categories (*see* p. 101) according to increasing order of risk documentation during pregnancy has become questionable, because evidence on teratogenic risk of drugs keeps accumulating, and the category of many drugs needs to be changed from time-to-time, e.g. the antiretroviral drug efavirenz is no longer contraindicated during pregnancy. The FDA is having a relook on this grading system.

While insufficient data are available to make definitive recommendations regarding choice of drugs for treating common problems likely to be encountered during pregnancy, the table on the succeeding pages attempts to delineate the relatively/probably safer alternatives. The list is not exhaustive and manufacturers literature/ package inserts or other authoritative texts should be consulted. Drugs marked (X) are contraindicated during pregnancy.

Principles of prescribing during pregnancy

- Where possible use nondrug therapy.
- Prescribe drugs only when definitely needed.
- Choose the drug having the best safety record over time.
- Avoid newer drugs, unless safety is clearly established.
- Over-the-counter drugs cannot be assumed to be safe.
- As far as possible, avoid medication in the initial 10 weeks of gestation.
- Use the lowest effective dose.
- Use drugs for the shortest period necessary.
- If possible, give drugs intermittently.

CHOICE OF DRUGS FOR COMMON PROBLEMS DURING PREGNANCY

Drug class (condition)	Safety uncertain/unsafe	Safer alternative
1. Antiemetics (morning sickness, other types of vomiting)	Domperidone (X), Ondansetron	Promethazine, Doxylamine, Dicyclomine, Prochlorperazine, Metoclopramide
2. Drugs for peptic ulcer and GERD	Cimetidine, Lansoprazole, Mosapride	Ranitidine, Famotidine, Omeprazole, Pantoprazole
3. Laxatives (constipation)	Senna, Bisacodyl, Docusates, Saline purgatives	Dietary fibre, Ispaghula, Lactulose
4. Antidiarrhoeals	Diphenoxylate-atropine, Loperamide	Oral rehydration salts
5. Analgesics (headache, bodyache, joint pain, visceral pain)	Aspirin, Metamizol, NSAIDs COX-2 inhibitors, Codeine, Morphine (X), Pethidine, Tramadol	Paracetamol, Ibuprofen (low dose)
6. Cold-cough remedies	Codeine, Dextromethorphan, Bromhexine, Expectorants	Xylometazoline, Oxymetazoline, Budesonide } Nasal drops
7. Antiallergics	Cetirizine, Loratadine, Fexofenadine	Chlorpheniramine, Promethazine
8. Antibacterials (systemic bacterial infections)	Cotrimoxazole, Fluoroquinolones (X), Tetracycline (X), Doxycycline (X), Chloramphenicol (X), Gentamicin, Streptomycin (X), Kanamycin (X), Tobramycin (X), Clarithromycin, Azithromycin, Clindamycin, Vancomycin, Nitrofurantoin	Penicillin G, Ampicillin, Amoxicillin-clavulanate, Cloxacillin, Piperacillin, Cephalosporins, Erythromycin
9. Antitubercular	Streptomycin (X)	Isoniazid, Rifampicin, Ethambutol, Pyrazinamide
10. Antiamoebic	Metronidazole, Tinidazole, Quiniodochlor	Diloxanide furoate, Paromomycin
11. Antimalarial	Artemether, Artesunate, Primaquine (X)	Chloroquine, Mefloquine, Proguanil, Quinine (only in 1st trimester), Pyrimethamine + Sulfadoxine (only single dose)
12. Anthelmintic	Albendazole (X), Mebendazole (X), Ivermectin, Pyrantel pamoate, Diethylcarbamazine (X)	Piperazine, Niclosamide, Praziquantel
13. Antifungal (superficial and deep mycosis)	Amphotericin B (X), Fluconazole, Itraconazole (X), Ketoconazole (X), Griseofulvin (X), Terbinafine	Clotrimazole, Nystatin, Tolnaftate } Topical

(X) Contraindicated during pregnancy.

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Drug class (condition)	Safety uncertain/unsafe	Safer alternative
14. Antiretroviral (HIV-AIDS)	Didanosine, Abacavir, Indinavir, Ritonavir	Zidovudine, Lamivudine, Tenofovir, Nevirapine, Nelfinavir, Saquinavir, Efavirenz
15. Antiviral (non-retroviral)	Acyclovir, Ganciclovir (X), Foscarnet (X), Amantadine (X), Vidarabine (X), α-interferon (X)	—
16. Antihypertensives	ACE inhibitors (X), Angiotensin antagonists (X), Thiazide diuretics, Furosemide, Propranolol, Nitroprusside	Methyldopa, Hydralazine, Atenolol, Metoprolol, Pindolol, Nifedipine, Prazosin, Clonidine
17. Antianaemic	—	Iron salts (oral), Iron dextran (i.m.), Folic acid, Vit B_{12}
18. Antidiabetics	Sulfonylureas (X), Metformin (X), Pioglitazone, Repaglinide, Nateglinide, Acarbose (X)	Insulin (preferably human insulin)
19. Corticosteroids	Betamethasone, Dexamethasone (high dose and prolonged use)	Inhaled corticosteroids, Topical corticosteroids, Prednisolone oral (low dose)
20. Thyroid hormone (hypothyroidism)	—	Thyroxine
21. Antithyroid drugs (thyrotoxicosis)	Carbimazole, Radioactive iodine (X), Iodide	Propylthiouracil
22. Antipsychotic (schizophrenia)	Chlorpromazine, Fluphenazine (X), Clozapine, Olanzapine, Risperidone	Haloperidol, Trifluoperazine
23. Antimanic (bipolar illness)	Lithium carbonate, Valproate, Carbamazepine	—
24. Antidepressants	Trimipramine (X), Dothiepin (X), Sertraline, Paroxetine, Citalopram, Trazodone, Venlafaxine, Moclobemide	Amitriptyline, Imipramine, Fluoxetine
25. Anticoagulants (thromboembolism)	Warfarin (X), Acenocoumarol, Phenindione (X)	Heparin (unfractionated), Heparin (LMW)
26. Antiasthmatic	Theophylline, Ketotifen (X), Montelukast, Zafirlukast, Systemic corticosteroids	Salbutamol/Salmeterol, Ipratropium bromide, Beclomethasone/Budesonide, Sod. cromoglycate } Inhaled

Appendix 3 Drugs in Breastfeeding

Administration of drugs to women who are breastfeeding may have ill effects on the suckling infant, and/or affect lactation. Estrogens (in oral contraceptives) and bromocriptine (D2 agonist) decrease milk production. Toxic effects on the infant are largely dependent on entry of the drug in milk in pharmacologically significant amounts. In the case of large number of drugs (except those acting on CNS and few others), the concentration in milk is low, and the breastfed infant receives insufficient quantity to produce adverse effects. Maternal medication or breastfeeding should not be interfered in case of such drugs. However, currently available data are insufficient to make specific recommendations in the case of many drugs, and the list given below is not exhaustive. Manufacturer's recommendations/package inserts should be consulted.

A. Drugs whose amount in milk is too small to be harmful to the infant, or those found to be safe in ordinary doses

Acetazolamide
Albendazole
Antacids
Antifungal drugs (topical)
Aspirin (low dose)
Baclofen
Beclomethasone (Inhaled)
Benzyl benzoate (topical)
Bupivacaine
Buprenorphine
Cephalosporins
Cloxacillin
Codeine
Cromoglycate sod.
Diclofenac
Digoxin
Domperidone
Ergometrine
Erythromycin
Ethambutol
Folic acid
Gentamicin
Heparin
Hydralazine
Ibuprofen
Insulins
Ipratropium Br. (inhalation)
Iron dextran (i.m.)
Iron salts (oral)
Ketoprofen
Lidocaine
Loperamide
Mebendazole
Methyldopa
Naproxen
Nefopam
Niclosamide
Paracetamol
Permethrin (topical)
Piperacillin
Piperazine
Piroxicam
Praziquantel
Pyrantel
Pyrazinamide
Salbutamol (inhalation)
Sucralfate
Terbutaline (inhalation)
Valproate sod.
Vitamins (maintenance dose)
Warfarin

B. Drugs to be used with special precaution in breastfeeding women or drugs contraindicated

Drug	Comment/possible adverse effect on breast-fed infant
ACE inhibitors (Enalapril, Lisinopril)	S/P amount in milk small, magnitude of risk not known, watch for hypotension
Acenocumarol	S/P; give prophylactic vit K to infant
Acyclovir	S/P; significant amount in milk
Alcohol	Intoxication, reduced suckling
Allopurinol	S/P; secreted in milk; no data on risk to infant
Amiloride	C/I; no information on risk to infant; may reduce lactation
Aminoglycosides	S/P; risk not known, most manufacturers advise caution
Amiodarone	C/I; risk of hypothyroidism from released iodine
Amlodipine	S/P; no data on risk to infant
Amphetamines	C/I; significant amount in milk
Ampicillin/Amoxicillin	S/P; diarrhoea, candidiasis in the infant
Androgens	C/I; masculinization of female infant, precocious development of male infant, reduced lactation
Anthraquinones (senna, etc.)	C/I; diarrhoea in the infant
Anticancer drugs	C/I; anaemia, diarrhoea, immunosuppression
Anticonvulsants	S/P; monitor infant for side effects
Antidepressants (tricyclic)	S/P; use doses <150 mg amitriptyline per day or equivalent; monitor infant for side effects, sedation, respiratory depression
Antihistamines (H_1)	S/P; significant amount in milk, watch for drowsiness, respiratory depression
Antihistamines (2nd generation)	No data on risk to infant; manufacturers advise avoid
Antipsychotics	S/P; drowsiness, muscle dystonia; avoid chlorpromazine, haloperidol, clozapine; amount in milk small, but long-term effect on developing nervous system not known
Aspirin	S/P; Avoid high doses, bleeding, Reye's syndrome
Atorvastatin	Avoid; no data on risk to infant
Atropine	S/P; monitor for anti-muscarinic effects
Azathioprine	C/I; immunosuppression
Azithromycin	Avoid; no information on risk to infant
Barbiturates	S/P; drowsiness, lethargy, withdrawal symptoms
Benzodiazepines	S/P; compatible in single dose; avoid repeated doses; lethargy, hypotonia, reduced suckling, weight loss
Beta blockers	S/P; amount in milk generally small; bradycardia, hypotension, cyanosis
Bromocriptine	Suppresses lactation
Buspirone	Avoid; no information on risk to infant
Caffeine	Avoid regular consumption of large amounts; irritability, CNS effects
Carbamazepine	S/P; amount in milk small but monitor infant
Carbimazole	S/P; hypothyroidism, use lowest effective dose, or suspend breastfeeding
Carisoprodol	S/P; concentrated in milk; avoid
Chloramphenicol	C/I; diarrhoea, bone marrow depression
Chloroquine	S/P; amount in milk small; haemolysis in <1 month old infant and in G-6-PD deficient
Cimetidine	S/P; significant amount in milk, but no harmful effect reported
Ciprofloxacin	C/I; high concentration in milk, theoretical risk of arthropathy
Clindamycin	S/P; amount in milk small, but risk of diarrhoea, watch for blood in stools
Clofazimine	S/P; skin discolouration
Clonidine	S/P; sedation, hypotension

C/I=Contraindicated or suspend breastfeeding
S/P = Use with special precaution while breastfeeding; and monitor infant

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Contd...

Drug	Comment/possible adverse effect on breast-fed infant
Corticosteroids	: S/P; compatible in single doses; pituitary-adrenal suppression possible with >10 mg prednisolone daily to mother, impaired growth
Cotrimoxazole	: S/P; folate deficiency, risk of kernicterus, haemolysis in G-6-PD deficient; safe for healthy older infants
Cyclosporine	: C/I; significant amount in milk
Dapsone	: S/P; haemolytic anaemia, jaundice
Depot medroxyprogesteron acetate (i.m.)	: Compatible with breastfeeding from 6 weeks postpartum
Diltiazem	: S/P; significant amount in milk
Disopyramide	: S/P; small amount in milk, antimuscarinic effects
Doxepin	: S/P; sedation, respiratory depression
Ergotamine	: C/I; ergotism in the infant; may suppress lactation
Estrogens	: C/I; gynaecomastia in male infant, may suppress lactation
Famotidine	: S/P; present in milk, but harm to infant not known
Fluconazole	: C/I; secreted in milk, but harm to infant not known
Fluoxetine	: S/P; small amount in milk, but can accumulate in infant; avoid if possible
Furosemide	: S/P; small amount in milk, electrolyte disturbances in the infant
Gemfibrozil	: Avoid; no information on risk to infant
Indomethacin	: C/I; CNS effects, convulsions
Iodine/Iodides	: C/I; concentrated in milk, hypothyroidism and goiter in the infant
Iodine radioactive	: C/I; suspend breastfeeding for 24 hr after diagnostic dose and for long-term after therapeutic dose
Isoniazid	: S/P; neuropathy, convulsions, jaundice, give prophylactic pyridoxine
Itraconazole	: Avoid unless essential; amount in milk small
Ketoconazole	: C/I; secreted in milk but harm to infant not known.
Ketorolac	: Avoid as no data on safety
Lansoprazole	: Avoid unless essential; no data on safety
Levodopa/Carbidopa	: S/P; no data on safety
Lithium carbonate	: C/I; intoxication in the infant, cardiac arrhythmias
Losartan	: S/P; magnitude of risk not known; avoid if possible
Mefloquine	: S/P; secreted in milk, but harm to infant unlikely
Metformin	: C/I; secreted in milk; hypoglycaemia, lactic acidosis
Mesalazine	: S/P; amount in milk small; watch for diarrhoea
Methotrexate	: C/I; toxicity in infant
Metoclopramide	: S/P; watch for diarrhoea, dystonia in infant
Metronidazole	: Significant amount in milk: avoid high doses; suspend breastfeeding for 12 hr after single dose therapy
Montelukast	: Avoid; no data on risk to infant
Morphine (and other opioids)	: S/P; usual doses unlikely to affect infant; lethargy, poor growth, withdrawal symptoms in infants of dependent mothers
Neostigmine	: S/P; small amount in milk but monitor infant
Nifedipine	: S/P; small amount in milk but monitor infant
Nitrofurantoin	: S/P; small amount in milk, haemolysis in G-6-PD deficient infant
Norfloxacin	: Avoid; no information on risk to infant
Omeprazole	: Not known to be harmful, manufacturer advises 'avoid'
Oral contraceptives	: Avoid until 6 month after birth, *see* estrogens
Penicillins	: Toxicity unlikely but risk of allergy
Phenytoin	: S/P; small amount in milk, but monitor infant
Progestins	: Low doses safe, may suppress lactation at high doses
Propylthiouracil	: S/P; hypothyroidism with high doses only
Pyrimethamine-sulfadoxine	: S/P; significant amount in milk; appears safe if infant is older

Contd...

Contd...

Drug	Comment/possible adverse effect on breast-fed infant
Quinidine	: S/P; significant amount in milk but harm to infant not known
Ranitidine	: S/P; significant amount in milk but harm to infant not known
Rifampin	: S/P; amount in milk small, but monitor infant for jaundice
Sertraline	: S/P; present in milk but no harm reported in short-term
Spironolactone	: S/P; drowsiness, hirsutism, gynaecomastia
Streptomycin	: Compatible with breastfeeding; monitor infant for diarrhoea and thrush
Sulfonamides	: S/P; rashes, small risk of kernicterus in neonate, haemolysis in G-6-PD deficient; safer for older infants
Sulfonylureas	: S/P; no adverse effect reported, but watch for hypoglycaemia
Tetracyclines	: C/I; growth retardation, candidiasis, tooth discolouration
Theophylline	: S/P; irritability, CNS effects
Thiazide diuretics	: S/P; amount in milk small; may reduce lactation
Thyroxine	: S/P; monitor for hyperthyroidism
Tinidazole	: S/P; present in milk; suspend breastfeeding till 3 days after stopping
Vancomycin	: S/P; present in milk, but absorption from infant's gut unlikely
Verapamil	: S/P; small amount in milk, but monitor infant
Vigabatrin	: C/I; present in milk, no data on risk to infant
Vitamin A and D	: Avoid high doses, risk of hypervitaminosis
Zolpidem	: Avoid unless essential; amount in milk small, but watch for sedation in infant

Appendix 4 Drugs and Fixed Dose Drug Combinations Banned in India (updated till June 2017)

List of drugs prohibited for manufacture and sale by Ministry of Health and Family Welfare, Govt. of India[$]

A. Single drug preparations (or combinations of)

1. Amidopyrine.
2. Phenacetin.
3. Nialamide.
4. Methaqualone.
5. Methapyriline (and its salts).
6. Practolol.
7. Penicillin skin/eye ointment.
8. Tetracycline/Oxytetracycline/Demeclocycline liquid oral preparations.
9. Chloral hydrate.
10. Dover's powder and Dover's powder tablets I.P.
11. Chloroform exceeding 0.5% w/w or v/v in pharmaceutical preparations.
12. Mepacrine HCl (Quinacrine and its salts) in any dosage form for use for female sterilization or contraception.
13. Fenfluramine
14. Dexfenfluramine
15. Terfenadine
16. Astemizole
17. Phenformin
18. Rofecoxib
19. Valdecoxib
20. Rimonabant
21. Rosiglitazone
22. Nimesulide formulations for children below 12 years age
23. Cisapride
24. Phenylpropanolamine
25. Sibutramine and R-Sibutramine
26. Gatifloxacin
27. Tegaserod
28. Human placental extract formulations, except for:
    i. topical application for wound healing
    ii. injection for pelvic inflammatory disease
29. Halogenated hydroxyquinolines in liquid oral antidiarrhoeals or any other dosage form for pediatric use.
30. Letrozole for induction of ovulation in anovulatory infertility.
31. Analgin.
32. Dextropropoxyphene.

B. Fixed dose combination with any other drug

1. Corticosteroids with any other drug for internal use, except for metered dose inhalers and dry powder inhalers.
2. Chloramphenicol with any other drug for internal use.
3. Sodium bromide/chloral hydrate with other drugs.
4. Crude ergot with any drug except preparations containing ergotamine, caffeine, analgesics, antihistamines for treatment of migraine, headache.
5. Anabolic steroids with other drugs.
6. Metoclopramide with other drugs (except with aspirin/paracetamol).
7. Pectin and/or kaolin with any drug which is systemically absorbed from g.i. tract, except for

[$] www.cdsco.nic.in>banddrug17.

combination of pectin and/or kaolin with drugs not systemically absorbed.
8. Hydroxyquinolines with any other drug except in preparations for external use.
9. Oxyphenbutazone or phenylbutazone with any other drug.
10. Fixed dose combination of haemoglobin in any form.

C. Fixed dose drug combinations (FDCs) of

1. Penicillins with sulfonamides.
2. Tetracyclines with vitamin C.
3. Antitubercular drugs with Vitamins (except Isoniazid with Pyridoxine HCl).
4. Vitamins with Analgesics/Antiinflammatory drugs.
5. Vitamins with Tranquillisers.
6. Atropine and Analgesic-antipyretics.
7. Yohimbine and Strychnine with Testosterone and Vitamins.
8. Strychnine and Caffeine in tonics.
9. Iron with Strychnine, Arsenic and Yohimbine.
10. Antihistaminics with Antidiarrhoeals.
11. More than one Antihistamine in the same preparation.
12. Sedatives/Hypnotics/Anxiolytics with Analgesic-antipyretics.
13. H_2 receptor antagonists with Antacids (except those combinations approved by Drugs Controller, India).
14. Anthelmintics (except Piperazine) with a Cathartic/Purgative.
15. Salbutamol (or any other bronchodilator) with centrally acting Antitussive and/or an Antihistamine.
16. Centrally acting Antitussives with Antihistamines having atropine like activity in expectorants.
17. Centrally acting Antitussive and/or Antihistamine in preparations for cough associated with asthma.
18. Laxatives and/or antispasmodic drugs in enzyme preparations.
19. Glycerophosphates and/or other phosphates, and/or CNS stimulant in liquid oral tonics.
20. Estrogen and Progestin (other than oral contraceptives) containing per tablet estrogen more than 50 µg ethinylestradiol (or equivalent) and progestin more than 3 mg of norethisterone acetate (or equivalent), and all fixed dose combination injectable preparations containing synthetic estrogen and progesterone.
21. Ethambutol with Isoniazid, except in the following daily doses:
    Isoniazid 200 mg + Ethambutol 600 mg or
    Isoniazid 300 mg + Ethambutol 800 mg.
22. Pyrazinamide with other antitubercular drugs, except that which provide the following daily doses:
    Rifampicin 450 to 600 mg
    Isoniazid 300 to 400 mg
    Pyrazinamide 1000 to 1500 mg
23. Essential oils with Alcohol having percentage higher than 20% proof (except preparations given in the I.P.).
24. Liquid oral tonic preparations containing alcohol more than 20% proof.
25. Streptomycin with penicillin in parenteral preparation.
26. Antidiarrhoeals containing adsorbants like kalolin, pectin, attapulgite, activated charcoal etc.
27. Antidiarrhoeals containing phthalylsulfathiazole, succinyl sulfathiazole, sulfaguanidine, neomycin, streptomycin, dihydrostreptomycin.
28. Antidiarrhoeal formulations for pediatric use containing diphenoxylate, loperamide, atropine, hyoscyamine.
29. Antidiarrhoeals with electrolytes.
30. Pancreatine or pancrelipase containing amylase, protease and lipase with any other enzyme.
31. Oral rehydration salts other than those conforming to the following parameters:
    (a) Oral rehydration salts on reconstitution to one litre shall contain: sodium–50 to 90 mM; total osmolarity–240 to 290 mOsm; dextrose: sodium molar ratio–not less than 1:1 and not more than 3:1.
    (b) Cereal based ORS on reconstitution to one litre shall contain: total osmolarity not more than 2900 mOsm. Precooked rice equivalent to not less than 50 g and not more than 80 g as total replacement of dextrose.
    (c) ORS may contain amino acids in addition to ORS conforming to the parameters specified above and labelled with the indication for "Adult Choleratic Diarrhoea" only.
    (d) ORS shall not contain mono or polysaccharides or saccharin sweetening agent.

32. A drug, standards of which are prescribed in the 2nd schedule to Drugs and Cosmetics Act with an Ayurvedic, Siddha or Unani drug.
33. Vitamin B_1, vit B_6, and vit B_{12} for human use.
34. Diazepam with diphenhydramine HCl.
35. Nitrofurantoin with trimethoprim.
36. Phenobarbitone with any antiasthmatic drug, or with hyoscine and/or hyoscyamine, or ergotamine and/or belladonna.
37. Haloperidol with any anticholinergic agent including propantheline Br.
38. Nalidixic acid with any antiamoebic including metronidazole.
39. Loperamide with furazolidone.
40. Cyproheptadine with lysine or peptone.
41. Flupenthixol with melitracen

D. List of FDCs banned on 10.03.2016

1. Aceclofenac + Paracetamol + Rabeprazole
2. Nimesulide + Diclofenac
3. Nimesulide + Cetirizine + Caffeine
4. Nimesulide + Tizanidine
5. Paracetamol + Cetirizine + caffeine
6. Diclofenac + Tramadol + Chlorzoxazone
7. Dicyclomine + Paracetamol + Domperidone
8. Nimesulide + Paracetamol dispesible tablets
9. Paracetamol + Phenylephrine + Caffeine
10. Diclofenac + Tramadol + Paracetamol
11. Diclofenac + Paracetamol + chlorzoxazone + Famotidine
12. Naproxen + Paracetamol
13. Nimesulide + Serratiopeptidase
14. Paracetamol + Diclofenac + Famotidine
15. Nimesulide + Pitofenone + Fenpiverinium + Benzyl Alcohol
16. Omeprazole + Paracetamol + Diclofenac
17. Nimesulide + Paracetamol injection
18. Tamsulosin + Diclofenac
19. Paracetamol + Phenylephirine + Chlorpheniramine + Dextromethorphan + Caffeine
20. Diclofenac + Zinc carnosine
21. Diclofenac + Paracetamol + Chlorpheniramine maleate + Magnesium trisillicate
22. Paracetamol + Pseudoephedrine + Cetirizine
23. Phenylbutazone + Sodium Salicylate
24. Lornoxicam + Paracetamol + Trypsin
25. Paracetamol + Mefenamic acid + Ranitidine + Dicyclomine
26. Nimesulide + Dicyclomine
27. Heparin + Diclofenac
28. Glucosamine + Methyl Sulfonyl Methane + Vitamin D3 + Manganese + Boron + Copper + Zinc
29. Paracetamol + Tapentadol
30. Tranexamic acid + Proanthocyanidin
31. Benzoxonium chloride + Lidocaine
32. Lornoxicam + Paracetamol + Tramadol
33. Lornoxicam + Paracetamol + Serratiopeptidase
34. Diclofenac + Paracetamol + Magnesium trisilicate
35. Paracetamol + Domperidone + Caffeine
36. Ammonium Chloride + Sodium citrate + Chlorpheniramine maleate + Menthol
37. Paracetamol + Prochlorperazine maleate
38. Combikit of 3 tablets of Serratiopeptidase (enteric coated 20000 units) + Diclofenac Potassium & 2 tablets of Doxycycline
39. Nimesulide + Paracetamol suspension
40. Aceclofenac + Paracetamol + Famotidine
41. Aceclofenac + Zinc Carnosine
42. Paracetamol + Disodium hydrogen citrate + Caffeine
43. Paracetamol + DL Methionine
44. Disodium hydrogen citrate + Paracetamol
45. Paracetamol + Caffeine + Codeine phosphate
46. Aceclofenac (SR) + Paracetamol
47. Diclofenac + Paracetamol injection
48. Azithromycin + Cefixime
49. Amoxicillin + Dicloxacillin
50. Amoxicillin 250 mg + Potassium Clavulanate diluted 62.5 mg
51. Azithromycin + Levofloxacin
52. Cefixime + Linezolid
53. Amoxicillin + Cefixime + Potassium Clavulanic acid
54. Ofloxacin + Nitazoxanide
55. Cefpodoxime proxetil + Levofloxacin
56. Combikit of Azithromycin dihydrate, Secnidazole and Fluconazole
57. Levofloxacin + Ornidazole + Alpha Tocopherol acetate
58. Nimorazole + Ofloxacin
59. Azithromycin + Ofloxacin
60. Amoxycillin + Tinidazole
61. Doxycycline + Serratiopeptidase
62. Cefixime + Levofloxacin
63. Ofloxacin + Metronidazole + Zinc acetate
64. Diphenoxylate + Atropine + Furazolidone

65. Combikit of Fluconazole Tablet, Azithromycin Tablet and Ornidazole Tablets
66. Ciprofloxacin + Phenazopyridine
67. Amoxycillin + Dicloxacillin + Serratiopeptidase
68. Azithromycin + Cefpodoxime
69. Lignocaine + Clotrimazole + Ofloxacin + Beclomethasone
70. Cefuroxime + Linezolid
71. Ofloxacin + Ornidazole + Zinc bisglycinate
72. Metronidazole + Norfloxacin
73. Amoxicillin + Bromhexine
74. Ciprofloxacin + Fluticasone + Clotrimazole + Neomycin
75. Metronidazole + Tetracycline
76. Cephalexin + Neomycin + Prednisolone
77. Azithromycin + Ambroxol
78. Cilnidipine + Metoprolol succinate + Metoprolol tartrate
79. L-Arginine + Sildenafil
80. Atorvastatin + vitamin D3 + folic acid + vitamin B12 + pyridoxine
81. Metformin + Atorvastatin
82. Clindamycin + Telmisartan
83. Olmesartan + Hydrochlorothiazide + Chlorthalidone
84. L-5-Methylterahydrofolate calcium + Escitalopram
85. Pholcodine + Promethazine
86. Paracetamol + Promethazine
87. Betahistine + Ginkgo biloba extract + Vinpocetine + Piracetam
88. Cetirizine dihydrochloride + Diethyl Carbamazine
89. Doxylamine + Pyridoxine + Mefenamic acid + Paracetamol
90. Drotaverine + Clidinium + Chlordiazepoxide
91. Imipramine + Diazepam
92. Flupentixol + Escitalopram
93. Paracetamol + Prochloperazine
94. Gabapentin + Mecobalamin + Pyridoxine + Thiamine
95. Imipramine + Chlordiazepoxide + Trifluoperazine + Trihexyphenidyl
96. Chlorpromazine + Trihexyphenidyl
97. Ursodeoxycholic acid + Silymarin
98. Metformin 1000/1000/500/500 mg + Pioglitazone 7.5/7.5/7.5/7.5 mg + Glimepiride 1/2/1/2 mg
99. Gliclazide 80 mg + Metformin 325 mg
100. Voglibose + Metformin + Chromium picolinate
101. Pioglitazone 7.5/7.5 mg + Metformin 500/1000 mg
102. Glimepiride 1 mg/2 mg/3 mg + Pioglitazone 15 mg/15 mg/15 mg + Metformin 1000 mg/1000 mg/1000 mg
103. Glimepiride 1 mg/ 2mg + Pioglitazone 15 mg/15 mg + Metformin 85 0mg/850 mg
104. Metformin 850 mg + Pioglitazone 7.5 mg + Glimepiride 2 mg
105. Metformin 850 mg + Pioglitazone 7.5 mg + Glimepiride 1 mg
106. Metformin 500 mg/500 mg + Gliclazide SR 30 mg/60 mg + Pioglitazone 7.5 mg/7.5 mg
107. Voglibose + Pioglitazone + Metformin
108. Metformin + Bromocriptine
109. Metformin + Glimepiride + Methylcobalamin
110. Pioglitazone 30 mg + Metformin 500mg
111. Glimepiride + Pioglitazone + Metformin
112. Glipizide 2.5mg + Metformin 400mg
113. Pioglitazone 15mg + Metformin 850 mg
114. Metformin ER + Gliclazide MR + Voglibose
115. Chromium polynicotinate + Metformin hydrochloride
116. Metformin hydrochlopride + Gliclazide
117. Metformin + Gliclazide + Chromium polynicotinate
118. Glibenclamide + Metformin (SR) + Pioglitazone
119. Metformin (sustainded release) 500mg + Pioglitazone 15 mg + Glimepride 3mg
120. Metformin (SR) 500mg + Pioglitazone 5mg
121. Chloramphenicol + Beclomethasone
122. Clotrimazole + Ofloxaxin + Lignocaine + glycerine and propylene glycol
123. Chloramphennicol + Lignocaine + Betamethasone + Clotrimazole + Ofloxacin + Antipyrine
124. Ofloxacin + Clotrimazole + Betamethasone + Lignocaine
125. Gentamicin sulphate + Clotrimazole + Betamethasone + Lignocaine
126. Clotrimazole + Beclomethasone + Ofloxacin + Lignocaine
127. Beclomethasone + Clotrimazole + Chloramphenicol + Gentamicin + Lignocaine ear drops
128. Flunarizine + Paracetamole + Domperidone
129. Rabeprazole + Zinc carnosine
130. Magaldrate + Famotidine + Simethicone
131. Cyproheptadine + Thiamine

132. Magaldrate + Ranitidine + Pancreatin + Domperidone
133. Ranitidine + Magaldrate + Simethicone
134. Magaldrate + Papain + Fungul diastase + Simethicone
135. Rabeprazole + Zinc + Domperidone
136. Famotidine + Oxytacaine + Magaldrate
137. Ranitidine + Domperidone + Semithicone
138. Alginic acid + Sodium bicarbonate + Dried Aluminium hydroxide + Magnesium hydroxide
139. Clidinium + Paracetamol + Dicyclomine + activated Dimethicone
140. Furazolidone + Metronidazole + Loperamide
141. Rabeprazole + Diclofenac + Paracetamol
142. Ranitidine + Magaldrate
143. Norfloxacin + Metronidazole + Zinc acetate
144. Zinc Carnosine + Oxetacaine
145. Oxetacaine + Magaldrate + Famotidine
146. Pantoprazole (as enteric coated tablet) + Zinc Carnosine (as film coated tablets)
147. Zinc Carnosine + Magnesium hydroxide + Dried Aluminium hydroxide + Simethicone
148. Zinc Carnosine + Sucralfate
149. Mebeverine hydrochloride & Inner HPMC capsule (*Streptococcus faecalis* + *Clostridium butyricum* + *Bacillus mesentricus* + Lactic acid Bacillus)
150. Clindamycin + Clotrimazole + Lactic acid Bacillus
151. Sildenafil + Estradiol valerate
152. Clomifene citrate + Ubidecarenone + Zinc + Folic acid + Methylcobalamin + Pyridoxine + Lycopene + Selenium + Levocarnitine tartrate + L-Argenine
153. Thyroxine + Pyridoxine + Folic acid
154. Gentamycin + Dexamethasone + Chloramphenicol + Tobramycin + Ofloxacin
155. Dextromethorphan + Levocetirizine + Phenylephrine + Zinc
156. Nimesulide + Loratadine + Phenylephrine + Ambroxol
157. Bromhexine + Phenylephrine + Chlorpheniramine maleate
158. Dextromethorphan + Bromhexine + Guaiphenesin
159. Paracetamol + Loratadine + Phenylephrine + Dextromethorphan + Caffeine
160. Nimesulide + Phenylephrine + Ceffeine + Levocetirizine
161. Azithromycin + Acebrophyline
162. Diphenhydramine + Terpine + Ammonium chloride + Sodium chloride + Menthol
163. Nimesulide + Paracetamol + Cetirizine
164. Paracetamol + Loratadine + Dextromethophan + Pseudoepheridine + Caffeine
165. Chlorpheniramine maleate + Dextromethophan + Guaiphenesin + Ammonium chloride + Menthol
166. Chlorpheniramine maleate + Ammonium chloride + Sodium citrate
167. Cetirizine + Phenylephrine + Paracetamol + Zinc gluconate
168. Ambroxol + Guaiphenesin + Ammonium chloride + Phenylephrine + Chlorpheniramine maleate + Menthol
169. Dextromethophen + Bromhexine + Chlorpheniramine maleate + Guaiphenesin
170. Levocetirizine + Ambroxol + Phenylephrine
171. Dextromethorphan + Chlorpheniramine maleate
172. Cetirizine + Ambroxol + Guaiphenesin + Ammonium chloride + Phenylephrine + Menthol
173. Chlorpheniramine + Phenylephrine + Caffeine
174. Dextromethorphan + Triprolidine + Phenylephrine
175. Terpinhydrate + Dextromethorphan + Menthol
176. Dextromethorphan + Phenylephrine + Zinc gluconate + Menthol
177. Chlorpheniramine + Codeine + Sodium citarte + Menthol syrup
178. Enrofloxacin + Bromhexin
179. Bromhexine + Dextromethorphan + Phenylephrine + Menthol
180. Levofloxacin + Bromhexine
181. Levocetirizine + Ranitidine
182. Levocetirizine + Phenylephrine + Ambroxol + Guaiphenesin + Paracetamol
183. Cetirizine + Dextromethorphan + Phenylephrine + Zinc gluconate + Paracetamol + Menthol
184. Paracetamol + Pseudoephedrine + Dextromethorphan + Cetirizine
185. Diphenhydamine + Guaiphenesin + Ammonium chloride + Bromhexine
186. Chlorpheniramine + Dextromethorphan + Phenylephrine + Paracetamol
187. Dextromethorphen + Promethazine
188. Diethylcabamazine + Cetirizine + Guaiphenesin
189. Pseudoephedrine + Dextromethorphan + Cetirizine
190. Chlorpheniramine + Phenylephrine + Dextromethorphan + Menthol

191. Ambroxol + Terbutaline + Dextromethorphan
192. Dextromethorphan + Chlorpheniramine + Guaiphenesin
193. Terbutaline + Bromhexine + Guaiphenesin + Dextromethorphan
194. Dextromethorphan + Tripolidine + Phenylephrine
195. Paracetamol + Dextromethorphan + Chlorpheniramine
196. Pholcodine + Phenylephrine + Promethazine
197. Codeine + Levocetirizine + Menthol
198. Dextromethorphan + Ambroxol + Guaifenesin + Phenylephrine + Chlorpheniramine
199. Cetirizine + Phenylephrine + Dextromethorphan + Menthol
200. Roxithromycin + Serratiopeptidase
201. Paracetamol + Phenylephrine + Triprolidine
202. Acetaminophen + Loratadine + Ambroxol + Phenylephrine
203. Cetirizine + Acetaminophen + Dextromethorphan + Zinc gluconate + Phenylephrine
204. Diphenhydramine + Guaifenesin + Bromhexine + Ammonium chloride + Menthol
205. Chlorpheniramine maleate + Codeine syrup
206. Cetirizine + Dextromethorphan + Zinc gluconate + Menthol
207. Paracetamol + Phenylephrine + Desloratadine + Zinc gluconate + Ambroxol
208. Levocetirizine + Montelukast + Acebrophylline
209. Dextromethorphan + Phenylephrine + Ammonium chloride + Menthol
210. Dextromethorphan + Bromhexine
211. Acrivastine + Paracetamol + Caffeine + Phenylephrine
212. Naphazoline + Carboxy methyl cellulose + Menthol + Camphor + Phenylephrine
213. Dextromethorphan + Cetirizine
214. Nimesulide + Paracetamol + Levocetirizine + Phenylephrine + Caffeine
215. Terbutaline + Ambroxol + Guaphenesin + Zinc + Menthol
216. Codeine + Chlorpheniramine + Alcohol syrup
217. Dextromethorphan + Phenylephrine + Guaiphenesin + Triprolidine
218. Ammomium chloride + Bromhexine + Dextromethorphan
219. Diethylcarbamazine + Cetirizine + Ambroxol
220. Ethylmorphine + Noscapine + Chlorpheniramine maleate
221. Cetirizine + Dextromethorphan + Ambroxol
222. Bromhexine + Dextromethorphan + Ammonium chloride + Menthol
223. Ambroxol + Guaifenesin + Phenylephrine + Chlorpheniramine
224. Paracetamol + Phenylephrine + Chlorpheniramine + Zinc gluconate
225. Dextromethorphan + Phenylephrine + Cetirizine + Paracetamol + Caffeine
226. Dextromethorphan + Chlorpheniramine + Guaiphenesin + Ammonium chloride
227. Levocetirizine + Dextromethorphan + Zinc
228. Paracetamol + Phenylephrine + Levocetirizine + Caffeine
229. Chlorpheniramine + Ammonium chloride + Sod. chloride
230. Paracetamol + Dextromethorphan + Bromhexine + Phenylephrine + Diphenhydramine
231. Salbutamol + Bromhexine + Guaiphenesin + Menthol
232. Chlorpheniramine + Ammonium chloride + Noscapine + Sodium citrate
233. Cetirizine + Dextromethorphan + Bromhexine + Guaiphenesin
234. Diethyl Carbamazine + Chlorpheniramine + Guaiphenesin
235. Ketotifen + Cetirizine
236. Terbutaline + Bromhexine + Etofylline
237. Ketotifen + Theophylline
238. Ambroxol + Salbutamol + Theophylline
239. Cetirizine + Nimesulide + Phenylephrine
240. Chloropheniramine + Phenylephrine + Paracetamol + Zinc gluconate
241. Acetaminophen + Guaifenesin + Dextromethorphan + Chlorpheniramine
242. Cetirizine + Dextromethorphan + Phenylephrine + Tulsi
243. Cetirizine + Phenylephrine + Paracetamol + Ambroxol + Caffeine
244. Guaifenesin + Dextromethorphan
245. Levocetirizine + Paracetamol + Phenylephrine + Caffeine
246. Caffeine + Paracetamol + Phenylephrine + Chlorpheniramine
247. Ketotifen + Levocetirizine
248. Paracetamol + Levocetirizine + Phenylephrine + Zinc gluconate
249. Paracetamol + Phenylephrine + Triprolidine + Caffeine
250. Caffeine + Paracetamol + Phenylephrine + Cetirizine

251. Dextromethorphan + Phenylephirine + Guaiphenesin
252. Ambroxol + Levocetirizine + Phenylephrine + Guaiphenesin + Menthol
253. Pseudoephedrine + Cetirizine
254. Dextromethorphan + Chlorpheniramine + Ammonium chloride + Menthol
255. Paracetamol + Caffeine + Phenylephrine + Chlorpheniramine
256. Salbutamol + Aminophylline + Guaifenesin
257. Salbutamol + Thoephylline + Bromhexine
258. Chlorpheniramine + Dextromethorphan + Guaiphenesin + Phenylephrine
259. Caffeine + Paracetamol + Chlorpheniramine
260. Ammonium chloride + Dextromethorphan + Cetirizine + Menthol
261. Dextromethorphan + Paracetamol + Cetirizine + Phenylephrine
262. Chlorpheniramine + Terpin + Antimony potassium tartrate + Ammonium chloride + Sodium citrate + Menthol
263. Terbutaline sulphate + Etofylline + Ambroxol
264. Paracetamol + Codeine + Chlorpheniramine
265. Paracetamol + Pseudoephedrine + Cetirizine + Caffeine
266. Chlorpheniramine + Ammonium chloride + Menthol
267. N-Acetyl Cysteine + Ambroxol + Phenylephrine + Levocetirizine
268. Dextromethorphan + Phenylephrine + Tripolidine + Menthol
269. Salbutamol + Cetirizine + Ambroxol
270. Dextromethorphan + Phenylephrine + Bromhexine + Guaiphenesin + Chlorpheniramine
271. Nimesulide + Cetirizine + Phenylephrine
272. Naphazoline + Chlorpheniramine + Zinc sulphate + Boric acid Ip + Sodium chloride + Chlorbutol
273. Paracetamol + Bromhexine + Phenylephrine + Chlorpheniramine + Guaiphenesin
274. Salbutamol + Bromhexine
275. Dextromethorphan + Phenylephrine + Guaiphenesin + Cetirizine + Acetaminophen
276. Guaifenesin + Bromhexine + Chlorpheniramine + Paracetamol
277. Chlorpheniramine + Ammonium chloride + Chloroform + Menthol
278. Salbutamol + Choline theophylinate + Ambroxol
279. Chlorpheniramine + Codeine phosphate + Menthol syrup
280. Pseudoephedrine + Bromhexine
281. Cetirizine + Phenylephrine + Paracetamol + Caffeine + Nimesulide
282. Dextromethorphan + Cetirizine + Guaifenesin + Ammon. chloride
283. Ambroxol + Salbutamol + Choline theophyllinate + Menthol
284. Paracetamol + Chlorpheniramine + Ambroxol + Guaifenesin + Phenylephrine
285. Chlorpheniramine + Vasaka + Tolu balsam + Ammonium chloride + Sodium citrate + Menthol
286. Bromhexine + Cetirizine + Phenylephrine + Guaiphenesin + Menthol
287. Dextromethorphan + Ambroxol + Ammonium chloride + Chlorpheniramine + Menthol
288. Dextromethorphan + Phenylephrine + Cetirizine + Zinc + Menthol
289. Terbutaline + N-Acetyl L-Cysteine + Guaifenesin
290. Calcium Gluconate + Levocetirizine
291. Paracetamol + Levocetirizine + Pseudoephedrine
292. Salbutamol + Choline Theophylinate + Carbocisteine
293. Chlorpheniramine + Vitamin C
294. Calcium Gluconate + Chlorpheniramine + Vitamin C
295. Chlorpheniramine + Paracetamol + Pseudoephedrine + Caffeine
296. Guaifenesin + Bromhexine + Chlorpheniramine + Phenylephrine + Paracetamol + Serratiopeptidase (as enteric coated granules)10000 SP Units
297. Paracetamol + Pheniramine
298. Betamethasone + Fusidic Acid + Gentamycin + Tolnaftate + Iodochlorohydroxyquin
299. Clobetasol + Ofloxacin + Miconazole + Zinc Sulphate
300. Clobetasol + Gentamicin + Miconazole + Zinc sulphate
301. Levocetirizine + Ambroxol + Phenylephrine + Paracetamol
302. Permethrin + Cetrimide + Menthol
303. Beclomethasone + Clotimazole + Neomycin + Iodochlorohydroxyquin
304. Neomycin + Doxycycline
305. Ciprofloxacin + Fluocinolone + Clotrimazole + Neomycin + Chlorocresol
306. Clobetasol + Ofloxacin + Ketoconazole + Zinc sulphate
307. Betamethasone + Gentamicin + Tolnaftate + Iodochlorhydroxyquin

308. Clobetasol + Gentamicin + Tolnaftate + Iodochlorhydroxyquin + Ketoconazole
309. Allantoin + Dimethieone + Urea + Propylene glycol + Glycerin + Liquid paraffin
310. Acriflavine + Thymol + Cetrimide
311. Betamethasone + Neomycin + Tolnaftate + Iodo chloro hydroxy quinoline + Chlorocresol
312. Clobetasol + Neomycin + Miconazole + Clotrimazole
313. Ketoconazole + Tea Tree oil + Allantion + Zinc oxide + Aloe vera + Jojoba oil + Lavander oil + Soap noodles
314. Clobetasol + Ofloxacin + Ornidazole + Terbinafine
315. Clobetasol + Neomycin + Miconazole + Zinc sulphate
316. Beclomethasone + Neomycin + Tolnaftate + Iodochlorhydroxyquin + Chlorocresol
317. Betamethasone + Gentamycin + Zinc sulphate + Clotrimazole + Chlorocresol
318. Borax + Boric acid + Naphazoline + Menthol + Camphor + Methylhydroxybenzoate
319. Bromhexine + Dextromethorphan
320. Dextromethophan + Chlopheniramine + Bromhexine
321. Menthol + Anesthetic Ether
322. Dextrometharphan + Chlopheniramine + Ammonium chloride + Sodium citrate + Menthol
323. Ergotamine tartrate + Belladona dry extract + Caffeine + Paracetamol
324. Phenytoin + Phenobarbitone sodium
325. Gliclazide 40mg + Metformin 400mg
326. Paracetamol + Ambroxol + Phenylephrine + Chlorpheniramine
327. Oflaxacin + Ornidazole suspension
328. Albuterol + Etofylline + Bromhexine + Menthol
329. Albuterol + Bromhexine + Theophylline
330. Salbutamol + Hydroxyethyltheophylline (Etofylline) + Bromhexine
331. Paracetamol + Phenylephrine + Levocetirizine + Sodium citrate
332. Paracetamol + Propyphenazone + Caffeine
333. Guaifenesin + Diphenhydramine + Bromhexine + Phenylephrine
334. Dried Aluminium hydroxide gel + Propantheline bromide + Diazepam
335. Bromhexine + Phenylephrine + Chlorpheniramine + Paracetamol
336. Beclomethasone + Clotrimazole + Gentamicin + Iodo-chlorhydroxyquinoline
337. Telmisartan + Metformin
338. Ammonium citrate + Vitamin B 12 + Folic acid + Zinc sulphate
339. Levothyroxine + Pyridoxine + Nicotinamide
340. Benfotiamine + Metformin
341. Thyroid + Thiamine + Riboflavin + Pyridoxine + Calcium pantothenate + Tocopheryl acetate + Nicotinamide
342. Ascorbic acid + Menadione sodium bisulphite + Rutin + Dibasic calcium phosphate + Adrenachrome monosemicarbazone
343. Phenylephrine + Chlorpheniramine + Paracetamol + Bromhexine + Caffeine
344. Clotrimazole + Beclomethasone + Lignocaine + Ofloxacin + Acetic acid + Sodium methyl paraben + Propyl paraben

E. List of FDCs banned on 08.06.2017

1. Nimesulide + Levocetirizine
2. Ofloxacin + Ornidazole Injection
3. Gemifloxacin + Ambroxol
4. Glucosamine + Ibuprofen
5. Etodolac + Paracetamol

Note: An expert committee is currently reexamining the list of banned FDCs for their safety, efficacy and therapeutic justification.

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