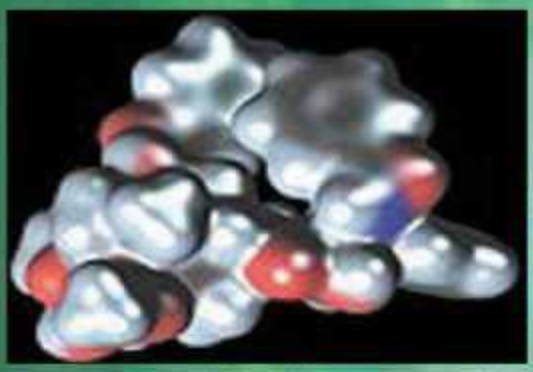
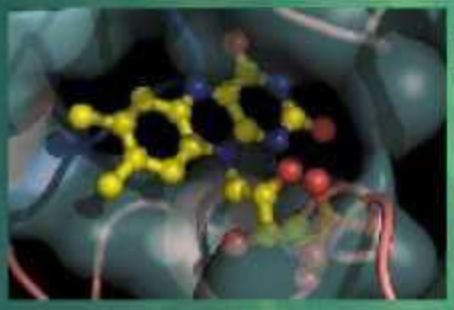
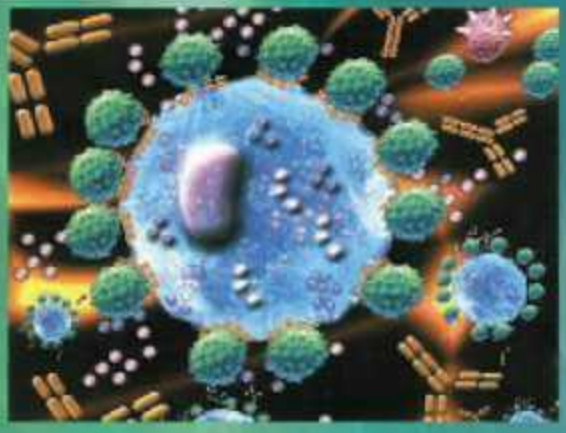
26th Year of Publication

Clinico-Basic PHARMACOLOGY

5th Revised Edition







Muhammad Shamim

Clinico - Basic

PHARMACOLOGY

5th Revised Edition

Comprehensive & Quick Review for Undergraduates & Postgraduates

Based on Lectures, Demonstrations, Tutorials & Practicals of Most Medical Colleges & Universities of Pakistan, Bangladesh, China, Russia, Saudi Arabia, UAE, Sudan, Yemen, Egypt & Malaysia.

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Preface

Clinico - Basic PHARMACOLOGY has been written in view of changing examination pattern from subjective type to MCQ type, esp.in Karachi. It has been compiled in a very comprehensive way with the aim of encompassing all details about Pharmacology & Therapeutics, & it will best serve as a review for students of MBBS, BDS, USMLE, MCPS, FCPS, M Phil, PhD, FRCS, MRCP, B Pharm, D Pharm, & MSc in the final weeks of examination, & also for doctors practicing privately or, in hospitals.

Format of this book

* Basic format for the description of each drug or groups of drugs remains the same, which consists of:
  1. Classification ——— update & unmatchable.
  2. Mechanism of action —— given in a concept - making, easy, arrow - form.
  3. Pharmacological effects —— described under subheads of systems & organs.
  4. Clinical uses.
  5. Adverse effects —— also described under subheads of systems & organs.
  6. Contraindications.
  7. Dosage.
* A brief description about system or disease has been given, that is affected by a group of drugs.
* Proprietary names are given to get you familiar with market names of drugs.
* Self - assessment questions are given at the end of every chapter (a total of 171 MCQs).
* Two separate chapters on MCQs are added in the end of the book, one consisting of true/false type MCQs (81) & the other one-best type of MCQs (192).

This book is useful for answering

1. **MCQs**
   * All topics have been discussed in a very comprehensive way, making sure that any MCQ asked in pharmacology will be answered correctly.
   * In addition, T/F types MCQs are given at the end of every chapter, & two additional chapters at the end of book (making an overall total of 444 MCQs).
2. **Short & long questions**
   * Format of the book adopted is such that any short or long question in Pharmacology will be answered.
   * Also comparisons of important drugs are given in chapter 27, Comparative Pharmacology, which will ensure answering of comparative questions.
3. **Viva**
   * Each drug or group of drugs has been discussed in appropriate subheadings with numbering of matter, which will ensure better answering in Viva.
   * What one should memorize for viva exam. is also given in chapter 31, Get Thru Pharmacology Viva.
   * In addition, viva for practical exam. is given in chapter 28, Practical Pharmacology.

Thanks

Our thanks are due to the following persons for every sort of co-operation they have provided: Dr. Syeda Ghazala Arfa, Dr. Shumaila Bano, M. Ashar Khan, M. Shafiq, Dr. Naved Akthar, M. Aamir Pervez, Dr. Sarwar Hussain, Khurram & Brothers, Dr. Lubna, Dr. Nuzhat Shama, Dr. Azharuddin, Dr. Azhar Iqbal, Dr. Mumtaz, Dr. Kamal, Dr. Shahid, & Dr. Farah Yasmeen.

Suggestions

Any suggestion for the improvement of this book will be acknowledged with thanks.

Dr. Muhammad Shamim

21st January, 2009

Dedicated

To

- My Parents
- My Wife
- My Daughter
- My Sons
- My Brothers
- My Sisters &
- My Friends

WHO ALL HAS COOPERATED & HELP ME IN ONE WAY OR THE OTHER.

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01 GENERAL PHARMACOLOGY

Unit I

General Pharmacology

PHARMACOLOGY

PHARMACOLOGY

(1) It refers to the study of substances that interacts with living systems thru chemical processes, esp. by binding to regulatory molecules & activating or inhibiting normal body processes.
(2) It is also defined as the study of biochemical & physiologic aspects of drug effects, including absorption, distribution, metabolism, elimination, toxicity, & specific mechanism of drug action.

BRANCHES OF PHARMACOLOGY

(1) Pharmacokinetics
It refers to the way the body handles drug absorption, distribution, biotransformation, & excretion.

(2) Pharmacodynamics
It refers to the study of biochemical & physiologic effects of drugs & their mechanism of action.

(3) Pharmacognosy
It refers to the study of biological, biochemical, & economic features of natural drugs & their constituents.

(4) Pharmacotherapeutics (Medical Pharmacology)
It refers to the science of substances used to prevent, diagnose, & treat diseases.

(5) Toxicology
It refers to the study of adverse (undesirable, untoward, or side) effects of chemicals on living systems, from individual cells to complex ecosystems.

(6) Pharmacy
It refers to the science of preparation, dispensing, & proper utilization of drugs.

DRUG

DRUG

It refers to any substance that brings about a change in biologic function thru its chemical actions.

Drug Nomenclature

Any drug has 3 names:
(1) Chemical name: Based upon chemical structure of drug, & is unsuitable for prescribing.
(2) Generic (approved) name: Official name that is used in pharmacopoeias.
(3) Proprietary name: Market name that is given by pharmaceutical company.

Examples

Imipramine, an antidepressant, is named as:
(1) Chemical name 2 3 - (10, 11 - dihydro - 5H - dibenz [b,f] - azepin - 5 - yl).
(2) Generic name 2 Imipramine.
(3) Proprietary name 2 Tofranil.

PRODRUGS

It refers to compounds that, on administration, must undergo chemical conversion by metabolic processes before becoming an active pharmacological agent.

Examples

Methyldopa, an antihypertensive, is first converted into α - methylnorepinephrine to produce its pharmacological effects.

PLACEBO

It refers to an inactive substance or preparation given to satisfy the patient's symbolic need (psychic need) for drug therapy, & used in controlled studies to determine the efficacy of medicinal substances.

Unit II

Pharmacokinetics

DOSAGE FORMS OF DRUGS

ORAL PREPARATIONS

(1) Liquids
(a) *Mixtures*
Drugs dissolved or suspended in water.
(b) *Emulsions*

Mixture of 2 immiscible liquids (eg oil & water) by means of an emulsifying agent (eg gum acacia).

(c) *Syrups*
Concentrated sol. of sugar containing flavoring, coloring, & therapeutically active substances.

(d) *Elixirs*
Sweetened, flavored hydroalcoholic sol. containing drug, or without any drug (for use as a vehicle).

(e) *Tinctures*
Alcoholic or hydroalcoholic sol. of vegetable drugs.

(2) Solids

(a) *Tablets*
Solid discs prepared by compressing the drug in granular form.
Enteric coated tablets: Coated with substances which resist dissolution in acidic gastric juice, but dissolves in alkaline juice of intestine.

(b) *Capsules*
Shells of gelatin containing drug. It may be enteric coated.

RECTAL PREPARATIONS

(1) *Suppositories*
Solid preparations for insertion into rectum.

(2) *Enemas*
Liquid preparations for insertion into rectum.

PARENTERAL PREPARATIONS

Solution or suspension containing drug, that may be dispensed in:

(1) Ampoules: Containing single dose.

(2) Vials: Rubber-capped bottles containing a number of doses.

INHALATIONAL PREPARATIONS

(1) *Gases*
Administered thru special devices.

(2) *Volatile Liquids*

(3) *Steam Inhalation*

(4) *Aerosols*
Released into respiratory passages in the form of a fine mist of liquid droplets.

TOPICAL PREPARATIONS

(1) *Ointments*
Semi - solid preparations for cutaneous or mucosal applications.

(2) *Liniments*
Preparations of various substances in an oily, soapy, or alcoholic vehicle intended to be applied to skin by rubbing.

(3) *Lotions*
Aqueous suspensions intended for application to skin without rubbing.

(4) *Lozenges*
Tablet-like formulations for slow dissolution in mouth.

(5) *Eye, Ear, & Nose Drops*
Aqueous solutions for local applications.

(6) *Mouth - washes & Gargles*

(7) *Powders*

(8) *Vaginal Douches*
Aqueous solution with cleansing or antiseptic properties.

DOSAGE

It refers to the determination & regulation of size, frequency, & number of doses (quantity to be administered at one time).

DOSAGE TYPES

(1) *Therapeutic Dose*
Average dose for an adult to produce a therapeutic effect.

(2) *Loading Dose (LD)*
A dose that promptly & quickly raises the conc. of drug in plasma to target conc. (that will produce the desired therapeutic effect).

$$LD = Vd \times TC$$

[Vd = Vol. of distribution, TC = Target conc.]

(3) *Maintenance Dose (MD) or Dosing Rate*
A dose that maintains a steady state of drug in body, ie, just enough dose of drug that replace the drug eliminated since preceding dose.

$$MD = CL \times TC$$

[CL = Clearance of drug]

(4) *Maximal Tolerated Dose*
Largest dose of a drug that can be taken safely.

(5) *Fatal Dose*
A dose that produces death.

DOSAGE FOR CHILDREN

Children require smaller doses of drugs than adults.

(1) *Young's Formula*

$$\text{Child dose} = \frac{\text{Adult dose} \times \text{Age in years}}{\text{Age} + 12}$$

(2) *Dilling's Formula*

$$\text{Child dose} = \frac{\text{Adult dose} \times \text{Age in years}}{20}$$

(3) *Clark's Formula*

$$\text{Child dose} = \frac{\text{Adult dose} \times \text{Wt. in Ib}}{150}$$

ROUTES OF DRUG ADMINISTRATION

ENTERAL

It involves drug administration via alimentary tract.

(1) Oral

Advantages

(a) Most convenient, & most acceptable.
(b) Used for local as well as systemic actions of drugs.

(c) Dosage forms do not require sterile techniques for administration.
(d) Delivery of drug into circulation is slow, so that rapid, high blood conc. are avoided & adverse effects are less.

Disadvantages

(a) Rate of absorption is variable.
(b) Irritation of mucosal surfaces can occur.
(c) Extensive hepatic metabolism (first-pass effect) may occur before the drug reaches its site of action.
(d) Onset of action is delayed, thus unsuitable in emergency situations.
(e) Impractical in unconscious or uncooperative pts.
(f) Drugs destroyed by digestive enzymes (insulin, pituitary hormones) or by gastric acidity (benzyl penicillin) can not be administered.

(2) Sublingual (Beneath Tongue)

Advantages

(a) Rapid absorption & effect (eg, glyceryl trinit-rate in angina).
(b) Effect can be terminated by spitting out tablet.

Disadvantages

(a) Inconvenient for frequent use.
(b) Irritation of oral mucosa, & excessive salivation.

(3) Rectal

Advantages

(a) Drug irritant to stomach can be given by suppository (eg aminophylline, indomethacin).
(b) Suitable in vomiting, motion sickness, migraine, or when a pt can not swallow, & when cooperation is lacking.
(c) Used for local effects, eg in proctitis, or colitis, & for bowel evacuation.

Disadvantages

(a) Psychological in that the pt may be embarrassed.
(b) Rectal inflammation may occur with repeated use.

PARENTERAL

It involves drug administration via injection into a blood vessel, soft tissue, or a body cavity.

Examples

(1) Intravenous (IV).
(2) Intramuscular (IM).
(3) Intradermal (ID).
(4) Subcutaneous (SC).
(5) Intraperitoneal (IP).
(6) Intra-arterial (IA).
(7) Intracardiac (IC).
(8) Intrathecal (IT).
(9) Intra-articular or joint (IJ).
(10) Intra-bone marrow (IBM).

Advantages

(1) Drugs get to the site of action more rapidly, providing a rapid response, which may be required in an emergency.
(2) Dose can be more accurately delivered.
(3) Can be used when alimentary route is not feasible (eg in unconscious pts).
(4) Suitable for drugs that are not absorbed from GIT, or are too irritant to be given by other routes.

Disadvantages

(1) More rapid absorption can lead to increased adverse effects.
(2) A sterile formulation, & an antiseptic technique are required.
(3) Local irritation may occur at the site of injection.

MISCELLANEOUS ROUTES

(1) Inhalational

It involves drug administration directly into the respiratory tract.

Advantages

Drugs as gases or aerosols can be rapidly taken up or eliminated.

Disadvantages

(a) Special apparatus is needed.
(b) Drug must be non-irritant for conscious pts.

(2) Topical

It involves application of drugs over skin or mucus membrane, to produce local effects.

Advantages

High local conc. can be achieved without systemic effects.

Disadvantages

Absorption can occur, esp. when there is tissue destruction, that results in systemic effects.

DRUG ABSORPTION

It refers to passage of a drug from its site of administration into bloodstream.

MECHANISM OF ABSORPTION

See 'Drug Permeation' below.

FACTORS AFFECTING DRUG ABSORPTION

(A) Drug Factors

(1) Lipid - Water Partition Coefficient

Directly proportional to drug absorption.

(2) Degree of Ionization

Inversely proportional to drug absorption.

(3) Chemical Nature (ie, Organic or Inorganic)

Eg, inorganic iron preparations are better absorbed from GIT.

(4) Dosage Forms

Solutions are better absorbed than suspensions.

(B) Patient Factors

(1) Route of Administration

(a) First - order (Exponential) Kinetics

A constant 'fraction' of drug is absorbed, eg following administration via any route except intravenous.

(b) Zero - order Kinetics
A constant 'amount' (ie, 100%) of drug is absorbed, after intravenous administration.

(2) Area & Vascularity of Absorbing Surface
Directly proportional to drug absorption.

(3) State of Health of Absorbing Surface

(4) Rate of General Circulation
This influences the rate of transport of drug.

(5) Specific Factors
Eg, intrinsic factor is necessary for vit. B_{12} absorption.

BIOAVAILABILITY

It refers to the extent of absorption of a drug following its administration by routes other than IV injection.

Factors Affecting Bioavailability

(1) First-pass hepatic metabolism.
(2) Solubility of drug.
(3) Chemical instability.
(4) Nature of drug formulation.
(5) Dietary patterns.

DRUG PERMEATION

It refers to movement of drug molecules thru various barriers into the body from site of administration (absorption), between different compartments of body (distribution), & out of body (excretion).

MECHANISM OF DRUG PERMEATION

(A) Passive Diffusion

It refers to passage of drug molecules by diffusing as un-ionized moiety thru lipid memb. It depends on molecule's size & charge, lipid-water partition co-efficient, & conc. gradient.

(1) Simple Diffusion
Passive diffusion of un-ionized molecules thru lipid memb., driven by conc. gradient.

(a) Fick's Law of Diffusion
It states that the passive flux (F) of unionized molecules across lipid memb. is;

(i) Directly proportional to conc. gradient (C1 – C2), area across which diffusion occurs (A), & permeability coefficient (P).

(ii) Inversely proportional to thickness of diffusion path (T).

$$F \text{ (molecules per unit time)} = \frac{(C1 - C2) \times A \times P}{T}$$

Note: P is directly proportional to temperature, & inversely related to molecular size.

(b) Diffusion of Weak Acids & Bases
Many drugs are either weak acids or weak bases.

(i) Acidic drugs (HA) dissociates as;

$$HA \text{ (protonated)} \; 4 \; H^+ + A^-$$

(ii) Weak bases (BH) dissociates as;

$$BH^+ \text{ (protonated)} \; 4 \; B \text{ (unprotonated)} + H^+$$

Diffusing State

(i) For weak acids 2 Protonated form.

(ii) For weak bases 2 Unprotonated form.

Handerson - Hasselbalch Equation

According to it, the relative conc. of protonated & unprotonated form is determined by pH at the site of diffusion & by the strength of weak acid or base (pKa).

$$\log \frac{\text{Protonated}}{\text{Unprotonated}} = pKa - pH$$

(i) Lower the pH relative to pKa, the greater will be the fraction of drug in protonated form 2 1 absorption of weak acids, & 3 absorption of weak bases.

(ii) Similarly 1 pH relative to pKa 2 1 unprotonated form 2 1absorption of weak bases, & 3 absorption of weak acids.

(2) Filtration
It refers to passage of molecules (eg, water, ions, & some polar & nonpolar molecules of low molecular weight) thru memb. via pores or channels (eg, in glomerulus).

(B) Carrier Mediated Transport

It refers to drug movement across the memb. mediated by a macromolecule (carrier protein) in the memb. It is a saturable process, & is selective for the chemical structure of a drug.

(1) Facilitated Diffusion
Movement is driven by conc. gradient, for which no energy is required.

(2) Active Transport
Movement occur against a conc. gradient (an active process), that requires energy which is generated by Na^+ - K^+ - ATPase.

(C) Endocytosis & Exocytosis

(1) Endocytosis refers to the process by which drug molecule is engulfed by cell memb. & carried into cell by pinching off of newly formed vesicles inside the memb. 2 Molecule is then released inside the cytosol by breakdown of vesicle memb.

(2) Reverse process (exocytosis) is responsible for secretion of many substances from cells.

DRUG DISTRIBUTION

It refers to the extent of localization of drug after absorption, eg confined to plasma, whole ECF, both ICF & ECF, or to specific areas such as brain or placenta.

FACTORS AFFECTING DISTRIBUTION

(A) Physical & Chemical Characteristics of Drug

(1) Molecular Weight
eg, high mol. wt. drugs such as dextran is largely confined to plasma.

(2) Ionization

eg, unionized drug readily move across most biological membranes including blood-brain barrier.

(B) Capillary Permeability

It varies widely in various tissues, eg;

(1) In brain, capillary endothelial cells are continuous & have no slit junctions; so that only lipid - soluble (unionized) drug can cross.

(2) In liver & spleen, a large part of basement memb. is exposed by large discontinuous capillaries 2 Large plasma proteins can cross.

(C) Blood Flow

Blood flow to brain, liver, & kidneys is greater than that to skeletal muscles & adipose tissue 2 More drug is delivered to greater blood flow areas.

(D) Binding of Drugs to Plasma Proteins

Some drugs can bind non-specifically & reversibly to various plasma proteins, eg albumin & globulin.

(1) Bound & free drug reach an equilibrium.

(2) Only the free drug exerts a biologic effect.

(3) Bound drug stays in vascular space, & is not metabolized or eliminated.

(E) Tissue Affinity

Some drugs are localized in specific tissues which possess specific drug receptors, eg iodine in thyroid gland, & chloroquine in liver.

APPARENT VOLUME OF DISTRIBUTION (VD)

It is a quantitative estimate of tissue localization of drug, & is expressed as,

$$Vd = \frac{\text{Total amount of drug in body}}{\text{Conc. of drug in plasma}}$$

Note: A high Vd indicates high lipophilicity or many receptors for drug.

BIOTRANSFORMATION

It refers to the process of chemical alteration of drugs in body.

SITES OF BIOTRANSFORMATION

(1) Liver

First - Pass Effect

Following oral administration, many drugs are absorbed intact from small intestine & transported via portal system to liver, where they undergo extensive metabolism referred as first - pass effect.

Example of Drugs: Isoproterenol, Meperidine, Pentazocine, Morphine, etc.

(2) Gastrointestinal Tract

Some orally administered drugs are more extensively metabolized in GIT than in liver, by intestinal microorganisms, gastric acid, & digestive enzymes.

Examples of Drugs: Clonazepam, Chlorpromazine, Penicillin, Insulin, Catecholamines.

(3) Other Sites

Lungs, kidneys, & adrenal glands can also metabolize drugs.

PHASES OF BIOTRANSFORMATION

(A) Phase I Reactions

It alters chemical reactivity & increases aqueous solubility of drugs.

(1) Oxidation

It involves addition of oxygen or removal of hydrogen from drug.

(a) Microsomal Mixed Function Oxidase System

It causes drug oxidation by oxidative drug - metabolizing enzymes, located in lipophilic memb. of smooth endoplasmic reticulum of liver & other tissues.

Components

(i) NADPH - cytochrome P450 reductase.

(ii) Cytochrome P450.

Reaction Examples

(i) Aromatic hydroxylations, eg of propranolol, phenytoin, warfarin.

(ii) Aliphatic hydroxylations, eg of chlorpropamide, ibuprofen, digitoxin.

(iii) Epoxidation, eg of aldrin.

(iv) Oxidative dealkylation, eg of theophylline, codeine, acetaminophen.

(v) S - oxidation, eg of thioridazine, cimetidine, chlorpromazine.

(vi) Deamination, eg of diazepam.

(vii) Desulfuration, eg of thiopental.

(viii) Dechlorination, eg of CCl_4.

Enzyme Induction

Some drugs induce (inc. activity of) cytochrome P450 by enhancing its rate of synthesis & / or reducing its rate of degradation 2 Acceleration of metabolism & usually a dec. in pharmacological action of inducer & also of co-administered drugs.

Drug examples: Phenobarbital, polycyclic aromatic hydrocarbons, glucocorticoids, macrolide antibiotics, antiepileptics, steroids, isoniazid, clofibrate, chronic ethanol administration.

Enzyme Inhibition

Some drugs inhibit cytochrome P450 enzyme activity.

Drug examples: Cimetidine, ketoconazole, chloramphenicol, ethinyl estradiol, norethindrone, spironolactone, fluroxene, secobarbital, allobarbital, ethchlorvynol, carbon disulfide, propylthiouracil.

(b) Non-Microsomal (Cytochrome P450 Independent) Oxidation

It involves drug oxidation by soluble enzymes found in cytosol or mitochondria of cells.

Examples

(i) Alcohol dehydrogenase 2 Converts ethanol to acetaldehyde.
(ii) Aldehyde dehydrogenase 2 Converts acetaldehyde to acetate.
(iii) Xanthine oxidase 2 Converts hypoxanthine to xanthine, & xanthine to uric acid.
(iv) Tyrosine hydroxylase 2 Converts tyrosine to dopa.
(v) Monoamine oxidase 2 Metabolizes catecholamines, & serotonin.
(vi) Flavin monooxygenase 2 Metabolizes chlorpromazine, amitriptyline, nortriptyline, desipramine, methimazole, & propylthiouracil.

(2) Reduction

It occur in both microsomal & non - microsomal metabolizing system.

Examples

(a) Azo reduction, eg of prontosil, tartrazine.
(b) Nitro reduction, eg of chloramphenicol, clorazepam, dantrolene.
(c) Carbonyl reduction, eg of metyrapone, methadone, naloxone.

(3) Hydrolysis

It involves nonmicrosomal hydrolases present in various body systems including plasma.

Examples

(a) Esterases 2 Metabolizes acetylcholine, succinylcholine, procaine, aspirin, etc.
(b) Amidases 2 Metabolizes procainamide, lidocaine, indomethacin.

(B) Phase II Reactions (Conjugation)

It involves coupling or conjugation reactions of parent drugs or their phase I metabolites with an endogenous substance to yield drug conjugates, & is catalyzed by various transferases, located in microsomes or in cytosol. Conjugates are polar molecules that are readily excreted, & often inactive.

Examples

(1) Glucoronidation, eg of morphine, acetaminophen, diazepam, meprobamate, digoxin.
(2) Acetylation, eg of sulfonamides, isoniazid, clonazepam, dapsone.
(3) Glutathione conjugation, eg of ethacrynic acid, bromobenzene.
(4) Glycine conjugation, eg of salicylic acid, cholic acid, deoxycholic acid.
(5) Sulfate conjugation, eg of estrone, phenol, acetaminophen, methyldopa.
(6) Methylation, eg of dopamine, epinephrine, histamine.
(7) Water conjugation, eg of benzopyrene epoxide, carbamazepine epoxide, leukotriene A_4.

FACTORS AFFECTING BIOTRANSFORMATION

(1) Genetics

It may alter enzyme level &/or cause polymorphism, eg of enzymes involved in;

(a) Hydrolysis of succinylcholine.
(b) Acetylation of isoniazid.
(c) Hydroxylation of warfarin.

(2) Chemical Properties of Drug

Certain drugs may stimulate or inhibit the metabolism of other drugs (see above).

(3) Route of Administration

Oral route can result in extensive first - pass effect.

(4) Diet

Starvation depletes glycine, & alters glycine conjugation.

(5) Dosage

Toxic doses can deplete enzymes.

(6) Age

Liver cannot detoxify drugs as well in neonates than in adults.

(7) Sex

Young males are more prone to sedation from barbiturates than females.

(8) Disease

(a) Liver disease dec. drug metabolism.
(b) Kidney disease dec. drug excretion.

DRUG ELIMINATION (EXCRETION)

It refers to the process by which a drug or its metabolite is eliminated from body.

ROUTES OF ELIMINATION

(1) Kidney

Excretion of drugs & their metabolites into urine involves;

(a) Glomerular filtration, eg of water-soluble & polar compounds.
(b) Active tubular secretion, eg of penicillins, quinine.
(c) Passive tubular reabsorption.

(2) Liver

It can secrete drugs or their metabolites (eg, glucoronide conjugates of opioids) into bile, that are lost in feces. However, some drug may be reabsorbed in intestine to again enter the circulation, referred as entero-hepatic circulation.

(3) GIT

Some drugs are excreted thru GIT, eg;

(a) Thiocynates, iodides, & mercury in saliva.
(b) Morphine thru passive diffusion in stomach (when its blood level is high).

(4) Lungs

Gaseous & volatile general anesthetic are excreted in expired air.

(5) Other Routes

(a) Sweat.
(b) Tears.
(c) Breast milk.

DRUG CLEARANCE

It refers to the ratio of rate of drug elimination by all routes to the conc. of drug in a biologic fluid (C).

$$CL = \text{Rate of elimination} / C$$

Total Body Clearance

Drug is eliminated via several routes. Dividing the rate of elimination at each organ by conc. of drug presented to it yields respective clearance at that organ, & sum of these is total body clearance.

(1) CL_{renal} = Rate of elimination $_{renal}$ / C
(2) CL_{liver} = Rate of elimination $_{liver}$ / C
(3) CL_{other} = Rate of elimination $_{other}$ / C
(4) $CL_{total} = CL_{renal} + CL_{liver} + CL_{other}$

Rate of Elimination

For most drugs elimination is not saturable, & rate of drug elimination is directly proportional to conc.

$$\text{Rate of elimination} = CL \times C$$

This is referred as first - order elimination.

(1) Capacity - Limited (Saturable) Elimination

Elimination pathways of some drugs (eg ethanol, phenytoin, aspirin) become saturated if the dose is high enough. Provided that the blood flow to an organ does not limit elimination, its rate is expressed as;

$$\text{Rate of elimination} = (V_{max} \times C) / (K_m + C)$$

[V_{max} = maximum elimination capacity, K_m = drug conc. at which rate of elimination is 50% of V_{max}].

Thus, increment in elimination rate becomes less as conc. increases, & at conc. higher than K_m, the elimination rate is almost independent of conc. & is referred as ' pseudo - zero order ' elimination.

(2) Flow - Dependent Elimination

Some drugs are very readily cleared by organ of elimination & they eliminated on first pass to the organ. Their elimination will thus depends on blood flow thru the organ.

Drug Examples of Hepatic Blood flow -Limited Clearance

Alprenolol, amitriptyline, isoniazid, lidocaine, pentazocine, morphine, propranolol, verapamil.

HALF - LIFE

It is the time required to change the amount of drug in body by one - half during elimination (or during a constant infusion), & is expressed as;

$$t_{1/2} = \frac{0.693 \times Vd}{CL}$$

Factors Increasing Drug Half - Life

(1) Dec. renal plasma flow, eg in cardiogenic shock, cardiac failure, hemorrhage.
(2) Addition of a second drug, that displaces first from albumin, increasing its Vd.
(3) Dec. extraction ratio, eg in renal disease.
(4) Dec. metabolism, eg when another drug inhibits its biotransformation.

STEADY - STATE CONCENTRATION (C_{ss})

A steady-state plasma concentration of drug occurs when the rate of drug elimination is equal to the rate of administration, & is expressed as,

$$C_{ss} = R_o / CL_{Total}$$

[R_o = Infusion rate].

Note: Approx.. 5 $t_{1/2}$ are required to reach a steady-state conc.

Unit III

Pharmacodynamics

RECEPTORS

It refers to specific drug-binding sites in a cell or on its surface, which mediate the action of drug.

Note: Some drugs (eg, mannitol) do not require receptor for its action.

NATURE OF DRUG RECEPTORS

(1) Regulatory proteins, which mediate the actions of endogenous chemical signals eg neurotransmitters, autacoids, & hormones.
(2) Enzymes, eg dihydrofolate reductase.
(3) Transport proteins, eg Na^+ / K^+ ATPase.
(4) Structural proteins, eg tubulin.

RECEPTOR REGULATION

(1) Down - Regulation

Receptors become desensitized or dec. in number, when exposed to an agonist repeatedly.

(2) Up - Regulation

Receptors become supersensitive to agonists via synthesis of additional receptor, on chronic administration of an antagonist.

RECEPTOR LIGANDS

(1) Agonist

A drug that produces some of the effects of endogenous compounds when it interacts with receptor, eg isoproterenol at β - adrenoceptors.

Note: Drug must have affinity & intrinsic activity to be an agonist.

(2) Antagonist

A drug that binds to receptor without activating it, thereby blocking endogenous agonist from exerting its effect, eg propranolol at β - adrenoceptors.

Note: Drug must have affinity but no intrinsic activity to be an antagonist.

(3) Partial Agonist

A drug that binds to receptor blocking access of natural agonist, & also capable of a low degree of activation (ie, affinity + some intrinsic activity), eg pindolol & oxprenolol at β - adrenoceptors.

(4) Inverse Agonist

A drug that on binding to receptor produces effects which are specifically opposite to those of agonist, eg β - carbolines at benzodiazepine receptors.

SPARE RECEPTORS

Maximal pharmacological response can be elicited by an agonist at a conc. that does not result in occupancy of full complement of available receptors, & the receptors which left un-occupied are referred as spare receptors.

Note: Spare receptors are not hidden or unavailable, & when they are occupied, they can be coupled to response.

DRUG - RECEPTOR INTERACTIONS

MECHANISM OF ACTION

(1) Via Intracellular Receptors

Lipid - soluble drug crosses the plasma memb. & acts on intracellular receptors, that may results in;

(a) Stimulation of intracellular enzymes, eg guanyl cyclase by nitric oxide.

(b) Stimulation of gene transcription by binding to specific DNA sequences (response elements) whose expression is regulated, eg by corticosteroids, sex steroids, vit D, & thyroid hormone.

(2) Via Transmemb. Receptor Protein

Drug bind to a site on protein's extracellular domain, resulting in a conformational change in & activation of cytoplasmic enzyme domain which may be a protein tyrosine kinase, a serine kinase, or a guanyl cyclase.

Drug examples: Insulin.

(3) Via Transmemb. Ion Channels

Drug bind to a transmemb. ion channel that can be induced to open or close.

Drug example: Acetylcholine at nicotinic receptors.

(4) Via G Proteins & Second Messengers

Drug binds to a transmemb. receptor protein to stimulate a GTP - binding signal transducer protein (G protein) that in turn generates an intracellular second messenger or inhibits its generation.

Types of Second Messengers

(1) Cyclic adenosine monophosphate (cAMP).
(2) Calcium ions.
(3) Phosphoinositides.
(4) Cyclic Guanosine monophosphate (cGMP).

Drug Examples

Acetylcholine at muscarinic receptors, catecholamines, FSH, LH, ACTH, histamine, PGE_2, etc.

ANTAGONISM

(1) Pharmacological Antagonism

Antagonist bind to receptors preventing an agonist from interacting with its receptors to produce an effect.

(a) Competitive Antagonism

Antagonist compete with agonists in a reversible fashion for the same receptor site.

(i) High antagonist conc. prevent agonist's response completely.

(ii) Sufficiently high conc. of agonist can completely surmount the effect of a given conc. of antagonist.

Drug example: Propranolol at β - adrenoceptors.

(b) Irreversible Antagonism

Antagonist binds irreversibly to receptor site, & this antagonism can not be overcome, no matter how much agonist is given.

Drug example: Phenoxybenzamine at α - adrenoceptors.

(2) Physiologic Antagonism

Two drugs acts on different receptors, & produces effect exactly opposite to each other.

Example

Drugs acting on cholinoceptors & adrenoceptors are physiologic antagonists of each other.

(3) Chemical Antagonism (Neutralization)

Two drugs combine with one another to form an inactive compound, without involving any receptor.

Example

Protamine & heparin.

DOSE - RESPONSE RELATIONSHIPS

GRADED - DOSE RESPONSE

As the dose of drug administered is increased, pharmacological effect will also increase, & at a certain dose, the resulting effect will reach a maximum level. Expressed as;

$$E = (E_{max} \times C) / (C + EC_{50})$$

[where E = effect, C = conc. E_{max} = maximal response, EC_{50} = conc. of drug that produces 50% of maximal effect].

(1) Efficacy

It is the maximum effect of a drug (E_{max}).

(2) Potency

It refers to different doses of two drugs that are needed to produce the same effect. It is measured by EC_{50} or ED_{50}.

Note: Clinical effectiveness of a drug depends on its efficacy, & not on its potency.

ENHANCEMENT OF DRUG EFFECT

(1) Addition

Two drugs with same effect, when given together, produce an effect that is equal in magnitude to the sum of effects when the drugs are given individually (ie, 1 + 1 = 2).

(2) Synergism
Two drugs with same effect, when given together, produce an effect that is greater in magnitude than the sum of effects when the drugs are given individually (ie, 1 + 1 > 2).

(3) Potentiation
A drug lacking an effect of its own increases the effect of a second, active drug (ie, 0 + 1 > 1).

EVALUATION OF DRUG SAFETY & USEFULNESS

(1) Therapeutic Index
It is a ratio b/w doses of a drug required to produce undesired & desired effects. Expressed as;

$$TI = LD_{50} / ED_{50}$$

[where LD_{50} = minimum dose that is lethal for 50% of population, ED_{50} = minimum dose that is effective for 50% of population].

(2) Standard Margin of Safety
It shows the percentage by which ED_{99} (dose effective in 99% of population) must be increased to cause lethal effects in 1% of population (LD_1). Expressed as;

$$SMS = (LD_1 / ED_{99}) - 1 \times 100$$

VARIATION IN DRUG RESPONSIVENESS

(1) Idiosyncrasy
It refers to an unusual drug response in an individual than in most individuals.

Causes
(a) Genetic differences in drug metabolism.
(b) Immunologic mechanism, including allergic reactions.

(2) Hyporeactivity
It refers to decreased intensity of effect of a given dose of drug, in comparison to effect seen in most individuals.

(3) Hyperreactivity
It refers to increased intensity of drug's effect for a given dose, in comparison to effect seen in most individuals.

(4) Hypersensitivity
It refers to allergic or other immunologic responses to drugs.

Clinical Manifestations
(a) Skin reactions: Urticaria, rashes, angioneurotic edema.
(b) Blood dyscrasias: Thrombocytopenia, granulocytopenia, aplastic anemia, hemolysis.
(c) Others: Anaphylaxis, asthma, serum-sickness, fever, systemic lupus erythematosus, hepatitis, cholestatic jaundice, nephropathy.

(5) Tolerance
It refers to decreased responsiveness to a drug as a consequence of continued administration of a given dose of drug.

(6) Tachyphylaxis
It refers to a rapid decrease in responsiveness after administration of a drug.

Unit IV

Self - Assessment (T/F)

(See answers on page no. 240)

(1) ***Following are mechanisms of drug permeation***
(A) Aqueous diffusion.
(B) Aqueous hydrolysis.
(C) Lipid diffusion.
(D) Pinocytosis or endocytosis.
(E) Active (carrier) transport.

(2) ***Following statements about routes of drug administration are correct***
(A) Conc. in blood often rise faster after IM injection than after oral dosing.
(B) First - pass effect is more likely to occur in sub-lingual administration than in oral.
(C) Bioavailability of most drugs is lower with rectal (suppository) administration than with IV route.
(D) Oral route can be used in comatose pts or in pts with emergency.
(E) Sterile formulation & aseptic technique are required in parenteral administration.

(3) ***Distribution of drugs to tissues***
(A) Is independent of blood flow to the organ.
(B) Is independent of solubility of drug in a given tissue.
(C) Depends on conc. gradient b/w blood & tissue.
(D) Is increased for drugs that are strongly bound to plasma proteins.
(E) Has no effect on half - life of drug.

(4) ***Drugs bound to plasma proteins***
(A) Cannot leave vascular space.
(B) Is not metabolized.
(C) Is eliminated early.
(D) Is active pharmacologically.
(E) Forms a storage depot from which a small proportion of active drug is freed constantly.

(5) ***Following are sites of biotransformation***
(A) Liver.
(B) GIT.
(C) Spleen.
(D) Kidneys.
(E) Brain.

(6) ***Examples of phase I biotransformation reactions are***

(A) Hydrolysis.

(B) Reduction.

(C) Cytochrome P450 independent oxidation.

(D) Carboxylation.

(E) Conjugation.

(7) ***Regarding absorption of drugs***

(A) Unionized form is readily absorbed.
(B) Suspensions are better absorbed than solutions.
(C) Intrinsic factor is necessary for absorption of vit B_{12}.
(D) In first - order kinetics 100% drug is absorbed into blood.
(E) In zero - order kinetics a constant fraction of drug is absorbed into blood.

(8) ***First - pass effect occur in following routes of administration***

(A) Oral.
(B) Sub - lingual.
(C) Rectal.
(D) Intravenous.
(E) Subcutaneous.

(9) ***Induction of drug metabolism***

(A) Results in increased production of rough endoplasmic reticulum.
(B) Results in increased production of smooth endoplasmic reticulum.
(C) Requires 3 - 4 months to reach completion.
(D) Results in decreased pharmacologic actions of inducer.
(E) Is irreversible.

(10) ***Most drug receptors are***

(A) Small molecules with a molecular weight b/w 100 & 1000.
(B) Lipids arranged in a bilayer configuration.
(C) Proteins located on cell memb. or in cytosol.
(D) DNAs.
(E) RNAs.

(11) ***Following statements are correct***

(A) Maximum efficacy of a drug is directly correlated with its potency.
(B) Therapeutic index is LD_{50} divided by ED_{50}.
(C) A partial agonist has no effect on its receptors unless another drug is present.
(D) Antagonist has affinity but no intrinsic activity.
(E) Agonist has both affinity & intrinsic activity.

(12) ***Major organs for drug excretion are***

(A) Kidneys.
(B) Liver.
(C) GIT.
(D) Lungs.
(E) Breast.

(13) ***Administration of 2 or more drugs simulta-neously may results in***

(A) Additions.
(B) Antagonism.
(C) Synergism.
(D) Potentiation.
(E) Increased excretion.

02 SYMPATHETIC NERVOUS SYSTEM DRUGS

Unit I

Introduction

NERVOUS SYSTEM

It is a system that, along with endocrine system, coordinates the regulation & integration of body functions.

DIVISIONS OF NERVOUS SYSTEM

(A) Central Nervous System

It includes;

(1) Brain.

(2) Spinal cord.

(B) Peripheral Nervous System

It includes neurons (or nerves) located outside the brain & spinal cord.

(1) Somatic Nervous System

It is concerned with consciously controlled functions (voluntary activities), eg movement, respiration, & posture.

It consists of ;

Two components, afferent & efferent, both contained in;

(a) Cranial nerves ➜ 12 pairs.

(b) Spinal nerves ➜ 31 pairs.

(2) Autonomic Nervous System

It is concerned with activities that are not under direct conscious control (ie visceral functions), eg cardiac output, blood flow to various organs, digestion, etc.

Components

(a) Afferent fibres that run from periphery to integrating centres (enteric plexuses in gut, autonomic ganglia, & CNS). It evokes reflex visceral activities.

(b) Efferent fibers (see below).

Sub-divisions

(a) Sympathetic nervous system (Thoracolumbar or Adrenergic system).

(b) Parasympathetic nervous system (Craniosacral or cholinergic system).

(c) Enteric nervous system (ENS)

It is a collection of neurons located in gut wall, & sometimes considered a 3rd division of ANS;

(i) Consists of ➜ Myenteric plexus (of Auerbach), & submucus plexus (of Meissner).

(ii) Receives ➜ Preganglionic parasympathetic fibres, postganglionic sympathetic fibres, & also sensory input from within the gut wall.

(iii) Fibres from its cell bodies go to smooth muscle & secretory cells of gut, & control motility & secretions respectively.

SYMPATHETIC NERVOUS SYSTEM (SNS)

ANATOMY

Efferent (motor) portion of SNS consists of:

(1) Preganglionic Neurons

Cell bodies of preganglionic neurons are found in spinal cord (ie CNS), in the lateral grey horn of all the thoracic & upper two lumbar segments. Their axons constitute the preganglionic fibres.

(2) Preganglionic Fibres

Leave the CNS, from T1 to L2 segments of spinal cord, & travel upto sympathetic ganglia.

(3) Ganglia

Preganglionic fibres terminate by synapsing with the cell bodies of sympathetic ganglia (paravertebral chain of ganglia & prevertebral ganglia).

(4) Postganglionic Fibres

These are axons of cell bodies in sympathetic ganglia, extending to the effector organs (viscera & glands).

NEUROTRANSMITTERS

Transmission of nerve impulse across a synapse occurs thru the release of specific chemical signals, called neurotransmitters, from nerve terminals. These substances rapidly diffuse across the synapse b/w nerve endings & combine with specific receptors on postsynaptic (target) cell.

Sympathetic Neurotransmitters

(1) Acetylcholine

Released by;

(a) Preganglionic fibres at ganglionic synapses.

(b) Postganglionic fibres at neuroeffector synapses, of;

(i) Eccrine (thermoregulatory) sweat glands.
(ii) Skeletal muscle blood vessels.

(2) Norepinephrine & Epinephrine

(a) Norepinephrine is released by postganglionic fibres at most neuroeffector synapses.
(b) A mixture of epinephrine & norepinephrine is released by adrenal medullary cells (embryologically analogous to postganglionic sympathetic neurons).

(3) Dopamine

Released by postganglionic fibres in renal blood vessels.

(4) Cotransmitters

These are substances other than primary transmitters (mentioned above) that may provide a slow, long-lasting action to supplement or modulate the more transient effects of primary transmitters. They may have feedback inhibitory effect.

Examples

Adenosine triphosphate (ATP), Calcitonin gene-related peptide (CGRP), Neuropeptide Y, Serotonin, etc.

SYMPATHETIC NEUROTRANSMISSION

Neurotransmission refers to the transmission of nerve impulse from one neuron to another neuron or to an effector organ by releasing neurotransmitters. Basically, two types of neurotransmission occur in SNS, depending on the type of neurotransmitter released.

(A) Cholinergic Transmission

Here acetylcholine is the neurotransmitter, eg at ganglionic synapses, some sympathetic neuro-effector synapses, & all parasympathetic neuro-effector synapses. (See chapter 3, unit I).

(B) Adrenergic Transmission

Here norepinephrine is the neurotransmitter, found at most of the sympathetic neuro-effector synapses. It involves 5 steps:

(1) Synthesis of Norepinephrine

Tyrosine is transported into cytoplasm of adrenergic neuron ➜ Hydroxylated to DOPA by tyrosine hydroxylase ➜ Decarboxylated to form dopamine.

(2) Storage of Norepinephrine in Vesicles

Dopamine is transported into synaptic vesicles using an amine transporter system 2 Hydroxylated to form norepinephrine (2 Methylated to form epinephrine in adrenal medulla).

(3) Release of Norepinephrine

Arrival of action potential at presynaptic nerve terminal ➜ Triggers Ca^{++} influx into cytoplasm of neuron ➜ Inc. Ca^{++} destabilizes the storage vesicles by interacting with a special protein "synaptotagmin" in vesicular memb. ➜ Vesicular memb. fuses with the terminal memb. ➜ Exocytotic expulsion of norepinephrine occur in synaptic cleft.

(4) Binding to Receptors

Released norepinephrine diffuses across the synaptic cleft, & binds to either postsynaptic receptors on effector organs or to presynaptic receptors on nerve terminal ➜ Triggers formation of intracellular 2nd messengers, eg cAMP, IP_3, etc. (See Box 2.1 below).

(5) Removal of Norepinephrine (& Epinephrine)

Termination of action of released norepinephrine can results from:

(a) Diffusion

Simple diffusion of norepinephrine away from the receptor site, with eventual metabolism in plasma or liver.

(b) Reuptake

(i) Uptake I

Norepinephrine is taken back into the same nerve terminal, where it may re-enter synaptic vesicle via amine transporter system or, oxidized by MAO (present in neuronal mitochondria).

(ii) Uptake II

Norepinephrine is taken back into perisynaptic glia or smooth muscle cells.

(c) Metabolism (Degradation)

(i) Oxidation

By monoamine oxidase (MAO) present in neuronal mitochondria.

(ii) Methylation

By catechol-O-methyltransferase (COMT) present in postsynaptic memb.

AUTO- & HETERO-RECEPTORS

These are meant for feedback control at presynaptic level, in both sympathetic & parasympathetic nervous system.

Autoreceptors

These are presynaptic receptors that respond to the transmitter substances released by the nerve ending.

Examples

(A) Inhibitory Autoreceptors

(1) Alpha-2 at adrenergic terminals ➜ Activated by norepinephrine, & in turn diminishes further release of norepinephrine.
(2) D_2 at adrenergic terminals ➜ Activated by dopamine, inhibits further transmitter release.

(B) Excitatory Autoreceptors

(1) Beta-1 at adrenergic terminals ➜ Activated by epinephrine, stimulates further transmitter release.
(2) N_M at somatic motor cholinergic terminals ➜ Activated by acetylcholine, stimulates further transmitter release.

Heteroreceptors

These are also presynaptic receptors that respond to many other substances, which diffuses to the receptor sites from blood or from nearby tissues. It may also be activated by substances released from nerve terminals that synapse with the nerve ending.

Examples

(A) Inhibitory Heteroreceptors

Box 2.1	ADRENOCEPTORS ------- Location & Effects		
Receptors	**Location**	**Pharmacological Effects**	**2nd Messenger Effects**
~1	Postsynaptic effector cells 1) Most vascular smooth muscle (innervated) 2) Radial muscle of iris 3) Pilomotor smooth muscle 4) GIT sphincters 5) Prostate & bladder sphincter 6) Heart	 Contraction → Vasoconstriction, ↑ peripheral resistance & ↑ BP Contraction → Mydriasis (dilatation of pupil) Contraction → Hair erection Contraction Contraction Increases force of contraction	• ↑ IP_3, ↑ DAG (common to all sub-types) • ↑ Ca^{++} influx (α-1B,1D)
~2	1) Presynaptic adrenergic & cholinergic nerve terminals 2) Some vascular smooth muscle (non-innervated) 3) Platelets 4) Lipocytes 5) CNS (post-synaptically)	Inhibition of transmitter release Contraction Aggregation Inhibition of lipolysis Probably multiple	• Inhibition of adenyl cyclase → ↓ cAMP (common to all sub-types) • ↑ K+ channels, • ↓ Ca^{++} channels
1	1) Presynaptic adrenergic nerve terminals 2) Heart (postsynaptic) a) SA node b) Ectopic pacemakers c) Contractility 3) Kidneys (postsynaptic)	Stimulation of transmitter release Acceleration (+ve chronotropic effect) Acceleration (+ve chronotropic effect, arrhythmias) Increases (+ve inotropic effect) Stimulation of renin release	Stimulation of adenyl cyclase → ↑ cAMP
2	Postsynaptic effector cells 1) Bronchiolar smooth muscle 2) GIT wall smooth muscle 3) Bladder wall smooth muscle 4) Pregnant uterus 5) Vascular smooth muscle in skeletal muscle 6) Liver 7) Skeletal muscle	 Relaxation Relaxation Relaxation Relaxation Relaxation (vasodilatation) Stimulation of glycogenolysis & gluconeogenesis Promotion of K^+ uptake	Stimulation of adenyl cyclase → ↑ cAMP
3	Lipocytes (postsynaptic)	Stimulation of lipolysis	Stimulation of adenyl cyclase → ↑ cAMP
D_1	1) Brain a) Putamen (presynaptic) b) Zona compacta of substantia nigra (postsynaptic) 2) Vascular smooth muscle esp of renal vascular bed (postsynaptic)	Associated with motor function control Relaxation (renal vasodilation)	Stimulation of adenyl cyclase → ↑ cAMP
D_2	1) Brain → Both pre- & postsynaptically on neurons in caudate - putamen, nucleus accumbens, & olfactory tubercle 2) Presynaptic adrenergic nerve terminals	Associated with motor function control Inhibition of transmitter release	Inhibition of adenyl cyclase → ↓ cAMP, ↑ K^+ conductance
D_3	Brain → Frontal cortex, medulla, & midbrain		Inhibition of adenyl cyclase → ↓ cAMP
D_4	Brain		Inhibition of adenyl cyclase → ↓ cAMP
D_5	Brain → Hippocampus, & hypothalamus		Stimulation of adenyl cyclase → ↑ cAMP

(1) EP_3 at adrenergic terminals ➜ Activated by prostaglandin E_1, E_2.
(2) M_2 at adrenergic terminals ➜ Activated by acetylcholine.
(3) 5-HT_1, 5-HT_2, & 5-HT_3, at cholinergic preganglionic terminals ➜ Activated by serotonin (5-HT).

(B) Excitatory Heteroreceptors

A II-1 at adrenergic terminals ➜ Activated by angiotensin II.

ADRENERGIC RECEPTORS (ADRENOCEPTORS)

These are receptors that mediate the actions of sympathetic nervous system, by interacting with primary neurotransmitter or exogenously administered drugs. Three classes (types) of adrenoceptors are identified with many subtypes, based on affinity for various agonists & antagonists, & molecular cloning.

(A) Alpha Adrenoceptors

Exhibits following series of agonist's potency:

Epinephrine ≥ Norepinephrine >> Isoproterenol.

Sub-Types

Two sub-types are identified with antagonist (blocker) drugs, & each have further sub-types as well ;

(1) Alpha-1 ➜ Blocked by Prazosin.
  (a) Alpha - 1A
  (b) Alpha - 1B
  (c) Alpha - 1C
  (d) Alpha - 1D
(2) Alpha-2 ➜ Blocked by Yohimbine.
  (a) Alpha - 2A
  (b) Alpha - 2B
  (c) Alpha - 2C

(B) Beta Adrenoceptors

Exhibits following series of agonist's potency :

Isoproterenol > Epinephrine ≥ Norepinephrine.

Sub-Types

(1) Beta-1 ➜ Exhibits approx. equal affinity for epinephrine & norepinephrine.
(2) Beta-2 ➜ Exhibits higher affinity for epinephrine than for norepinephrine.
(3) Beta-3 ➜ Recently demonstrated on the basis of molecular cloning, & shows agonist activity for BRL 37344.

(C) Dopamine Receptors

Exhibits agonist activity for dopamine.

Sub-Types

Five sub-types are identified ➜ D_1, D_2, D_3, D_4, & D_5.

Unit II

Sympathomimetics

[Adrenoceptors - Activating Drugs, Sympathetic Agonists, or Adrenoceptor Agonists]

CLASSIFICATION OF SYMPATHOMIMETICS

ACCORDING TO CHEMICAL NATURE

(1) Catecholamines

Norepinephrine (Noradrenaline), Epinephrine (Adrenaline), Isoproterenol (Isoprenaline), Dopamine, Dobutamine, Ibopamine.

(2) Non-Catecholamines

Phenylephrine, Methoxamine, Ephedrine, Pseudoephedrine, Albuterol (Salbutamol), Terbutaline, Metaproterenol (Orciprenaline), Ritodrine, Amphetamine, Hydroxyamphetamine, Methamphetamine, Xylometazoline, Oxymetazoline, Phenmetrazine, Methylphenidate, Pemoline, Phenylpropanolamine, Mephenteramine, Clonidine, Naphazoline, Tetrahydrozoline.

Box 2.2

CHARACTERISTICS OF CATECHOL- & NONCATECHOLAMINES

Catecholamines

- Presence of catechol (a 3 ,4 – dihydroxybenzene group) in the structure
- Rapid onset of action
- Brief duration of action
- Can not be administered orally
- Do not penetrate blood - brain barrier

Non - Catecholamines

- Longer duration of action
- All can be administered orally

ACCORDING TO MECHANISM OF ACTION

(1) Direct - Acting Agonists

These drugs act directly on adrenoceptors

Examples

Epinephrine, Norepinephrine, Isoproterenol, Dobutamine, Phenylephrine, Methoxamine, Albuterol, Terbutaline, Ritodrine, Metaproterenol, Clonidine.

(2) Indirect - Acting Agonists

These drugs causes release of catecholamines.

Examples

Amphetamine, Tyramine, Modafinil.

(3) Mixed-Acting Agonists

Dopamine, Ephedrine, Methamphetamine, Hydroxyamphetamine, Metaraminol.

(4) Inhibitors of catecholamine reuptake

Dexmethylphenidate.

ACCORDING TO RECEPTOR SELECTIVITY

(1) Alpha Selective

(a) Alpha-1 Selective

Phenylephrine, Methoxamine, Midodrine.

(b) Alpha-2 Selective

Clonidine, Aproclonidine, Brimonidine, Dexmedetomidine, Methylnorepinephrine, Guanabenz, Guanfacine.

(2) Beta Selective

(a) Beta-1 Selective

Dobutamine.

(b) Beta-2 Selective

Albuterol, Terbutaline, Ritodrine, Metaproterenol, Bitolterol, Procaterol, Fenoterol, Pirbuterol, Salmeterol.

(c) Beta-1 & -2 Non-Selective

Isoproterenol.

(3) Alpha & Beta Non-Selective

Epinephrine, Norepinephrine.

(4) Dopamine Selective

Dopamine (D non-selective), Fenoldopam(D1 selective).

MECHANISM OF ACTION OF SYMPATHOMIMETICS

Sympathomimetics bind to adrenoceptors, which are coupled with G proteins (G_s stimulatory, G_i inhibitory, or G_q phospholipase C related) ➜ GDP dissociates from α subunit of appropriate G protein ➜ GTP then binds to this G protein & α subunit dissociates from β - γ unit ➜ Activated GTP - bound α subunit then regulate the activity of its effector (ie, adenyl cyclase, cGMP phosphodiesterase, phospholipase C, ion channels).

(**Note :** One or more effector mechanism is associated with each receptor type [See Box 2-1], that results in final cellular effect).

(A) Alpha-1 Adrenoceptors

A rise cytosolic Ca^{++} conc. occurs, thru ;

(1) Opening of receptor-operated Ca^{++} channels (α-1A & α -1D)

(2) G_q mediated phospholipase C ➜ Breakdown of polyphosphoinositides into inositol triphosphate (IP_3) & diacylglycerol (DAG) ➜ IP_3 promotes release of Ca^{++} from intracellular stores.

(B) Alpha-2 Adrenoceptors

(1) G_i mediated inhibition of adenyl cyclase ➜ Dec. intracellular cAMP level.

(2) Activation of K^+ channels (α -2A).

(3) Closing of Ca^{++} channels (α -2A, α -2B).

(C) Beta Adrenoceptors

G_s mediated activation of adenyl cyclase ➜ Inc. intracellular cAMP level.

(D) D_1 & D_5 Adrenoceptors

Activation of adenyl cyclase ➜ ↑ cAMP.

(E) D_2, D_3 & D_4 Adrenoceptors

(1) Inhibition of adenyl cyclase ➜ 3 cAMP.

(2) Opening of K^+ channels (D_2, D_4).

(3) Closing of Ca^{++} channels (D_2, D_4).

PHARMACOLOGICAL EFFECTS OF SYMPATHOMIMETICS

CARDIOVASCULAR SYSTEM (CVS)

(1) Blood Vessels

(a) Vasoconstriction of cutaneous & splanchnic vessels (α effect).

(b) Vasoconstriction (α) or vasodilation (β_2) of vessels in skeletal muscle, depending on whether α or β_2 receptors are activated.

(c) Vasodilation of renal, splanchnic, coronary, & cerebral arteries (D_1 effect).

(2) Heart

β_1 adrenoceptor activation results in increased Ca^{++} influx in cardiac cells, that results in ;

(a) Increased pacemaker activity, both normal (SA node) & abnormal (eg Purkinje fibres) ➜ ↑ heart rate (+ve chronotropic effect). However, normally due to reflux vagal response to BP changes, the heart rate is decreased.

(b) Increased conduction velocity in AV node, & decreased refractory period.

(c) Increased intrinsic contractility (+ve inotropic effect), accelerated relaxation ➜ Intraventricular pressure rises & falls more rapidly, & ejection time is decreased.

(3) Blood Pressure

(a) Alpha Effect eg, by Phenylephrine

(i) Vasoconstriction ➜ Increased arterial resistance & decreased venous capaci- tance ➜ Inc. blood pressure (BP).

(ii) However, normally, a rise in BP elicits baroreceptor-mediated vagal response ➜ Decreases heart rate; but cardiac output may not diminish, due to increased venous return & modest +ve inotropic effect.

(b) Beta Effect eg, by Isoproterenol

Net effect is:

(i) A fall in diastolic pressure due to decreased peripheral resistance from skeletal muscle vasodilation (β_2).

(ii) Slight increase or no change in systolic pressure due to increased cardiac output (β_1).

(iii) Decreased mean blood pressure.

EYE

(1) Alpha Effect eg, by Phenylephrine

(a) Contraction of radial pupillary dilator muscle of iris ➜ Dilatation of pupil (mydriasis).

(b) Increase in outflow of aqueous humor ➜ Decrease intra-ocular pressure.

(2) Beta Effect

(a) Relaxation of ciliary muscle to a minor degree ➜ Insignificant decrease in accommodation.

(b) Increased production of aqueous humor ➜ Increased intra-ocular pressure.

RESPIRATORY TRACT

(1) Alpha-1 Effect eg, by Phenylephrine
Vasoconstriction in mucosal vessels of upper respiratory tract ➜ Decongestion.

(2) Beta-2 Effect eg, by Albuterol
Relaxation of bronchial smooth muscles ➜ Bronchodilation.

GASTROINTESTINAL TRACT (GIT)

(1) Alpha-2 Effect
(a) GI smooth muscle relaxation by indirectly decreasing muscle activity, thru presynaptic inhibition of acetylcholine release.
(b) Decrease salt & water flux into intestinal lumen.

(2) Beta-2 Effect
Direct relaxation of GI smooth muscles via hyperpolarization & decreased spike activity in smooth muscle cells.

GENITOURINARY TRACT

(1) Uterus
(a) α effect ➜ Smooth muscle contraction.
(b) β_2 effect ➜ Smooth muscle relaxation in pregnant uterus.

(2) Urinary Bladder
(a) Alpha-1 Effect
Contraction of urethral sphincter, bladder base, & prostate ➜ Promote continence.
(b) Beta-2 Effect
Relaxation of bladder wall.

(3) Male Genitalia
Alpha effect on ductus deferens, seminal vesicles, prostate, & penis ➜ Ejaculation.

EXOCRINE GLAND

(1) Salivary Glands
(a) Regulation of amylase & water secretion, via adrenoceptors contained in them.
(b) Dry mouth, via central effect eg by clonidine.

(2) Apocrine (Stress, or Nonthermoregulatory) Sweat Glands
Increased sweat production (α effect).

METABOLIC EFFECTS

(1) Lipocytes
(a) Activation of lipolysis (β_3 effect).
(b) Inhibition of lipolysis (α_2 effect).

(2) Liver
Activation of glycogenolysis & gluconeogenesis (α or β_2 effect. depending on species).

(3) Skeletal Muscle
Increases K^+ uptake into the cells (β_2 effect) ➜ Hypokalemia.

ENDOCRINE SYSTEM

(1) Insulin Secretion
(a) Stimulation (β effect).
(b) Inhibition (α_2 effect).

(2) Renin Secretion
(a) Stimulation (β_1 effect).
(b) Inhibition (α_2 effect).

CENTRAL NERVOUS SYSTEM (CNS)

Here effects are not due to α or β mediated actions, but probably represent enhancement of dopamine-mediated processes in CNS.

(1) Catecholamines
They have almost no effect except, for nervousness to a feeling of impending disaster, noted at highest rates of infusion.

(2) Non-Catecholamines
(a) Mild alerting, with improved attention to boring tasks.
(b) Elevation of mood, insomnia, euphoria, & anorexia.
(c) Psychotic behavior at very highest level.

CLINICAL USES OF SYMPATHOMIMETICS

EPINEPHRINE

(1) To treat bronchospasm, eg in acute asthma & anaphylactic shock.
(2) As primary treatment of anaphylaxis, to relieve hypersensitivity reactions.
(3) To reduce regional blood flow (via vasoconstriction);
(a) For achieving hemostasis in surgery.
(b) For reducing diffusion of local anesthetics away form administration site.
(c) For reducing mucous memb. congestion.
(4) To restore cardiac activity in cardiac arrest.
(5) To facilitate aqueous drainage in chronic open- angle glaucoma.

NOREPINEPHRINE

As a pressor agent in hypotension, to preserve cerebral & coronary blood flow, eg in;
(1) Severe hemorrhage.
(2) Spinal cord injury.
(3) Overdosage of antihypertensives or CNS depres-sants.
(4) During anesthesia.

OTHERS

Isoproterenol
(1) As a cardiac stimulant, eg in cardiogenic shock, complete heart block, & cardiac arrest.
(2) As a bronchodilator, eg in asthma.

Dopamine
(1) Shock esp. cardiogenic shock.
(2) Chronic refractory congestive heart failure.

Dobutamine
To improve myocardial function in congestive heart failure & cardiogenic shock.

Fenoldopam
As an antihypertensive agent postoperatively, to treat hypertensive crisis.

Apraclonidine & Brimonidine
For the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Phenylephrine
(1) As a pressor agent.
(2) As a local mucous memb. decongestant, eg in nose to relieve hay fever & common cold.
(3) As an adjunct for local anesthesia (to reduce regional blood flow).
(4) To treat paroxysmal atrial tachycardia.
(5) As a mydriatic agent to facilitate examination of retina, & in diagnosis of Horner's syndrome.

Methoxamine
(1) As a pressor agent.
(2) To treat paroxysmal atrial tachycardia.

Ephedrine
(1) As a nasal decongestant.
(2) To treat bronchial asthma.
(3) As a pressor agent in spinal anesthesia.
(4) As a mydriatic.
(5) To treat stress incontinence.

Amphetamine, Methamphetamine & Methylphenidate
(1) To treat narcolepsy.
(2) To treat attention-deficit hyperkinetic syndrome of children.

Hydroxyamphetamine
(1) As a mydriatic
(2) As a decongestant
(3) As a pressor agent
(4) To diagnose Horner's syndrome.

Metaraminol
To treat hypotension.

Metaproterenol & Albuterol
To treat bronchospasm, eg in asthma.

Terbutaline & Ritodrine
(1) To treat bronchospasm.
(2) To reduce uterine contractions in premature labor.

Xylometazoline, Oxymetazoline, & Phenylpropanolamine
As a topical decongestant.

ADVERSE EFFECTS OF SYMPATHOMIMETICS

EPINEPHRINE
(1) CNS
Anxiety, fear, tension, headache, tremor, cerebral hemorrhage.

(2) CVS
Hypertension, cardiac arrhythmias, angina.

(3) Resp. Tract
Pulmonary edema.

OTHERS
(1) Norepinephrine & Isoproterenol
Similar to epinephrine.

(2) Dopamine
(a) CVS
Anginal pain, arrhythmias, hypertension.
(b) GIT
Nausea.
(c) Overdosage
Results in excessive sympathomimetic effects.

(3) Dobutamine
Similar to epinephrine.
Precaution
Used with caution in atrial fibrillation, because it increases AV conduction.

(4) Phenylephrine
(a) CNS
Headache.
(b) CVS
Hypertension, cardiac irregularities.
(c) Resp. Tract
Rebound nasal congestion (with chronic use).
Precaution
It can be systemically absorbed from topical sites; so, their use in pts. taking β blockers increases the risk of cardiac irregularities, myocardial infarction, & intracranial hemorrhage.

(5) Methoxamine
(a) CNS
Headache.
(b) CVS
Hypertension.
(c) GIT
Vomiting.

(6) Ephedrine
Similar to epinephrine.
Precaution
Used with caution in pts. with CVS disease or hyperthyroidism, because it is a powerful heart stimulant.

(7) Amphetamine
(a) CNS
Toxic psychosis, mental depression, fatigue, restlessness, insomnia.
(b) CVS
Tachycardia, hypertension.
(c) Eye
Mydriasis.
(d) GIT
Vomiting.
(f) Tolerance &, psychic & physical dependence.

(8) Beta-2 Agonists

(a) CNS

Fine tremor, tension, headache.

(b) CVS

Peripheral vasodilatation, tachycardia.

Precaution

Used with caution in pts. with CVS disease or hyperthyroidism, because they can still stimulate (though minimally) β_1 receptors of heart.

CONTRAINDICATIONS OF SYMPATHOMIMETICS

EPINEPHRINE

(1) Coronary disease, as it may induce anginal attacks.
(2) Hyperthyroidism, because of enhanced drug effect due to increased production of adrenergic receptors in hyperthyroid individuals.
(3) Hypertension
(4) Chloroform, cyclopropane, trichloroethylene, & halothane anesthesia.
(5) Pts. receiving digitalis therapy.

AMPHETAMINE

(1) Pts with cardiovascular diseases.
(2) Pts receiving MAO inhibitors or guanethidine.
(3) Insomnia.
(4) Anorexia.
(5) Mentally unstable pts.

DOSAGE OF SYMPATHOMIMETICS

(A) Epinephrine

(1) In Bronchospasm

(a) 0.4 ml of 1:1000 sol., SC.
(b) 320 µg per puff, inhaled as a microaerosol from a pressurized container.

(2) In Anaphylaxis

0.3-0.5 mg (0.3-0.5 ml of 1: 1000 sol.), SC.

(3) As an Adjunct to Local Anesthesia

0.5 ml of 1: 80,000 or 1: 200,000 sol., 1M.

(B) Norepinephrine

(1) Diluted in ➜ 5% Dextrose water.
(2) Concentration (1 amp = 4 mg) ➜ 4 mg /250 ml = 16 µg/ml.
(3) Administered IV at a rate of 2 µg/min (8 ml/hr), & may be increased upto 4 µg/min (15 ml/hr).

(C) Isoproterenol

Isoproterenol HCl is given in 2 dosage forms:
(1) IV ➜ 1 mg in 250 ml 5% dextrose or NS, & titrated; given at a rate of 1-4 µg/min.
(2) Oral ➜ 30 mg sustained-release tabs.

(D) Dopamine

Dopamine HCl 400 mg is diluted in 250 ml of 5% dextrose or NS, & titrated; given IV at a rate of 2 µg/Kg/min. & may be increased upto 5-10 µg/Kg/min.

(E) Phenylephrine

(1) IV ➜ 10 mg in 250 ml of 5% Dextrose or NS & titrated; given at a rate of 0.04 - 0.08 mg/min.
(2) Eye drops ➜ 10% sol. in HCl; 1-2 drops 2-3 hourly for 2 days, then one instillation TDS for 5-6 days.
(3) Nasal drops ➜ 0.25 % / 0.50 % sol; 2-3 drops, 4-6 hourly daily.

GENERIC & TRADE NAMES

(A) Catecholamines

Epinephrine: Xylocaine*, Medicaine*.
Dopamine: Dopamine, Intropin, Tropin.
Dobutamine: Buta, Dobuject, Dobutrex, Dobutamine.

(B) Non-Catecholamines

Phenylephrine: Bronex, Ethifrin, Fenox, Isonefrine, Mediphrine, Oculoforte*, Zincfrin*.....
Ephedrine: Alcof D*, Amcodrin*, Davenol*, Efed.
Pseudoephedrine: Actified P*, Arinac*, Dexodine*, Rondex*…….
Albuterol (Salbutamol): Aerolin, Asthamol, Bronchilate, Butamol, Clenil*, Ventide, Ventolin .....
Terbutaline: Bricanyl, Terbulin, Terbutil…...
Ritodrine: Yutopar.
Xylometazoline: Nasavin, Rhezole, Xoline, Xynosine.
Oxymetazoline: Rinerge.
Methylphenidate: Phenida.
Naphazoline: Curin, Deltarhinol*, Efemoline*, Nafamine*, Naphcon-A*.
Tetrahydrozoline: Famecon*, Murin Plus*, Vasoflam*.
Procaterol: M-butamol, Meptin air.
Salmeterol: Axinat, Serevent.

Unit III

Sympatholytics

[Adrenoceptor-Blocking Drugs, Sympathetic Antagonists, or Adrenoceptor Antagonists]

CLASSIFICATION OF SYMPATHOLYTICS

(A) Alpha - Adrenoceptor Antagonists

(1) Alpha-1 Antagonists

Alfuzosin, Prazosin, Terazosin, Doxazosin, Tamsulosin, Phenoxybenzamine, Indoramin, Uradipil.

(2) Alpha-2 Antagonists

Tolazoline, Yohimbine, Rauwolscine.

(3) Alpha-1 & -2 Antagonists

Phentolamine, Ergot derivatives eg ergotamine, dihydroergotamine.

(B) Beta-Adrenoceptor Antagonists

(1) Beta-1 Antagonists
Metoprolol, Acebutolol, Alprenolol, Atenolol, Betaxolol, Celiprolol, Esmolol, Bisoprolol.

(2) Beta-2 Antagonists
Butoxamine.

(3) Beta-1 & -2 Antagonists
Propranolol, Metipranolol, Carteolol, Penbutolol, Pindolol, Timolol, Nadolol, Carvedilol, Levobunolol, Sotalol, Cloranolol, Medroxalol, Bucindolol.

(C) Mixed (~:&) Adrenoceptor Antagonists
Labetalol ($\beta_1 = \beta_2 \geq \alpha_1 > \alpha_2$).

(D) Centrally Acting Sympatholytics
Methyldopa, Clonidine, Guanfacine, Guanabenz.

(E) Adrenergic Neuron Blockers
Guanethidine, Reserpine, Bretylium, Guanadrel.

(F) Inhibitors of Catecholamine synthesis
Metirosine.

ALPHA-ADRENOCEPTOR ANTAGONISTS

PHENOXYBENZAMINE

Mechanism of Action

(1) It binds covalently to alpha-adrenoceptors ($\alpha_1 > \alpha_2$) ➜ Irreversible blockade of long duration (14 - 48 hrs).
Note: Block can be overcome only by the synthesis of new adrenoceptors.
(2) It inhibits reuptake of released norepinephrine by presynaptic adrenergic terminals.
(3) It also blocks histamine (H_1), acetylcholine, & serotonin receptors.

Pharmacological Effects

(A) CNS
Stimulates CNS, producing;
(1) Nausea
(2) Hyperventilation
(3) Loss of time perception

(B) CVS
(1) Blocks catecholamine-induced vasoconstriction ➜ Decrease in total peripheral resistance & BP. It will reduce BP more when sympathetic tone is high, eg as a result of upright posture (postural hypotension) or, b/c of reduced blood volume.
(2) Increases cardiac output, due to;
(a) Reflex effects
(b) Some blockade of presynaptic α_2 receptors in cardiac sympathetic nerves.

Clinical Uses

(1) For controlling hypertension in pheochromocytoma, esp. in preoperative management &, in cases of inoperable or metastatic tumor.
(2) To relieve vasospasm in Raynaud's phenomenon, & other conditions involving excessive reversible vasospasm in peripheral circulation.
(3) To relieve urinary obstruction;
(a) In pts. with prostatic hypertrophy (by partial reversal of smooth muscle contraction in prostate or in bladder base).
(b) In pts with spinal cord injury (by relieving bladder neck hypertonus).
(4) To control autonomic hyperreflexia due to spinal cord transection.

Adverse Effects

(1) CNS: Fatigue, Sedation.
(2) Eye: Miosis.
(3) CVS: Postural hypotension, reflex tachycardia.
(4) Resp. Tract: Nasal stuffiness.
(5) GIT: Nausea & vomiting (with oral administration).
(6) Reproduction: Inhibition of ejaculation.
(7) Local: Local tissue irritation by injection.

Dosage

(1) 10-20 mg/day, orally; may be increased to 200 mg, gradually.
(2) 1 mg/kg, diluted in 5% dextrose or 0.9% saline, by IV infusion.

PRAZOSIN, TERAZOSIN, & DOXAZOSIN

Mechanism of Action

Selective blocked of postsynaptic α_1-adrenoceptors.

Pharmacological Effects

(A) CVS
(1) Dilatation of both resistance & capacitance vessels ➜ Decreases blood pressure, more in upright than in supine position.
(2) Only minimal changes in cardiac output.
(3) No reflex tachycardia.

(B) Kidneys
(1) Retention of salts & fluid when administered without a diuretic or during long- term therapy.
(2) Only minimal changes in renal blood flow & glomerular filtration rate.

Clinical Uses

(1) Mild to moderate chronic hypertension (more effective when used in combination with a diuretic or propranolol).
(2) Acute congestive heart failure (Prazosin).
(3) To relieve urinary obstruction (Terazosin).

Adverse Effects

(1) CNS: Dizziness, headache, lassitude.
(2) CVS: Postural hypotension , first-dose phenomenon (a precipitous drop in standing BP after the first dose that results in syncope, & occur esp. in pts who are salt- & volume-depleted).
(3) Resp. Tract: Nasal congestion.
(4) GIT: GI hypermotility.
(5) Kidneys: Salt & fluid retention.

Dosage

(1) Prazosin
(a) First dose ➜ 0.5 mg at bed time, orally.
(b) Then 0.5 mg BD or TDS, for 3-7 days.
(c) Followed by 1 mg BD or TDS, for 3-7 days.

(d) Thereafter increases gradually as required, upto max. of 20 mg /day.

(2) Terazosin

(a) Initially 1 mg at bed time, orally.
(b) Titrate by approx. doubling dose at weekly intervals.
.(c) Usual maintenance dose is 2-10 mg OD.

PHENTOLAMINE

Mechanism of Action

(1) Competitive blockade of alpha-adrenoceptors ($\alpha_1 = \alpha_2$).
(2) Inhibits response to serotonin.
(3) Stimulates muscarinic &, H_1 & H_2 histamine receptors.

Pharmacological Effects

(A) CVS

(1) Vasodilatation thru both α-adrenoceptor blockade & an additional nonadrenergic action on vascular smooth muscle ➜ Dec. peripheral resistance, & inc. venous capacitance.
(2) Cardiac stimulation thru,
  (a) Reflex effect
  (b) α_2-adrenoceptor blockade.

(B) Glands

Stimulate lacrimal, salivary, pancreatic, & respiratory tract secretions.

Clinical Uses

(1) Diagnosis of pheochromocytoma & other clinical situations associated with excess release of catecholamines.
(2) Hypertensive emergencies from pheochromocytoma, sympathomimetics overdosage or, clonidine withdrawal.
(3) Raynaud's phenomenon
(4) Frost-bite
(5) To reverse intense local vasoconstriction caused by inadvertent infiltration of α-agonists into subcutaneous tissue during IV administration.
(6) To cause erection in male sexual dysfunction.

Adverse Effects

(1) CVS: Severe tachycardia, arrhythmias, angina, postural hypotension.
(2) GIT: Diarrhea, increased gastric acid production.

Precautions

(1) Pts with coronary artery disease.
(2) Pts with peptic ulcer.

TOLAZOLINE

Similar to phentolamine, but is some what less potent & its receptor affinity is $\alpha_2 > > \alpha_1$.

Clinical Uses

(1) Peripheral vasospastic disease, eg Raynaud's phenomenon.
(2) Pulmonary hypertension in neonates with respiratory distress syndrome.

Adverse Effects

Similar to phentolamine, except that it may cause paradoxical hypertension.

ERGOT DERIVATIVES

Examples

Ergotamine tartrate, Dihydroergotamine, Ergonovine maleate, Methylergonovine maleate, Methysergide, Bromocriptine, Lysergic acid diethylamide (LSD).

Box 2.3 EFFECTS OF ERGOT DERIVATIVES AT SEVERAL RECEPTORS

Ergot Derivatives	α - adreno-ceptors	Dopamine Receptors	Serotonin (5-HT2) Receptors
Ergotamine	- - (PA)	0	+ (PA)
Ergonovine	+	+	- (PA)
Methysergide	+ / 0	+ / 0	- - - (PA)
Bromocriptine	-	+ + +	-
LSD	0	+ + +	- -

[+ = Agonist, - = Antagonist, 0 = No effect, PA = Partial agonist, Relative affinity is indicated by no. of + or - signs]

Mechanism of Action

Each member have varying effects on several receptors (see box 2.3); include,
(1) Agonist, partial agonist, & antagonist actions at α-adrenoceptors.
(2) Agonist, partial agonist, & antagonist actions at serotonin receptors.
(3) Agonist action at CNS dopamine receptors.

Pharmacological Effects

(A) CNS

(1) They stimulate CNS & may cause:
  (a) Confusion
  (b) Irregular respiration
  (c) Anxiety
(2) LSD acts as a powerful hallucinogen.
(3) Bromocriptine directly suppresses prolactin secretion from pituitary cells by activating regulatory dopamine receptors.

(B) CVS

Effects are drug-, species-, & vessel-dependent.
(1) Ergotamine & related compounds constrict most human blood vessels in a predictable, prolonged, & potent manner, & is due to partial agonist effect.
(2) Different vascular beds have different sensitivities, & cerebral vessels esp cerebral arteriovenous anastomotic vessels are most sensitive.
(3) Blood pressure is elevated, due to vasoconstriction.

(C) Uterine Smooth Muscle

Stimulate uterine smooth muscle esp. of pregnant uterus, due to combine alpha & serotonin agonists effect.

Clinical Uses

(1) Ergotamine tartarate ➜ Migraine.
(2) Dihydroergotamine ➜ Intractable migraine.
(3) Ergonovine maleate ➜
  (a) To control late uterine bleeding (post-partum hemorrhage).
  (b) Prophylaxis of migraine.

(c) Diagnosis of variant angina.
(4) Methylergonovine maleate ➜ Post-partum hemorrhage.
(5) Methysergide ➜ Prophylaxis of migraine.
(6) Bromocriptine ➜ Hyperprolactinemia.

Adverse Effects
(1) CNS: Drowsiness.
(2) CVS: Gangrene (due to prolonged vasoconstriction).
(3) GIT: Nausea, vomiting, diarrhea.

BETA-ADRENOCEPTOR ANTAGONISTS

PROPRANOLOL
Mechanism of Action
Blocks both β_1- & β_2- adrenoceptors.
Pharmacological Effects
(A) CVS
(1) Anti-Hypertensive Effect
(a) Initially, due to decreased cardiac output associated with bradycardia.
(b) With continued use, due to decreased peripheral resistance resulting from inhibition of renin secretion.

(2) Anti-Anginal Effect
Decreases heart rate, contractility, & BP ➜ Dec. myocardial O_2 requirements at rest & during exercise.

(3) Anti-Arrhythmic Effect
(a) Decreases SA nodal firing.
(b) Increases AV nodal refractory period.
(c) Increases PR interval.

(4) Effect on Peripheral Blood Vessels & Flow
(a) Blocks β_2-mediated vasodilation ➜ Initially inc. peripheral resistance from unopposed α effects.
(b) Inhibition of renin secretion ➜ Dec. peripheral resistance.
(c) A favorable redistribution of coronary blood flow to ischemic myocardium.

(B) Respiratory Tract
Increases airway resistance, esp. in pts with asthma (β_2-blockade).

(C) Kidneys
(1) Increases Na^+ retention, due to a fall in renal perfusion that results from low BP.
(2) Antagonizes renin release (β_1-blockade).

(D) Metabolism
(1) Inhibit lipolysis (β_1-blockade).
(2) Partially inhibit glycogenolysis in liver (β_2-blockade) ➜ Hypoglycemia.
(3) Chronic use is associated with inc. plasma VLDL, dec. HDL, & a variable decline in HDL/LDL ratio.

Clinical Uses
(1) Hypertension (most often used with either a diuretic or a vasodilator).
(2) Angina pectoris & prophylaxis of myocardial infarction.
(3) Supraventricular & ventricular arrhythmias.
(4) Ventricular ectopic beats, esp if precipitated by catecholamines.
(5) Obstructive cardiomyopathy (to increase stroke volume).
(6) Dissecting aortic aneurysm (to decrease rate of development of systolic pressure).
(7) Hyperthyroidism.
(8) Prophylaxis of migraine.
(9) Anxiety (to reduce somatic manifestations).
(10) Cirrhosis (to reduce portal vein pressure).

Adverse Effects
(1) CNS: Sedation, sleep disturbances, depression.
(2) CVS: Peripheral arterial insufficiency, cardiac failure, bradycardia, cardiac conduction abnormalities.
(3) Resp. Tract: Bronchoconstriction.
(4) GIT: Nausea, vomiting, constipation, diarrhea.
(5) Metabolism: Hypoglycemia.
(6) Allergy: Rash, fever, purpura.
(7) Withdrawal Symptoms: Abrupt discontinuing after chronic use causes up-regulation of number of β-adrenoceptors, which can provoke anginal attacks, arrhythmias, or myocardial infarction.

Precautions
(1) Pts with asthma.
(2) Pts with diabetes mellitus esp IDDM.

Contraindications
(1) Cardiogenic shock
(2) Right ventricular failure secondary to pulmonary hypertension
(3) Congestive cardiac failure
(4) Asthma
(5) Greater than 1st degree heart block
(6) Hypotension
(7) Raynaud's phenomenon
(8) Pts on MAO inhibitors

Dosage
(1) 20-80 mg TDS or QID, orally.
(2) In emergency treatment of dysarrhythmias ➜ 1 mg over 1 min, IV; repeated at 2 min. interval to a maximum of 10 mg.

OTHER BETA ANTAGONISTS
Clinical Uses
Atenolol
(1) Hypertension
(2) Angina pectoris
(3) Cardiac dysarrhythmias

Note: Safe in pts with diabetes, or peripheral vascular disease.

Metoprolol
(1) Hypertension
(2) Angina pectoris
(3) Supraventricular arrhythmias

Note: Safe in pts with diabetes, or peripheral vascular disease.

Esmolol
(1) Supraventricular arrhythmias
(2) Perioperative hypertension
(3) Myocardial infarction

Bisoprolol
(1) Hypertension
(2) Angina pectoris

Pindolol
(1) Hypertension
(2) Angina pectoris

Note: Safe in asthmatics.

Timolol
(1) Glaucoma
(2) Hypertension
(3) Migraine prophylaxis

Nadolol
(1) Hypertension
(2) Angina pectoris
(3) Cardiac tachyarrhythmias
(4) Migraine prophylaxis

Carteolol
(1) Hypertension
(2) Angina pectoris
(3) Cardiac arrhythmias
(4) Glaucoma

MIXED ADRENOCEPTOR ANTAGONIST

LABETALOL

Mechanism of Action
Reversible adrenoceptor blockade:
(1) Non-selective β - blockade, with potency somewhat lower than that of propranolol.
(2) Relatively α_1 - selective blockade, with potency less than that of phentolamine.

Clinical Uses
Hypertension

Note: Safe in pts with peripheral vascular disease.

OTHER SYMPATHOLYTICS

Centrally Acting Sympatholytics
See chapter 11, CVS.

Adrenergic Neuron Blockers
See chapter 11, CVS.

GENERIC & TRADE NAMES

(A) Alpha Blockers
Alfuzosin: Xatral SR
Prazosin: Minipress.
Terazosin: Hytrin.
Doxazosin: Cardura, Prosdura.
Yohimbine: Vigrol Forte.
Ergotamine: Migranil, Migril*, Tagril*.

(B) Beta Blockers
Metoprolol: Betalock Zok, Mepresor, Meprol, Merol.
Atenolol: Atelor, Atenolol, Atenorm, Blokium*, Cardiolite, Normitab, Tenormin.....
Betaxolol: Betaxen, Betoptic, Vistagan.
Esmolol: Brevibloc.
Bisoprolol: Biscot, Concor, Corbis.
Propranolol: Betanol, Beta prograne, Blockonol, Cardinol, Inderal, Oprinol.
Carteolol: Carteol, Mikelan.
Pindolol: Vikaldix*.
Timolol: Betalol, Milosol, Optimol, Timop- tol, Timosol.
Nadolol: Corgard.
Carvedilol: Carveda, Vadil.
Cloranolol: Tobanum.
Methyldopa: Aldomet, Normet.
Bretylium: Bretylol.

Unit IV

Self-Assessment (T/F)

(See answers on page no. 240)

(14) ***Following are beta-2 selective agonists***
(A) *Albuterol.*
(B) *Prenalterol.*
(C) *Terbutaline.*
(D) *Fenoterol.*
(E) *Ritodrine.*

(15) ***Dilatation of vessels in muscle, constriction of cutaneous vessels, & positive inotropic & chronotropic effects on heart are all actions of***
(A) Metaproterenol.
(B) Norepinephrine.
(C) Acetylcholine.
(D) Epinephrine.
(E) Isoproterenol.

(16) ***An indirect sympathomimetic agent sometimes used orally for asthma is***
(A) Epinephrine.
(B) Ephedrine.
(C) Dobutamine.
(D) Isoproterenol.
(E) Phenylephrine.

(17) ***Selective beta-2 stimulants frequently cause***
(A) Skeletal muscle tremor.
(B) Tachycardia in direct proportion to bronchodilation.
(C) Vasodilation in skin.
(D) Increased cGMP in mast cells.
(E) Palpitations.

(18) ***Phenylephrine***
(A) Increases skin temperature.
(B) Causes mydriasis in eye.

(C) Constricts small vessels in nasal mucosa.
(D) Increases gastric secretion & motility.
(E) Causes all of the above.

(19) ***Beta-2 agonists are effective in***
(A) Raynaud's syndrome.
(B) Delayed or insufficiently strong labor.
(C) Ischemic ulcers of skin.
(D) Bronchial asthma.
(E) Coronary insufficiency manifested by angina.

(20) ***Epinephrine is clinically used in***
(A) Bronchial asthma.
(B) Primary treatment of anaphylaxis.
(C) Chronic open-angle glaucoma.
(D) Paroxysmal atrial tachycardia.
(E) Narcolepsy.

(21) ***Which of the following structures are more responsive to beta agonists than to alpha agonists***
(A) Bronchial smooth muscle.
(B) Radial muscle of iris.
(C) Vasculature of skeletal muscle.
(D) Vasculature of skin.
(E) Pregnant uterus.

(22) ***Following drugs are both alpha & beta receptor stimulator***
(A) Ephedrine.
(B) Isoproterenol.
(C) Epinephrine.
(D) Methoxamine.
(E) Dopamine.

(23) ***Following are alpha-2 antagonists***
(A) Prazosin.
(B) Yohimbine.
(C) Tolazoline.
(D) Phentolamine.
(E) Butoxamine.

(24) ***Following are centrally acting sympatholytics***
(A) Methyldopa.
(B) Clonidine.
(C) Guanfacine.
(D) Reserpine.
(E) Guanadrel.

(25) ***Phentolamine & tolazoline***
(A) Are beta-blockers.
(B) Induce vasospasm when administered in large doses.
(C) Causes tachycardia.
(D) Cause hypertension.
(E) Used in Raynaud's phenomenon.

(26) ***Propranolol is useful in***
(A) Hypertension.
(B) Angina pectoris.
(C) Congestive heart failure.
(D) Hypertrophic obstructive cardio-myopathies.
(E) Hyperthyroidism.

(27) ***Phenoxybenzamine is used in the treatment of***
(A) Pheochromocytoma.
(B) Essential hypertension.
(C) Raynaud's phenomenon.
(D) Angina pectoris.
(E) Shock.

(28) ***Adverse effects of propranolol includes***
(A) Tachycardia
(B) AV block.
(C) Depression.
(D) Hypoglycemia.
(E) Hypersensitivity reactions .ion.

03 PARASYMPATHETIC NERVOUS SYSTEM DRUGS

Unit I

Introduction

ANATOMY

EFFERENT (MOTOR) PORTION OF PNS

(1) Preganglionic Neurons

Cell bodies of preganglionic neurons are found in CNS &, their axons constitutes the preganglionic fibres.

(a) Cranial Part

Cell bodies are found in Edinger-Westphal nucleus, superior & inferior salivary nucleus, & dorsal motor nucleus of vagus.

(b) Sacral Part

Cell bodies are found in lateral grey horn of sacral segments 2-4 of spinal cord.

(2) Preganglionic Fibres

Leave the CNS from brainstem (cranial part) & 2-4 sacral segments of spinal cord (sacral part) & travel upto the parasympathetic ganglia near or on the effector organs.

(3) Ganglia

Preganglionic fibres terminates by synapsing with cell bodies of parasympathetic ganglia.

(a) Cranial Parasympathetic Ganglia

(i) Edinger-Westphal fibres 2 Ciliary ganglion.
(ii) Superior salivary fibres 2 Pterygopalatine & submandibular ganglion.
(iii) Inferior salivary fibres 2 Otic ganglion.
(iv) Vagal fibres 2 Postganglionic cell bodies in the visceral wall (heart, lungs, & gut).

(b) Sacral Parasympathetic Ganglia

Postganglionic cell bodies in the wall of pelvic viscera.

(4) Postganglionic Fibres

These are axons of cell bodies in parasympathetic ganglia, extending to effector organs (viscera & gland).

PARASYMPATHETIC NEUROTRANSMITTERS

Both preganglionic & postganglionic parasympathetic fibres release acetylcholine at their nerve terminals.

PARASYMPATHETIC NEUROTRANSMISSION

CHOLINERGIC TRANSMISSION

It involves 6 steps:

(1) Synthesis of Acetylcholine

Choline is transported into cytoplasm of cholinergic neuron by a carrier system that cotransports Na^+ 2 Reacts enzymically with acetyl CoA to form acetylcholine.

(2) Storage of Acetylcholine in Vesicles

Acetylcholine is transported into synaptic vesicles where it is stored in granules

(3) Release of Acetylcholine

Similar to norepinephrine release (see unit I , chapter 2).

(4) Binding to Receptors

Similar to norepinephrine binding (see unit I, chapter 2).

(5) Degradation of Acetylcholine

Released acetylcholine is rapidly degraded into choline & acetate by :

(a) Acetylcholinesterase (found in synaptic cleft & RBCs).
(b) Pseudocholinesterase (found in plasma, liver, glia) contribute to a smaller extent.

(6) Recycling of Choline

Choline may be recaptured by a high affinity transport system into the neuron, where it is acetylated & stored until release by subsequent action potential.

CHOLINOCEPTORS (CHOLINERGIC RECEPTORS)

These are receptors that mediate the actions of parasympathetic nervous system, by interacting with acetylcholine or exogenously administered drugs. Two classes (types) of cholinoceptors are identified, with further sub-types.

(A) Muscarinic Cholinoceptors

(1) Agonist 2 Muscarine
(2) Antagonist 2 Atropine
(3) Sub-types 2 M_1 , M_2, M_3, M_4, & M_5.

(B) Nicotinic Cholinoceptors

(1) Agonist 2 Nicotine (first stimulates, then block).
(2) Antagonist 2 d-Tubocurarine.
(3) Sub-types 2 N_G (ganglionic), & N_M (muscular end-plates).

Box 3.1	CHOLINOCEPTORS ------- Location & Effects		
Receptors	**Location**	**Pharmacological Effects**	**2nd Messenger Effects**
Muscarinic M_1	1) CNS neurons 2) Sympathetic post-ganglionic neurons 3) Some pre-synaptic sites 4) GIT myenteric plexus	Probably multiple Onward impulse transmission Inhibition of transmitter release Activation	Formation of IP_3 & DAC, ↑ Ca^{++} influx
M_2	1) Heart (postsynaptic) a) SA node b) Contractility 2) Some presynaptic sites 3) Smooth muscle	 Deceleration Decreases Inhibition of transmitter release Contraction	Opening of K^+ channels, inhibition of adenyl cyclase
M_3	1) Smooth muscle of eye a) Iris circular muscle b) Ciliary muscle 2) Bronchiolar smooth muscle 3) GIT a) Smooth muscle of walls b) Smooth muscle of sphincters c) Exocrine glands & secretory cells 4) Genitourinary smooth muscle a) Bladder wall b) Sphincters c) Pregnant uterus d) Penis, seminal vesicles 5) Vascular smooth muscle a) Skeletal muscle vessels b) Endothelium (uninnervated) 6) Thermoregulatory sweat glands	 Contraction Contraction Contraction Contraction Relaxation Increases secretions Contraction Relaxation Contraction Erection Relaxation Releases EDRF ≡ Vasodilation Increases secretions	Formation of IP_3 & DAG, ↑ Ca^{++} influx
M_4	CNS neurons, possibly vagal nerve endings	Probably multiple	Inhibition of adenyl cyclase
M_5	1) Vascular endothelium, esp. cerebral vessels 2) CNS neurons	Releases EDRF ≡ Vasodilation Probably multiple	Formation of IP_3 & DAC, ↑ Ca^{++} influx
Nicotinic N_G	1) Autonomic ganglion a) Sympathetic ganglion b) Parasympathetic ganglion 2) Some presynaptic cholinergic terminals	 Predominantly CVS effects (vaso-constriction, tachycardia & ↑ BP) Predominantly GIT effects (inc. tone & motility)	Opening of Na^+, K^+ channels, & depolarization
N_M	Skeletal muscle neuromuscular endplates	Skeletal muscle contraction	Opening of Na^+, K^+ channels, & depolarization

Unit II

Parasympathomimetics

[Cholinoceptor-Activating Drugs, Parasympathetic Agonists, or Cholinoceptor Agonists]

CLASSIFICATION OF PARASYMPATHOMIMETICS

DIRECT ACTING

(1) Muscarinic Agonists

(a) Choline Esters

Bethanechol, Cevimeline.

(b) Alkaloids

Muscarine, Pilocarpine.

(2) Nicotinic Agonists

(a) Choline Esters

Varenicline.

(b) Alkaloids

Nicotine, Lobeline.

(3) Mixed Agonists

Choline Esters

Acetylcholine, Methacholine, Carbachol.

INDIRECT ACTING (ANTI-CHOLINESTERASE)

(1) Reversible

(a) Quaternary Alcohols

Edrophonium.

(b) Carbamate Esters

Neostigmine, Physostigmine, Pyridostigmine, Rivastigmine, Ambenonium, Demecarium, Galantamine, Tacrine, Donepezil.

(2) Irreversible

Organophosfate compounds

Echothiofate, lsoflurofate, Paraoxon, Parathion (converted to active form paraoxon), Malaoxon Malathion, Soman.

DRUGS POTENTIATING ACETYLCHOLINE

Metoclopramide (see chapter 14, unit II).

MECHANISM OF ACTION OF PARASYMPATHO-MIMETICS

DIRECT ACTING PARASYMPATHOMIMETICS

(1) Muscarinic Cholinoceptors

It involves G proteins coupled mechanisms similar to that of adrenoceptors (see unit II, chapter 2), that result in various 2nd messenger effects (see box 3.1) which causes final cellular effects.

(a) Activation of IP_3, DAG cascade 2 DAG open smooth muscle Ca^{++} channels, & IP_3 evokes Ca^{++} release from endoplasmic & sarcoplasmic reticulum.
(b) Increase in intracellular cGMP.
(c) Increase in K^+ flux across cell memb.
(d) Inhibition of adenyl cyclase.

(2) Nicotinic Cholinoceptors

(a) Depolarization

Nicotinic agonists acts on nicotinic cholinoceptors 2 Conformational change in protein (channel opening) 2 Na^+ & K^+ ions diffuse rapidly down their conc. gradients 2 Depolarization of nerve cell or neuromuscular endplate 2 Nerve cell excitation or muscle contraction.

(b) Depolarizing Blockade

Prolonged agonist occupancy of nicotinic cholinoceptors prevents electrical recovery of postjunctional memb. 2 Postganglionic neurons stops firing & skeletal muscle cells relaxes 2 Depolarizing Blockade.

INDIRECT ACTING PARASYMPATHOMIMETICS

Acts by inhibiting acetylcholinesterase (& also pseudocholinesterase), & there by increasing conc. of endogenous acetylcholine in the vicinity of cholinoceptors. However, their interaction with enzymes varies, according to the chemical subgroups.

(1) Quaternary Alcohols, eg Edrophonium

Bind reversibly to enzyme's active site 2 Prevent access of acetylcholine to enzyme's active site. It is short lived (2-10 minutes).

(2) Carbamate Esters, eg Neostigmine

Bind to enzyme's active site 2 Form covalent carbamoylated enzyme. It is more resistant (lasting 30 min. to 6 hours).

(3) Organophosfates, eg Echothiofate

Bind to enzyme's active site 2 Result in covalent phosphorylated active site (extremely stable) 2 Further strengthening of phosphorus-enzyme bond by aging process, in which one of the oxygen- phosphorus bonds of inhibitor is broken.

PHARMACOLOGICAL EFFECTS OF PARASYM-PATHOMIMETICS

DIRECT ACTING PARASYMPATHOMIMETICS

(A) Eye

(1) Contraction of smooth muscle of iris sphincter 2 Miosis (pupillary constriction).
(2) Contraction of ciliary muscle 2 Accommodation of lens for near vision.
(3) Both effects facilitate outflow of aqueous humor into canal of Schlemm 2 Dec. intraocular pressure.

(B) Cardiovascular System

(1) Blood vessels & BP

Vasodilation via release of endothelium-derived relaxing factor (EDRF) 2 Reduction in peripheral vascular resistance 2 Dec. BP, often accompanied by a reflex (sympathetic) tachycardia.

(2) Heart

(a) Dec. pacemaker rate (negative chronotropism).
(b) Dec. atrial contractility (negative inotropism).
Note: Ventricular contractility dec. to a small extent.
(c) Dec. atrial refractory period, & inc. AV nodal refractory period.
(d) Dec. conduction velocity in AV node (negative dromotropism).

Cardiac Effects Results From

(a) Inc. K^+ flux in atrial, pacemaker, & AV nodal cells.
(b) Dec. slow inward Ca^{++} current in heart cells.
(c) Dec. hyperpolarization-activated current that underlies diastolic depolarization.

Reflex Modification

Direct slowing of pacemakers rate & AV conduction is often opposed by reflex sympathetic discharge, elicited by dec BP. Therefore, net cardiac effects depends on local conc. of agonist in heart & in vessels & on the level of reflex responsiveness.

(C) Respiratory Tract

(1) Contraction of bronchial smooth muscle.
(2) Stimulation of glands of tracheobronchial mucosa.

(D) Gastrointestinal Tract
(1) Inc. secretions of salivary, gastric, pancreatic & small intestinal glands.
(2) Inc. peristalsis thru-out the gut (due to depolarization of smooth muscle cell memb. & inc. Ca^{++} influx).
(3) Relaxation of sphincters.

(E) Genitourinary Tract
(1) Contraction of detrusor muscle.
(2) Relaxation of trigone & sphincter muscles.
(3) Both effects promote voiding of urine.

(F) Miscellaneous Secretory glands
Inc. secretions of sweat, lacrimal & nasopharyngeal glands.

(G) Central Nervous System
There is usually stimulation followed by depression, but variation b/w drugs is great, eg:
(1) Nicotine causes;
  (a) Mild alerting action.
  (b) Tremor, emesis & respiratory centre stimulation (at higher doses).
  (c) Convulsion & coma (at more higher doses).
(2) DMPP is relatively free of CNS effects b/c it doesn't cross the blood-brain barrier.

(H) Peripheral Nervous System
Nicotinic agonist causes marked activation of autonomic ganglia 2 Simultaneous discharge of both sympathetic & parasympathetic nervous system :
(1) In CVS, effects are sympathomimetic;
  (a) Hypertension
  (b) Sympathetic tachycardia, alternating with vagally mediated bradycardia.
(2) In GIT & urinary tract, effect are parasympathomimetic;
  (a) Nausea
  (b) Vomiting
  (c) Diarrhea
  (d) Voiding of urine

(I) Neuromuscular Junction
Nicotinic cholinoceptor stimulation causes :
(1) Immediate depolarization of endplate (due to inc. Na^+ & K^+ flux) 2 Disorganized fasciculation to strong muscular contraction, depending on synchronization of endplate depolarization.
(2) Continued presence of nicotinic agonists results in depolarization blockade 2 Flaccid paralysis.

INDIRECT ACTING PARASYMPATHOMIMETICS

(A) Eye
Similar to direct acting.

(B) Cardiovascular System
(1) Blood vessels & BP
Effects are less marked than direct-acting agonists &, it also depends on the balance of sympathetic & parasympathetic nervous system.
  (a) Activation of sympathetic ganglia tend to inc. vascular resistance & BP.
  (b) Activation of parasympathetic ganglia tend to dec. vascular resistance & BP.

(2) Heart
Parasympathetic effect predominate ;
  (a) Dec. heart rate.
  (b) Dec. AV conduction velocity.
  (c) Dec. atrial contractility.
  (d) Dec. cardiac output.

(3) Net CVS Effects
  (a) Moderate doses 2 Modest bradycardia, dec. cardiac output, & no change or modest fall in BP.
  (b) Large (toxic) doses 2 More marked brady-cardia & hypotension.

(C) Resp. , Gastrointestinal, & Urinary Tracts
Similar to direct-acting.

(D) Central Nervous System
(1) Low conc. causes;
  (a) Diffuse activation of EEG.
  (b) Subjective alerting response.
(2) Higher conc. causes;
  (a) Generalized convulsions.
  (b) Coma.
  (c) Respiratory arrest.

(E) Peripheral Nervous System
Similar to direct-acting.

(F) Neuromuscular Junction
(1) At Low (Therapeutic) Conc.
Inc. strength of muscle contraction, esp. in muscle weakened by curare-like neuromuscular blockers or by myasthenia gravis.

(2) At Higher Conc.
  (a) Fibrillation of muscle fibres.
  (b) Depolarizing blockade

Note: Neostigmine have an additional direct nicotinic agonist effect at neuromuscular junction.

CLINICAL USES OF PARASYMPATHOMIMETICS

DIRECT - ACTING PARASYMPATHOMIMETICS

(A) Acetylcholine
No clinical use.

(B) Methacholine & Carbachol
(1) Chronic glaucoma
(2) Accommodative esotropia
(3) As a miotic agent (carbachol).

(C) Bethanechol
(1) Postoperative ileus
(2) Congenital megacolon
(3) Reflux esophagitis (to inc. tone of lower esophageal sphincter).
(4) Urinary retention.

(D) Pilocarpine
(1) Chronic glaucoma.
(2) Acute angle-closure glaucoma (in combination with physostigmine).

(E) Cevimeline

Dry mouth associated with Sjögren's syndrome.

(F) Varenicline

Smoking cessation.

INDIRECT - ACTING PARASYMPATHOMIMETICS

(A) Edrophonium

(1) Diagnosis of myasthenia gravis.
(2) Assessment of treatment adequacy in myasthenia gravis.
(3) Antagonism of non-depolarizing neuromuscular blockers.

(B) Neostigmine

(1) Myasthenia gravis.
(2) Antagonism of non-depolarizing neuromuscular blockers.
(3) Postoperative ileus.
(4) Congenital megacolon.
(5) Reflux esophagitis.
(6) Urinary retention.

(C) Physostigmine

(1) Chronic glaucoma.
(2) Acute angle-closure glaucoma (in combination with pilocarpine).
(3) Intoxication of atropine, tricyclic antidepressants, & phenothiazine.

(D) Pyridostigmine

(1) Myasthenia gravis.
(2) Paralytic ileus.

(E) Ambenonium

Myasthenia gravis.

(F) Demecarium, Isoflurofate & Echothiofate

Chronic glaucoma.

(G) Galantamine, Rivastigmine, Donepezil & Tacrine

mild to moderate Vascular Dementia and Alzheimer's.

ADVERSE EFFECTS OF PARASYMPATHO-MIMETICS

DIRECT - ACTING MUSCARINIC AGONISTS

(1) CVS : Cutaneous vasodilation.
(2) Resp. Tract : Bronchial constriction.
(3) GIT : Nausea, vomiting, diarrhea, salivation.
(4) Skin : Sweating.

Mushroom Poisoning

(1) Caused by : Ingestion of mushrooms of genus Inocybe, that contain muscarinic alkaloids.
(2) Results in : Typical adverse effects (see above).

Treatment

Atropine 1-2 mg, parenterally.

DIRECT - ACTING NICOTINIC AGONISTS

(1) Acute Nicotinic Toxicity

(a) CNS : Convulsions, coma, respiratory arrest.
(b) CVS : Hypertension, cardiac arrhythmias.
(c) Skeletal muscle endplate: Depolarization blockade, respiratory paralysis.

Treatment

(a) Atropine.
(b) Anticonvulsants eg diazepam.
(c) Mechanical respiration.

(2) Chronic Nicotinic Toxicity

Caused by chronic tobacco smoking.
(a) CVS : Inc. risk of vascular disease & sudden coronary death.
(b) GIT : High incidence of peptic ulcer recurrence.

INDIRECT - ACTING PARASYMPATHOMIMETICS

(1) Acute Toxicity

Usually caused by pesticides used in agriculture & in home:
(a) CNS : Anxiety, headache, convulsions, respiratory arrest.
(b) Eye : Miosis.
(c) CVS : Bradycardia.
(d) Resp Tract: Broncho-constriction, inc. bronchial secretion.
(e) GIT : Salivation, vomiting, diarrhea.
(f) Skeletal system: Weakness, twitching, depolarization blockade.
(g) Skin : Sweating.

Treatment

(a) Maintenance of vital signs esp. respiration.
(b) Decontamination to prevent further absorption.
(c) Atropine parenterally in large doses.
(d) Pralidoxime

(2) Chronic Toxicity

Neuropathy associated with demyelination of axons.

CONTRAINDICATIONS OF PARASYMPATHO-MIMETICS

DIRECT-ACTING PARASYMPATHOMIMETICS

(1) Coronary insufficiency
(2) Hyperthyroidism
(3) Asthma
(4) Peptic ulcer

DOSAGE OF PARASYMPATHOMIMETIC

DIRECT-ACTING PARASYMPATHOMIMETICS

(A) Methacholine

(1) 10 - 25 mg, SC.
(2) 200 - 500 mg, orally.

(B) Carbachol

(1) 0.25 - 0.5 mg, SC.
(2) 0.5 - 1 mg, orally.

(C) Bethanechol

(1) 5 mg SC; repeated in 30 minutes, if necessary.
(2) 10 - 25 mg orally, TDS or QID.

(D) Pilocarpine
1, 2, or 4% eye drops ; 2 drops TDS.

INDIRECT-ACTING PARASYMPATHOMIMETICS

(A) Neostigmine
(1) Oral 2 15 - 30 mg TDS; in myasthenia gravis 75 - 300 mg in divided doses 2-4 hourly.
(2) Parenteral (SC or IM) 2 0.5 - 2.5 mg as required.

(B) Physostigmine
0.5 - 1% eye drops or ointment.

(C) Pyridostigmine
300 - 1200 mg orally, in 3-4 divided doses.

GENERIC & TRADE NAMES

(A) Direct-Acting
Pilocarpine: Medicarpine, Orbacarpine, Pilocar.

(B) Indirect-Acting
Neostigmine: Neostigmine, Prostigmin, Stigma.
Tacrine: Congnex.

Unit III

Parasympatholytics

[Cholinoceptor- Blocking Drugs, Parasympathetic Antagonists, or Cholinoceptor Antagonists]

CLASSIFICATION OF PARASYMPATHOLYTICS

ANTI-MUSCARINIC DRUGS

(1) Natural Alkaloids
Atropine, Scopolamine (Hyoscine), Hyoscyamine.

(2) Synthetic
(a) Mydriatic
Homatropine, Tropicamide, Cyclopentolate.

(b) Anti-Parkinsonism
Tertiary Amines
Benztropine.

(c) Anti-Asthmatics
Quaternary Amines
Ipratropium, Tiotropium.

(d) Gastrointestinal & Genitourinary
(i) Tertiary Amines
Pirenzepine, Dicyclomine, Darifenacin, Oxyphencyclimine, Oxybutynin, Propiverine, Solifenacin, Tolterodine.

(ii) Quaternary Amines
Propantheline, Glycopyrrolate, Isopropamide, Mepenzolate, Clidinium, Anisotropine, Tridihexethyl, Trospium, Methantheline, Methscopolamine, Oxyphenonium,

(iii) Others
Flavoxate.

ANTI- NICOTINIC DRUGS

(1) Ganglion Blockers
(a) Depolarizers
Nicotine.

(b) Competitive
(i) Secondary Amines
Mecamylamine.

(ii) Tertiary Amines
Pempidine.

(iii) Quaternary Amines
Hexamethonium, Trimethaphan.

(2) Neuromuscular Blockers
(a) Depolarizers
Suxamethonium (Succinylcholine), Decamethonium.

(b) Competitive
Tubocurarine, Atracurium, Cisatracurium, Doxacurium, Mivacurium, Metocurine, Pancuronium, Rocuronium, Vecuronium, Gallamine.

CHOLINESTERASE REGENERATORS
Pralidoxime, Diacetylmonoxime.

ANTI - MUSCARINIC DRUGS

MECHANISM OF ACTION
Anti-muscarinic drugs causes reversible blockade of the actions of parasympathomimetics at muscarinic cholinoceptors, via competition for a common binding site.

Selectivity
Atropine does not distinguish b/w different muscarinic cholinoceptors; whereas, other antimuscarinic drugs may have moderate selectivity (See Box 3.2).

Box 3.2 SELECTIVITY OF ANTI-MUSCARINIC DRUGS

Muscarinic Cholinoceptors	Primary Location	Antagonists
M_1	Nerves	Pirenzepine, Telenzepine, Dicyclomine, Trihexyphenidyl
M_2	Heart, nerves, smooth muscles	Gallamine, Methoctramine
M_3	Glands, smooth muscles, endothelium	Darifenacin, Solifenacin, Oxybutynin, Tolterodine

PHARMACOLOGICAL EFFECTS

(A) Central Nervous System
(1) At Therapeutic Doses
(a) Stimulation of vagal nucleus that causes bradycardia, which is later supplanted by

tachycardia due to antimuscarinic effects at SA node.
(b) Slower, longer-lasting sedation.
(c) Drowsiness & amnesia (with scopolamine).
(d) Dec. tremors of Parkinsonism.
(e) Prevent vestibular disturbances esp. motion sickness.

(2) At Toxic Doses

(a) Excitement.
(b) Agitation.
(c) Hallucination.
(d) Coma.

(B) Eye

(1) Paralysis of pupillary constrictor muscle 2 Unopposed sympathetic dilator activity 2 Mydriasis (dilatation of pupil).
(2) Paralysis of ciliary muscle, or cycloplegia 2 Loss of accommodation for near vision.
(3) Above 2 effects may precipitate acute glaucoma in pts with narrow anterior chamber angle.
(4) Dec. lacrimal secretion (dry & sandy eyes).

(C) Cardiovascular System

(1) Heart

(a) Initial bradycardia due to central parasympathetic (vagal) stimulation.
(b) Later, tachycardia due to anti-muscarinic effect at SA node.
(c) Dec. PR interval due to anti-muscarinic effect at AV node.
(d) Blockade of muscarinic effects on atrial muscle (of value only in atrial flutter & fibrillation).

(2) Blood Vessels

(a) Blockade of skeletal muscle vasodilation caused by sympathetic cholinergic nerves.
(b) Blockade of vascular uninnervated muscarinic cholinoceptors 2 Dec. EDRF release.
(c) Cutaneous vasodilation esp. in blush area.

(D) Respiratory Tract

(1) Bronchodilation.
(2) Dec. bronchial secretions.

(E) Gastrointestinal Tract

(1) Secretions

(a) Dec. salivary secretions 2 Dry mouth.
(b) Dec. gastric secretions esp. basal.
(c) Pancreatic & intestinal secretions are less effected, b/c they are primarily under hormonal control.

(2) Wall & Motility

Relaxation of GIT wall 2 Dec. tone & propulsive movements 2 Prolonged gastric emptying & intestinal transit times.

(F) Genitourinary Tract

(1) Relaxation of smooth muscle of ureters & bladder wall.
(2) Precipitate urinary retention in elderly men, esp. with prostatic hypertrophy.
(3) No significant effect on uterus.

(G) Sweat Glands

(1) Suppression of thermoregulatory sweating.
(2) Inc. body temperature (atropine fever in children).

CLINICAL USES

(A) Atropine

(1) As cycloplegic, for accurate measurement of refractive error.
(2) As mydriatic, to facilitate ophthalmoscopic examination of retina.
(3) As preoperative medication, to dec. upper & lower resp. tract secretions.
(4) In myocardial infarction, to treat SA node bradycardia or a high-grade A-V block.
(5) In hyperactive carotid sinus reflexes, to treat faintness or syncope
(6) As anti-diarrheal (combined with an opioid).
(7) As anti-spasmodic to treat ureteric & biliary colic (combined with an opioid).
(8) In minor inflammatory bladder disorders, to treat urinary urgency.
(9) In anti-cholinesterase poisoning, to reverse muscarinic effects.
(10) In rapid-onset type mushroom poisoning, to reverse muscarinic effects.

(B) Scopolamine

Similar to atropine; in addition, it is used in :
(1) Prophylaxis of motion sickness
(2) Anesthetic procedures esp. during childbirth, to produce amnesia.

(C) Other Anti-Muscarinics

(1) Homatropine

(a) As cycloplegic
(b) As mydriatic
(c) In uveitis & iritis, to prevent synechia (adhesion) formation.

(2) Tropicamide, & Cyclopentolate: As mydriatic & cycloplegic.
(3) Benztropine, & Trihexyphenidyl: Parkinsonism.
(4) Ipratropium, & Tiotropium: Asthma
(5) Pirenzepine: Peptic ulcer.
(6) Flavoxate, Oxybutynin, Tolterotine, & Darifenacin: To reduce urgency, spasm, & incontinence.
(7) Other tertiary & quaternary amines: Gastrointestinal & genitourinary conditions (see Atropine above).

ADVERSE EFFECTS

(A) Atropine

(1) CNS: Restlessness, confusion, hallucinations, delirium.
(2) Eye: Mydriasis, blurred vision.
(3) CVS: Tachycardia.
(4) GIT: Dry mouth.
(5) Skin: Hot & flushed skin.
(6) Body Temp: Elevated esp. in children.

Treatment

(1) Antidote 2 Physostigmine, 1-4 mg, slowly IV.
(2) Temp control with cooling blankets.
(3) Seizure control with diazepam.

(B) Scopolamine

Similar to atropine.

(C) Quaternary Amines

Similar to atropine, except ;

(1) CNS: Little or no effect.

(2) CVS: Orthostatic hypotension (due to ganglion blockade).

CONTRAINDICATIONS

(1) Pts with glaucoma, esp. angle-closure glaucoma.
(2) Pts with prostatic hypertrophy.

DOSAGE

(A) Atropine Sulfate

(1) Anti-cholinesterase & mushroom poisoning 2 1-2 mg, IV, every 5-15 minutes; upto a maximum of 1 gm/day for as long as one month.
(2) Other systemic use 2 0.4 mg, TDS or QID, orally or parenterally.
(3) Eye 2 1% eye drops; 1 drop TDS, or 1-2 drops before examination.

(B) Scopolamine

0.5-1 mg, TDS, orally or parenterally.

(C) Others

(1) Dicyclomine 2 10-20 mg, QID.
(2) Isopropamide 2 5 mg, BD.
(3) Propantheline 2 15 mg, QID.
(4) Homatropine 2 2% eye drops; 1 or more drops as required.

ANTI-NICOTINIC DRUGS

NICOTINE

See unit II, in association with parasympathomimetics.

COMPETITIVE GANGLION BLOCKERS

Examples

Mecamylamine, Pempidine, Hexamethonium, Trimethaphan.

Mechanism of Action

Non-depolarizing competitive blockade of ganglia.

(A) Hexamethonium

Produces blockade by occupying sites in or on the ion channels that is controlled by nicotinic cholinoceptors, not by occupying the cholinoceptor itself.

(B) Trimethaphan

Block nicotinic cholinoceptors, not the channels.

Pharmacological Effects

(A) Central Nervous System

(1) Hexamethonium & Trimethaphan

No effect.

(2) Mecamylamine

(a) Sedation.
(b) Tremor.
(c) Choreiform movements.
(d) Mental aberrations.

(B) Eye

(1) Cycloplegia with loss of accommodation.
(2) Modest mydriasis.

(C) Cardiovascular System

(1) Dec. arteriolar tone 2 Dec. peripheral vascular resistance.
(2) Dec. venomotor tone 2 Dec. venous return.
(3) Dec. BP due to above 2 effects, esp. marked in upright position (orthostatic or postural hypotension) b/c postural reflex that normally prevent venous pooling are blocked.

(D) Gastrointestinal Tract

(1) Dec. secretions.
(2) Markedly dec. motility.

(E) Genitourinary Tract

(1) Hesitancy in urination 2 Precipitate urinary retention in men with prostatic hypertrophy.
(2) Impaired erection & ejaculation.

Clinical Uses

(A) Trimethaphan

(1) Hypertensive emergencies.
(2) For controlled hypotension during surgery, to reduce bleeding in operative field.
(3) In acute pulmonary edema, to reduce pulmonary vascular pressure.
(4) Autonomic hyperreflexia.

(B) Mecamylamine

Hypertension.

Adverse Effects

Limited to the autonomic effects (described above).

NEUROMUSCULAR BLOCKERS

See chapter 7, Skeletal Muscle Relaxants.

CHOLINESTERASE REGENERATORS

Mechanism of Action

(1) Hydrolyze phosphorylated enzyme from organophosphorus-cholinesterase complex, if the complex has not aged.
(2) Most effective in regenerating cholinesterase associated with skeletal muscle neuromuscular junction.
(3) Pralidoxime does not enter CNS; however, diacetylmonoxime does enter CNS & can regenerate some of the CNS cholinesterase.

Clinical Uses

For the treatment organophosfate poisoning.

Dosage

Pralidoxime 1 gm IV, repeated every 3-4 hours as needed or preferably as a constant infusion 250-400 mg/hour.

GENERIC & TRADE NAMES

(A) Antimuscarinic Drugs

Atropine: Atrosol, Ethiatropine, Isopto atropine, Opta-atropine, Orbatropin, Lomotil*, Motilex*.
Scopolamine: Anapaz, Hyoscine, Buscopan*, Geospasmocin*, Hyscopan*, Spasler*, Spasmogin.....
Homatropine: Homatropine.
Tropicamide: Mydolate, Mydriacyl, Mydriaticum.
Cyclopentolate: Cyclopen.
Ipratropium: Ipratee, Optra.
Pirenzepine: Gastrozepin.
Dicyclomine: Blisscolic, Colenticon, Infacol*.
Oxybutynin: Butyn, Cystrin, Oxitrin.
Tolterodine: Detrusitol.
Glycopyrrolate: Pyrolate.
Isopropamide: Stelabid*.

(B) Anti- Nicotinic Drugs

Neuromuscular Blockers: See chapter 7.

Unit IV

Self-Assessment (T/F)

(See answers on page no. 240)

(29) ***Nicotinic receptor sites includes***
(A) Parasympathetic ganglia.
(B) Sympathetic ganglia.
(C) Skeletal muscle.
(D) Excitatory receptors on Renshaw cells in spinal cord.
(E) Bronchial smooth muscle.

(30) ***Following are both muscarinic & nicotinic receptor stimulants***
(A) Acetylcholine.
(B) Lobeline.
(C) Methacholine.
(D) Carbachol.
(E) Bethanechol.

(31) ***In the treatment of myasthenia gravis, best agent for distinguishing b/w myasthenic crisis (insufficient therapy) & cholinergic crisis (excessive therapy) is***
(A) Atropine.
(B) Physostigmine.
(C) Echothiofate.
(D) Pralidoxime.
(E) Edrophonium.

(32) ***Regarding clinical uses of parasympatho- mimetics, following are correct***
(A) Methacholine & carbachol are used in glaucoma
(B) Edrophonium is used in the treatment of myasthenia gravis
(C) Neostigmine is used in paralytic ileus
(D) Pyridostigmine is used in early stages of Alzheimer's disease
(E) Acetylcholine is used as mydriatic in cataract surgery

(33) ***Typical symptoms of cholinesterase inhibitor toxicity include***
(A) Anorexia, vomiting, diarrhea
(B) Salivation, sweating
(C) Miosis
(D) Paralysis of skeletal muscles
(E) Paralysis of accommodation

(34) ***Pilocarpine***
(A) Is used to dec. intraocular pressure in glaucoma
(B) Selectively binds to nicotinic receptors
(C) Is not cleaved by acetylcholinesterase
(D) Causes profuse sweating
(E) Is an alkaloid

(35) ***Ganglion blocking anti-nicotinic drugs include***
(A) Hexamethonium
(B) Tropicamide
(C) Propantheline
(D) Mecamylamine
(E) Trimethaphan

(36) ***Competitive neuromuscular blockers include***
(A) Pempidine
(B) Suxamethonium
(C) Tubocurarine
(D) Gallamine
(E) Atracurium

(37) ***Atropine overdosage may cause***
(A) Disorientation
(B) Relaxation of gastrointestinal smooth muscle
(C) Decrease in gastric secretion
(D) Pupillary constriction
(E) Tachycardia

(38) ***Which one of the following drugs most closely resembles atropine in its pharmacological actions***
(A) Scopolamine
(B) Trimethaphan
(C) Physostigmine
(D) Acetylcholine
(E) Carbachol

(39) ***Atropine is clinically used in***
(A) Anti-cholinesterase poisoning
(B) Prophylaxis of motion sickness
(C) Glaucoma
(D) High-grade AV block
(E) Asthma

04 OPHTHALMOLOGICAL DRUGS

Unit I

Ophthalmological Drugs

MIOTICS

It refers to drugs that produce constriction of pupil.

DRUG CLASSIFICATION

(A) Parasympathomimetics

(1) Direct Acting

Acetylcholine, Bethanechol, Carbachol, Pilocarpine.

(2) Anti- Cholinesterases

(a) Reversible

Neostigmine, Physostigmine, Demecarium.

(b) Irreversible

Diisopropyl fluorophosfate, Echothiofate.

(B) Sympatholytics

(1) Alpha - Adrenoceptor Blockers

Tolazoline, Phentolamine.

(2) Adrenergic Neuron Blockers

Guanethidine, Reserpine.

(C) Centrally Acting Drugs

Morphine, Codeine.

CLINICAL USES

(1) Glaucoma.
(2) To counteract effect of mydriatic cycloplegic drugs, eg homatropine.
(3) In alternation with mydriatics to break adhesions between iris &lens.

MYDRIATICS

It refers to drugs that produce dilatation of pupil by;
(1) Stimulation of dilator pupillae muscle (active mydriasis).
(2) Paralysis of sphincter pupillae muscle (passive mydriasis).

DRUG CLASSIFICATION

(A) Sympathomimetics

Alpha-adrenoceptor agonists, eg;
Epinephrine, Norepinephrine, Ephedrine, Phenylephrine.

(B) Parasympatholytics

Atropine, Scopolamine (Hyoscine), Homatropine, Tropicamide, Cyclopentolate.

(C) Centrally Acting Drugs

Cocaine, Pethidine, Chloroform, Thiopentone.

ANTI-GLAUCOMA DRUGS

GLAUCOMA

It refers to a disease characterized by increased intraocular pressure.

Types

(1) Primary

(a) Angle closure glaucoma.
(b) Open angle glaucoma.

(2) Secondary

eg, glaucoma caused by surgical procedures.

CLASSIFICATION OF ANTI - GLAUCOMA DRUGS

(A) Drugs used in Angle Closure Glaucoma

Pilocarpine, Physostigmine, Acetazolamide, Mannitol.

(B) Drugs used in Open Angle, & Secondary glaucoma

(1) Parasympathomimetics

Pilocarpine, Carbachol, Demecarium, Physostigmine, Echothiofate.

(2) Sympathomimetics

(a) Unselective

Epinephrine, Dipivefrin.

(b) Alpha-2 selective

Apraclonidine, Brimonidine.

(3) Beta - Adrenoceptor Blockers

Timolol, Betaxolol, Carteolol, Levobunolol, Metipranolol.

(4) Diuretics

Dorzolamide, Brinzolamide, Acetazolamide, Dichlorphenamide, Methazolamide.

(5) Prostaglandins

Latanoprost, Bimatoprost, Travoprost, Unoprostone.

DRUGS THAT PRECIPITATE GLAUCOMA

(1) Atropine.
(2) Amyl nitrate.
(3) Histamine.

Note: These drugs are "contraindicated" in glaucoma.

ANTI - INFECTIVES

DRUG CLASSIFICATION

(A) Antibiotics

(1) Quinolones (topically) 2 Ciprofloxacin, Gatifloxacin, Levofloxacin, Moxifloxacin, Ofloxacin.
(2) Tetracyclines 0=Gentamicin, Tobramycin.
(3) Chloramphenicol
(4) Erythromycin
(5) Sulfonamides
  (a) Systemically 0 Sulfadiazine, Sulfamethoxypyridazine.
  (b) Topically 0 Sulfacetamide.
(6) Bacitracin zinc
(7) Polymyxin B

(B) Antivirals

(1) Topical 0 Trifluridine, Vidarabine.
(2) Oral 0 Acyclovir, Valacyclovir, Famciclovir.
(3) Intravenous 0 Acyclovir, Foscarnet, Ganciclovir.
(4) Intravitreal 0 Cidofovir, Foscarnet, Ganciclovir.

(C) Antifungals

Amphotericin B, Miconazole.

(D) Others

(1) Boric acid.
(2) Zinc sulfate.
(3) Silver nitrate.
(4) Mercuric oxycyanide.

DRUGS TOXIC TO EYE

DRUG CLASSIFICATION

(A) Conjunctival Irritants

(1) Ethylmorphine.
(2) Chloroacetophenone (Tear gas).

(B) Special Drugs

(1) Methyl Alcohol
Has toxic effects on optic nerve, & retina.

(2) Cardiac Glycosides
Causes visual disturbances.

(3) Oxygen in High Conc.
Causes retrolental fibroplasia.

(4) Chloroquine
Causes retinopathy.

(5) Corticosteroids
Causes cataract.

Unit II

Self-Assessment (T/F)

(See answer on page no. 240)

(40) ***Which one of the following drugs does not produce miosis***
(A) Carbachol.
(B) Isoflurofate.
(C) Atropine.
(D) Pilocarpine.
(E) Neostigmine.

(41) ***Which of the following dilates pupil & dec. intraocular pressure***
(A) Atropine.
(B) Timolol.
(C) Pilocarpine.
(D) Phenylephrine.
(E) Tolazoline.

(42) ***In human eye, Echothiofate can cause***
(A) Miosis.
(B) Ciliary spasm.
(C) Reversal of cycloplegic action of atropine.
(D) Dec. incidence of cataract.
(E) Dec. intraocular pressure.

(43) ***All of the following may cause cycloplegia, when used topically in eye***
(A) Atropine.
(B) Physostigmine.
(C) Tropicamide.
(D) Cyclopentolate.
(E) Scopolamine.

(44) ***Following drugs may be used in glaucoma***
(A) Carbachol.
(B) Bethanechol.
(C) Phenylephrine.
(D) Physostigmine.
(E) Isoflurofate.

05 CENTRAL NERVOUS SYSTEM DRUGS

Unit I

Sedative - Hypnotics

INTRODUCTION

Sedative (Anxiolytic)
It refers to a drug that reduces anxiety & exerts a calming effect, with little or no effect on motor or mental functions.

Hypnotic
It refers to a drug that produces drowsiness, & encourages the onset & maintenance of a state of sleep that as far as possible resemble the natural sleep state.

Insomnia
Belief or feeling on the part of pts. that they are not getting enough sleep, is referred as insomnia. Its complaints include difficulty in falling asleep, frequent awakenings, short duration of sleep, & unrefreshing sleep.

Sleep
It is an active, circadian, physiological depression of consciousness characterized by cyclical EEG & eye movement changes.

Types
Two, occurring cyclically over an interval of about 90 min.;

(1) NREM (Non-Rapid Eye Movement) Sleep
It progresses thru 4 stages (1-4), with 50% of sleep being spent in stage 2. This is followed by delta or slow-wave sleep (stages 3 & 4), in which somnambulism & night terrors occur. Heart rate, BP, & respiration are steady or decline, muscles are relaxed & growth hormone secretion is maximal.

(2) REM (Rapid Eye Movement) Sleep
In this stage most recallable dreams occur. Heart rate, BP & respiration are fluctuant, cerebral blood flow inc., penis is erect (unless there is dream anxiety), & skeletal muscles are relaxed.

DRUG CLASSIFICATION

(A) Benzodiazepines

(1) Long Acting Benzodiazepines
Elimination half-life (t ½) 2 Upto 100 hrs., eg; Bromazepam, Chlordiazepoxide, Clorazepate, Clonazepam, Clobazam, Diazepam, Desmethyl-diazepam, Flurazepam, Halazepam, Ketazolam, Nitrazepam, Prazepam, Quazepam.

(2) Intermediate Acting Benzodiazepines
Elimination half-life (t ½) 2 Upto 30 hrs., eg; Alprazolam, Estazolam, Flunitrazepam, Lorazepam, Oxazepam, Temazepam.

(3) Short Acting Benzodiazepines
Elimination half-life (t ½) 2 Upto 8 hrs., eg; Midazolam, Triazolam.

(B) Barbiturates

(1) Long Acting Barbiturates
Duration of Action 2 Greater than 6 hrs., eg; Barbital, Phenobarbital, Mephobarbital.

(2) Intermediate Acting Barbiturates
Duration of Action 2 3 to 5 hrs., eg; Amobarbital (Amylobarbital), Aprobarbital, Butabarbital, Cyclobarbital, Talbutal.

(3) Short Acting Barbiturates
Duration of Action 2 About 2 hrs., eg; Pentobarbital, Hexobarbital, Secobarbital (Quinalbarbital).

(4) Ultra Short Acting Barbiturates
Duration of Action 2 30 min. eg; Thiopental, Methohexital, Thiamylal.

(C) Miscellaneous

(1) Chlorinated Compounds
Chloral hydrate, Ethchlorvynol, Trichloroethanol.

(2) Heterocyclic Compounds
Glutethimide, Methyprylon, Methaqualone.

(3) Aldehyde Group
Paraldehyde.

(4) Alcohol
Ethyl Alcohol.

(5) Propanediol Carbamate
Meprobamate.

(6) Anti-histamines
Hydroxyzine, Promethazine.

(7) Newer Anxiolytics
(a) Piperazinyl pyrimidine derivative eg Buspirone.
(b) Imidazopyridine derivative, eg Zolpidem.
(c) Pyrazolopyrimidines, eg Zaleplon.
(d) Cyclopyrrolones, eg Eszopiclon.
(e) Melatonin receptor agonist, eg Ramelteon.

BENZODIAZEPINES

BENZODIAZEPINE RECEPTORS

High-affinity receptor sites for benzodiazepines are located at GABA-ergic synapses, & are functionally coupled to GABA- responsive chloride channels but are separate macromolecules from either GABA receptors or chloride channels.

Benzodiazepine Receptor Ligands

(1) Classic Agonists

These are clinically useful benzodiazepines which causes anxiolytic, hypnotic, & antiepileptic effects.

(2) Antagonists

eg Imidazodiazepine, Flumazenil. They block the action of benzodiazepines.

(3) Inverse agonists

eg β - carbolines. They block the effects of classic agonists, & when administered alone produce anxiety, & seizures.

MECHANISM OF ACTION

Benzodiazepines enhances inc. chloride ion conductance induced by interaction of GABA with its receptors, due to inc. frequency of Cl^- channel opening. This effect occur at postsynaptic receptors at all level of neuroaxis, including cerebral cortex, cerebellar cortex, substantia nigra, hypothalamus, hippocampus, & spinal cord.

PHARMACOLOGICAL EFFECTS

(A) Central Nervous System

(1) Sedation

Responsiveness to a constant level of stimulation is dec., with dec. in spontaneous activity & ideation.

(2) Hypnosis

(a) Latency of sleep onset is dec.
(b) Duration of stage 2 NREM sleep is inc.
(c) Duration of REM sleep is dec.
(d) Duration of slow-wave sleep is dec.
(e) Withdrawal after continued use results in a "rebound" inc. in the frequency of occurrence & duration of REM sleep.

(3) Anticonvulsant Effects

Inhibits the development & spread of epileptiform activity in the CNS.

(4) Anesthesia

In large dose, may causes anesthesia due to CNS depression.

(B) Cardiovascular System

(1) Upto hypnotic doses, no significant effect in healthy individuals.
(2) In hypovolemic states, congestive cardiac failure or other diseases impairing cardiovascular function, normal doses may cause CVS depression due to actions on medullary vasomotor centres.
(3) At toxic levels, myocardial contractility & vascular tone is dec. both by central & peripheral effects 2 Circulatory collapse.

(C) Respiration

(1) Upto hypnotic doses, no significant effects in healthy individuals.
(2) In pts. with obstructive pulmonary disease, even normal dose can cause profound respiratory depression.
(3) At toxic levels, depression of medullary respiratory center may occur causing death.

(D) Skeletal Muscle

Relaxation occurs due to inhibitory effect on polysynaptic reflexes, & internuncial transmission. High doses may depress transmission at skeletal myoneural junction.

CLINICAL USES

(1) Anxiety.
(2) Hypnosis.
(3) For sedation & amnesia before medical & surgical procedures.
(4) Epileptic disorders.
(5) Anesthetic premedication.
(6) For control of ethanol or other sedative-hypnotic withdrawal states.
(7) For skeletal muscle relaxation in specific neuromuscular disorders.
(8) Night terrors.
(9) As diagnostic aids or for treatment in psychiatry.

ADVERSE EFFECTS

(1) CNS

(a) Ataxia, drowsiness, sedation, impaired judgement, diminished motor skills, lethargy.
(b) Paradoxically inc. anxiety including psychosis esp. with high doses.

(2) CVS

Myocardial depression.

(3) Respiration

Respiratory depression.

(4) Hypersensitivity Reactions

Skin rashes.

(5) Withdrawal Syndromes

Withdrawal of the drug after continued use results in; Anxiety, restlessness, weakness, hyperreactive reflexes, & generalized seizures.

CONTRAINDICATIONS

(1) Previously known hypersensitivity reactions.
(2) Psychoses.
(3) Acute narrow angle glaucoma.

DOSAGE

(1) For Sedation

(a) Diazepam 2 5 mg twice daily.
(b) Lorazepam 2 1-2 mg once or twice daily.

(c) Alprazolam 2 0.25 - 0.5 mg 2-3 times daily.

(2) For Hypnosis

(a) Diazepam 2 1-5 mg at bed - time.
(b) Lorazepam 2 2-5 mg at bed - time.
(c) Triazolam 2 0.5 - 1 mg at bed - time.

WHY BENZODIAZEPINES PREFERRED AS SEDATIVE - HYPNOTICS ?

Because of

(1) Relatively high therapeutic index.
(2) Low risk of drug interactions based on enzyme induction.
(3) Slow elimination rates, which may favor persistence of useful CNS effects.
(4) Low risk of physical dependence with minor withdrawal symptoms.

BARBITURATES

MECHANISM OF ACTIONS

(1) It either have a GABA-like action or enhance the effects of GABA (inhibitory neurotransmitter); by inhibiting the neuronal uptake system for GABA or by stimulating the release of GABA or by binding directly to the receptors at GABA -ergic synapses.
(2) It also depresses the actions of excitatory neurotransmitters.

PHARMACOLOGICAL EFFECTS

(1) Central Nervous System

Similar to benzodiazepines.

(2) Cardiovascular System

(a) At sedative doses, no significant effect.
(b) As the dose is inc., depressed ganglionic transmission results in dec. BP & heart rate.
(c) Toxic doses cause circulatory collapse due to medullary vasomotor centre depression.

(3) Respiration

(a) Potent respiratory centre depression, directly.
(b) Dec. sensitivity of respiratory center to CO_2.

(4) Skeletal Muscle

Large doses have a mild curare - like effect.

(5) Gastrointestinal Tract

Dec. tone & motility, either due to a direct action or to an action on intrinsic nervous mechanisms.

(6) Kidney

Large doses lead to dec. urine formation due to hypotension & release of ADH.

(7) Liver

Barbiturates, esp. phenobarbital, induces hepatic microsomal drug-metabolizing enzyme system. This results in;

(a) Inc. degradation of barbiturates leading to barbiturate tolerance.
(b) Inc. inactivation of anticoagulants, phenytoin, digitoxin, theophylline, & glucocorticoids.

(8) Uterus, Ureter, & Urinary Bladder

(a) Anesthetic doses lead to depression of smooth muscle of uterus, ureter, & urinary bladder.
(b) Barbiturates pass thru placental barrier, & may depress respiratory centre of the newborn.

(9) Blood

Barbiturate-induced porphyria can occur.

CLINICAL USES

(1) Anxiety.
(2) Hypnosis.
(3) Convulsions.
(4) As IV adjuncts to surgical anesthetics (ultra-short acting barbiturates).
(5) Cerebral edema due to surgery or trauma.
(6) During cerebral ischemia to protect cerebral infarction.
(7) Hyperbilirubinemia & kernicterus in the neonate (due to the ability of barbiturates to stimulate hepatic glucuronyl transferase).

ADVERSE EFFECTS

(1) CNS

Oversedation, dec. in REM sleep.

(2) Blood

Porphyria.

(3) Skin

Skin eruptions.

(4) Withdrawal Symptoms

Grand mal seizures, tremors, vivid hallucinations, psychoses.

(5) Acute Barbiturate Overdosage

Results in;

Coma, dec. reflexes (although deep tendon reflexes are intact), severe respiratory depression, circulatory collapse, & renal failure.

Treatment

(a) Support respiration & circulation.
(b) Alkalinize urine & promote diuresis, to inc. elimination of drug.
(c) Hemodialysis or peritoneal dialysis.

CONTRAINDICATIONS

(1) Acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, symptomatic porphyria.
(2) Respiratory obstruction, resp. depression, bronchial asthma.
(3) Shock.
(4) Advance liver disease.
(5) Advance kidney disease.

CHLORAL HYDRATE

ACTIVE METABOLITE

In liver chloral hydrate is metabolized by alcohol dehydrogenase to active metabolite "Trichloroethanol" that produces CNS effects.

PHARMACOLOGICAL EFFECTS

(1) Central Nervous System

It induces sleep in half an hour, lasting for about 6 hours, with relatively small reduction in REM sleep & with little effect on respiration or BP.

(2) Local Sites

It is irritant to the skin & mucus memb. & is quite bad tasting.

CLINICAL USES

(1) As hypnotic for children & elderly.
(2) Preanesthetic medication in the old where barbiturates are contraindicated.

ADVERSE EFFECTS

(1) CNS: Depressant effect leading to coma, respiratory depression & hypotension.
Note 2 Alcohol potentiates the CNS depressant effects.
(2) Eye: Pinpoint Pupil.
(3) GIT: Gastritis.
(4) Skin: Skin eruptions.

PARALDEHYDE

Pharmacological Effects

(1) Central Nervous System

(a) Produces hypnosis in about 15 min., which lasts 4 to 8 hours.
(b) Some anticonvulsant effect.

(2) Gastrointestinal Tract

Produces an irritant action.

Clinical Uses

It is useful for pts. with hepatic or renal disease, b/c it is mainly eliminated by the lung.
(1) Hypnosis.
(2) Tetanus.
(3) Eclampsia.
(4) Status epilepticus.
(5) For pts. undergoing withdrawal from alcohol.

Adverse Effects

(1) CNS: Depression (resemble that of alcohol, barbiturates, & chloral hydrate).
(2) GIT: Nausea, vomiting.

Contraindications

(1) Pulmonary disease.
(2) Peptic ulcer.

BUSPIRONE

Mechanism of Action

It may exert its anxiolytic effects by acting as a partial agonist at brain 5-HT_{1A} receptors, but it also has affinity for brain D_2 receptors.

Pharmacological Effects

Central Nervous System

(1) Relieves anxiety without causing marked sedative, hypnotic, or euphoric effects.
(2) No rebound anxiety or withdrawal signs on abrupt discontinuance.
(3) Less psychomotor impairment than benzodiazepines, & does not affect driving skills.
(4) No anticonvulsant or muscle relaxant effects.

Clinical Uses

Generalized anxiety states.

Adverse Effects

(1) CNS: Nervousness, paresthesias.
(2) CVS: Tachycardia, palpitations.
(3) GIT: Gastrointestinal distress.

Dosage

5-10 mg, 2-3 times daily.

GENERIC & TRADE NAMES

(1) Benzodiazepines

Alprazolam: ALP, Alpram, Azolex, Nervin, Neuxam, Xanax, Zolarem.
Bromazepam: Anxit, Anxolite, Brexotanil, Broma, Calmease, Lexilium, Lexotanil, Rektonil, Relaxin, Relaxitil, Sedonil.
Chlordiazepoxide: Elenium, Chlobrium.
Clobazam: Frisium.
Clorazepate: Tranxene.
Clonazepam: Clonatril, Klozepam, Rivotril.
Diazepam: Anglopam, Apaurin, Cerelium, Diazepam, Neopam, Relax, Relaxipam, Valium.
Estazolam: Esilgan.
Lorazepam: Ativan, Avor, Tenzil, Tranquil.
Midazolam: Dormicum, Hypozam.
Nitrazepam: Mogadon.
Prazepam: Verstran.
Temazepam: Calm, Restoril.
Triazolam: Halcion.

(2) Barbiturates

Phenobarbital: Fenton, Phenobarbitone, Phenotab*, Phenotone.
Thiopental: Pentothal sodium,Thiopentone.

(3) Miscellaneous

Chloral Hydrate: Apnotek, Chloral Hydrate.
Meprobamate: Meprogesic*.
Hydroxyzine: Meditrax, Roxyzin.
Promethazine: Metharex, Phenergan, Promazine, Promethazine.
Buspirone: Busron, Novatil.
Zolpidem: Slepzol, Zolp.

Unit II

Alcohols (Ethanol)

METABOLISM

Over 90% of alcohol consumed is oxidized in liver, while the rest is excreted thru lungs & in urine. Typical adult can metabolize 7-10 gm of alcohol per hour.

Alcohol Dehydrogenase Pathway

It involves the enzyme "alcohol dehydrogenase" that catalyzes conversion of alcohol to acetaldehyde.

$C_2H_5OH + NAD^+$ 2 $CH_3CHO + NADH + H^+$

Note: Alcohol dehydrogenase is found only in liver.

Microsomal Ethanol Oxidizing System

It uses NADPH instead of NAD as cofactor;

$C_2H_5OH + NADPH + H^+ + O_2$ 2 $CH_3CHO + NADP^+ + 2H_2O$

At low alcohol conc. alcohol dehydrogenase is the main oxidizing system, while at higher conc. & during chronic alcohol consumption MEOS plays more significant role.

Acetaldehyde Metabolism

(1) Over 90% of acetaldehyde formed from alcohol is also oxidized in liver.
(2) Mitochondrial NAD-dependent aldehyde dehydrogenase is involved in acetaldehyde oxidation.
(3) Acetate is produced, that is metabolized to CO_2 & water.
(4) Chronic alcohol consumption results in dec. rate of acetaldehyde oxidation in intact mitochondria.

MECHANISM OF ACTION

(1) Ethanol reduces the viscosity of (fluidizes) the memb. of many types of cells.
(2) Fluidizing effect causes changes in specific memb. functions, including;
  (a) Neurotransmitter receptors for dopamine, norepinephrine, glutamate, & opioids.
  (b) Enzymes, eg Na^+-K^+-ATPase, Ca^{++} ATPase, 5-nucleotidase, acetylcholinesterase, & adenyl cyclase.
  (c) Mitochondrial electron transport chain.
  (d) Ion channels, eg Ca^{++} channels.
(3) Acute ethanol exposure inc. the number of GABA-receptors.

CONSEQUENCES OF ACUTE ETHANOL ABUSE

(1) Central Nervous System

It produces a state of drunkenness characterized by sedation, relief of anxiety, slurred speech, ataxia, impaired judgment, & uninhibited behavior.

(2) Heart

Significant depression of myocardial contractility (at a blood conc. of 100 mg/dL).

(3) Smooth Muscle

(a) Ethanol is a vasodilator as a result of both vasomotor centre depression, & direct smooth muscle relaxation caused by acetaldehyde.
(b) In cases of severe overdose, hypothermia due to vasodilation is marked.
(c) It also relaxes uterus & has been given IV for suppression of premature labor.

CONSEQUENCES OF CHRONIC ETHANOL CONSUMPTION

(1) Central Nervous System

(a) Impairment of intellectual & motor functions, emotional liability, reduced perceptual acuity, & amnesia.
(b) Generalized symmetric peripheral nerve injury, that begins with distal paresthesias of the hands & feet.
(c) **Wernicke-Korsakoff Syndrome**
It is associated with thiamine def. & is characterized by paralysis of external eye muscles, ataxia, altered mentation & amnesia (esp. for recent events).
(d) **Withdrawal Symptoms on CNS**
It consists of discomfort & hyperexcitability in mild cases, & convulsions, toxic psychosis & delirium tremens in severe ones.

(2) Cardiovascular System

(a) Direct injury to myocardium, due to contaminants in alcoholic beverages or due to simultaneous thiamine def.
(b) Arrhythmias may occur.
(c) Elevated blood pressure directly related to the amount of alcohol intake.
(d) Withdrawal symptoms on CVS consists of arrhythmias, & syncope.

(3) Gastrointestinal Tract

(a) Ethanol inc. gastric & pancreatic secretion, & alters mucosal barriers that enhance the risk of gastritis & pancreatitis.
(b) Acute gastrointestinal bleeding may result from alcoholic gastritis.
(c) It also injures the small intestine, leading to diarrhea, weight loss & multiple vitamin def.

(4) Liver

(a) Inc. ratio of NADH to NAD leads to metabolic abnormalities, including reduced gluconeogenesis, hypoglycemia, ketoacidosis & accumulation of fat in liver parenchyma.
(b) Essential factors, eg glutathione is dec. in malnourished alcoholics.
(c) Alcoholic fatty liver may progress to alcoholic hepatitis, & finally to cirrhosis.
(d) Hepatic failure may occur causing death.

(5) Endocrine System

(a) Gynecomastia & testicular atrophy may occur in alcoholics with cirrhosis.
(b) Ascites, edema, & effusions may occur due to disturbances in fluid & electrolyte balance.
(c) Ketosis occurs, & is caused by excessive lipolytic factors esp. inc. cortisol & growth hormone.

(d) Hypokalemia occurs due to secondary hyperaldosteronism, & due to vomiting & diarrhea.

(6) Blood

(a) Anemia due to folic acid def.
(b) Iron def. anemia due to gastrointestinal bleeding.
(c) Hypoplasma-proteinemia due to gastritis & GIT bleeding.
(d) Abnormalities in platelets & leukocytes function.

(7) Eye

(a) Ethanol impairs visual acuity with painless bilateral blurring.
(b) This may be followed by optic nerve degeneration.

(8) Fetal Alcohol Syndrome

Chronic maternal alcohol abuse during pregnancy causes 'Fetal Alcohol Syndrome' characterized by;

(a) Retarded body growth.
(b) Microencephaly.
(c) Underdevelopment of midfacial region.
(d) Poor coordination.
(e) Minor joint anomalies.
(f) Congenital heart defects & mental retardation in more severe cases.

(9) Increased Risk of Cancer

Chronic alcoholism inc. the risk for cancer of mouth, pharynx, larynx, esophagus, liver, & breast.

ALCOHOL - DRUG INTERACTIONS

These occur b/c of proliferation of smooth endoplasmic reticulum of liver.

(1) Additive effect with other sedative - hypnotics.
(2) Potentiates the effects of vasodilators & oral hypoglycemic agents.
(3) Enhances the anti-platelet action of aspirin.

MANAGEMENT OF ALCOHOLISM

Acute Ethanol Intoxication

(1) To prevent severe respiratory depression.
(2) Aspiration of vomitus.
(3) To support cardiovascular system.
(4) Administration of glucose for hypoglycemia & ketosis.
(5) Administration of electrolyte solutions in pts who are dehydrated & vomiting.
(6) Administration of K for hypokalemia.
(7) Administration of pyridoxine to accelerate the metabolism of alcohol.

Alcohol Withdrawal Syndrome

(1) Restoration of potassium, magnesium & phosphate balance.
(2) Thiamine therapy.
(3) Substituting a long-acting sedative-hypnotic drug for alcohol, & then gradually reducing it. Benzodiazepines are preferred, eg chlordiazepoxide, clorazepate & diazepam.

Drugs To Treat Alcoholism

(1) **Naltrexone**, an orally active opioid receptor antagonist that blocks the effects at μ opioid receptors of exogenous & endogenous opioids.
(2) **Acamprosate**, a weak NMDA-receptor antagonist & a $GABA_A$-receptor activator.
(3) **Disulfiram**, an inhibitor of aldehyde dehydorgenase.

CLINICAL USES

(1) As skin disinfectant.
(2) Trigeminal neuralgia, to relieve pain.

INHIBITOR OF ALCOHOL DEHYDROGENASE

Fomepizole

It is a potent inhibitor of alcohol dehydrogenase, & is used as an antidote in methanol & ethylene glycol poisoning.

(3) As stomachics to improve appetite & digestion.
(4) As carminative to relieve flatulence.
(5) As antifoaming agent in acute pulmonary edema.
(6) For pyrexia.
(7) For hypnosis.

Unit III

Anti - Epileptic Drugs

INTRODUCTION

EPILEPSY

It refers to a heterogeneous symptom complex characterized by recurrent seizures.

SEIZURES

It refers to finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons.

Classification of Seizures

(A) Partial Seizures

Attack begins in a specific locus in brain, & the localized onset can be ascertained, clinically or by EEG.

(1) Simple Partial Seizures

It is characterized by minimal spread of abnormal discharge such that normal consciousness & awareness are preserved.

For examples, the pt. have a sudden onset of clonic jerking of an extremity lasting 60 - 90 sec., followed by residual weakness lasting for 15 - 30 min. Pt. is completely aware of the attack & can describe it in detail.

(2) Complex Partial Seizures

(a) It also has a localized onset, but the discharge becomes more widespread (usually bilateral), & almost always involves the limbic system.
(b) Most of it arise from one of the temporal lobes b/c of inc. susceptibility of this area to hypoxia or infection, & so-called temporal lobe epilepsy..
(c) Clinically, the pts. have a brief warning followed by an alteration of consciousness during which some pts. may even fall. They demonstrate automatism, eg lip smacking, swallowing, fumbling, scratching or even walking about. After 30 - 120 sec., pts. make a gradual recovery to normal consciousness but may feel tired or ill for several hrs after attack.

(3) Secondarily Generalized Partial Seizures
(a) Also called Jacksonian epilepsy.
(b) It includes those seizures in which a partial seizure immediately precedes a generalized tonic-clonic seizure.

(B) Generalized Seizures
It refers to seizures in which there is no evidence of localized onset.

(1) Generalized Tonic - Clonic Seizures
(a) Also called grand mal epilepsy.
(b) It is characterized by tonic rigidity of all extremities, followed in 15 - 30 sec. by a tremor (relaxation phase). As the relaxation phase becomes longer, the attack enters clonic phase with massive jerking of body. Clonic jerking slows over 60 - 120 sec. & the pt. is usually left in a stuporous state.
(c) Tongue or cheek may by bitten & urinary incontinence is common.

(2) Absence Seizures
(a) Also called petit mal epilepsy.
(b) Characterized by both sudden onset, & abrupt cessation.
(c) Duration is usually less than 10 sec., & rarely more than 45 sec.
(d) Consciousness is altered.
(e) Associated with mild clonic jerking of the eyelids or extremities, with postural tone changes, autonomic phenomenon & automatism.

(3) Atonic Seizures
Characterized by sudden loss of postural tone, eg standing pt. falls to the floor & may be injured.

(4) Myoclonic Seizures
It consists of myoclonic jerkings, that occurs in a variety of seizures including generalized tonic-clonic seizures, partial seizures, absence seizures & infantile spasms.

(5) Infantile Spasms
Characterized by brief, recurrent myoclonic jerks of the body of infants with sudden flexion or extension of body & limbs.

(6) Tonic Seizures
Characterized by tonic rigidity of all extremities.

(7) Status Epilepticus
It is a condition where grandmal epilepsies follow one after another without return of consciousness.

DRUG CLASSIFICATION

(A) Drugs Used In Partial Seizures & Generalized Tonic - Clonic Seizures

(1) Hydantoins
Phenytoin, Mephenytoin, Fosphenytoin, Ethotoin, Phenacemide.

(2) Iminostilbenes
Carbamazepine.

(3) Barbiturates
Phenobarbital, Mephobarbital, Metharbital, Primidone.

(4) Benzodiazepines
Diazepam, Lorazepam, Chlorazepate dipotassium, Clonazepam, Clobazepam, Nitrazepam.

(5) GABA Analog
Gabapentin, Pregabalin.

(6) Piracetams
Levetiracetam.

(7) Others
Oxcarbazepine, Vigabatrin, Lamotrigine, Felbamate, Tiagabine, Topiramate, Zonisamide.

(B) Drugs Used In Generalized Seizures Other Than Gen. Tonic-Clonic Seizures

(1) Succinimides
Ethosuximide, Phensuximide, Methsuximide.

(2) Valproates
Valproic acid, Na Valproate.

(3) Oxazolidinediones
Trimethadione, Paramethadione, Dimethadione.

(4) Benzodiazepines
Clonazepam, Nitrazepam, Clobazepam, Diazepam.

(5) Sulfonamide Derivatives
Acetazolamide, Sulthiame.

PHENYTOIN

MECHANISM OF ACTION

(1) Phenytoin blocks posttetanic potentiation by raising memb. potentials, & suppressing burst activity & repetitive firing, causing inhibition of development & spread of epileptiform discharges.
(2) At therapeutic conc., it suppresses repetitive action potentials by blocking Na channels & dec. influx of Na.
(3) At high conc., it also inhibits the release of serotonin & norepinephrine, promotes uptake of dopamine, & inhibits MAO activity.
(4) At high conc., it dec. GABA uptake & induce proliferation of GABA receptors.

(5) It also inhibit Ca influx across the cell memb., thereby inhibiting a variety of Ca- induced secretory processes.

CLINICAL USES

(1) Simple partial seizures.
(2) Complex partial seizures.
(3) Secondarily generalized partial seizures.
(4) Generalized tonic-clonic seizures.
(5) Ventricular arrhythmias, associated with digitalis toxicity or acute myocardial infarction.

ADVERSE EFFECTS

(1) CNS: Ataxia, sedation, peripheral neuropathy (manifested as dec. deep tendon reflexes in lower limbs), depression.
(2) Eye: Nystagmus, loss of smooth extraocular pursuit movements, diplopia.
(3) CVS: Circulatory collapse.
(4) GIT: Gingival hyperplasia, gastrointestinal irritation.
(5) Liver: Hepatitis.
(6) Endo: Hirsutism.
(7) Blood: Blood dyscrasias.
(8) Hypersensitivity reactions: eg skin rash, fever, lymphadenopathy, agranulocytosis, Stevens-Johnson synd., systemic lupus erythematosus.
(9) Vitamins: Osteomalacia (b/c vit. D def.), Megaloblastic anemia (b/c vit. B_9 def).

CONTRAINDICATIONS

(1) Liver disease.
(2) Absence seizures.
(3) Epilepsy resulting from fever or barbiturate withdrawal.

DOSAGE

Begin with 300 - mg/d orally. If seizures continues dosage inc. each time by 25 - 30 mg.

DRUG INTERACTIONS

(1) B/c phenytoin is highly plasma protein bound, other highly bound drugs eg phenylbutazone, sulfonamides, benzodiazepines or anticoagulants, can displace phenytoin from its binding sites causing an inc. free drug level & intoxication.
(2) It induces microsomal enzymes responsible for metabolism of many drugs.
(3) Phenobarbital & carbamazepine dec. its steady-state conc. thru induction of hepatic microsomal enzymes.
(4) Isoniazid inhibits metabolism of phenytoin resulting in its inc. steady - state conc.

CARBAMAZEPINE

Mechanism of Action

(1) It blocks Na^+ channels & inhibit the generation of repetitive action potentials in epileptic focus.
(2) It also inhibits uptake & release of norepinephrine from brain synaptosomes.

Clinical Uses

(1) Partial seizures.
(2) Generalized tonic-clonic seizures.
(3) Trigeminal neuralgia.

Adverse Effects

(1) CNS: Diplopia, ataxia, drowsiness.
(2) CVS: Congestive cardiac failure.
(3) GIT: Mild gastrointestinal upset.
(4) Liver: Liver toxicity.
(5) Renal: Kidney toxicity.
(6) Blood: Aplastic anemia, agranulocytosis, leukopenia.
(7) Hypersensitivity reactions: Erythematous skin rash.

Dosage

1-2 gm.

Drug Interactions

(1) It induces hepatic microsomal drug-metabolizing enzyme system, causing dec. steady-state conc. of its own & inc. metabolism of primidone, phenytoin, ethosuximide, valproic acid & clonazepam.
(2) Valproic acid inhibits its clearance & phenobarbital dec. its blood level.
(3) Phenytoin & phenobarbital dec. its steady-state conc. thru enzyme induction.

BARBITURATES

Phenobarbital

Antiepileptic Mechanism of Action

(1) It markedly prolongs posttetanic potentiation & enhances pre-synaptic inhibition.
(2) It selectively suppresses abnormal neurons, inhibiting spread & suppressing firing from loci.
(3) At therapeutic conc., it antagonizes glutamate excitation while at the same time enhancing GABA inhibition.

Primidone

In the body it is converted to phenobarbital, but its mech. of action is more like that of phenytoin.

ETHOSUXIMIDE

Mechanism of Action

(1) Exact mech. is unknown.
(2) It inhibits Na^+ -K^+ -ATPase, depresses cerebral metabolic rate, & inhibits GABA transaminase.

Clinical Uses

Absence seizures.

Adverse Effects

(1) CNS: Transient lethargy, headache, dizziness, euphoria.
(2) GIT: Abd. pain, nausea, vomiting.
(3) Blood: Eosinophilia, thrombocytopenia, leukopenia, pancytopenia.

VALPROIC ACID

Mechanism of Action

(1) Inhibits "GABA - transaminase" 2 Inc. GABA level by blocking conversion of GABA to succinic semialdehyde.
(2) Inc. K^+ conductance (at very high conc.)
(3) May cause a whole - body shift towards metabolic acidosis by stimulating beta oxidation of fatty acids 2 Inc. circulating ketone bodies 2 These ketone bodies are then utilized to inc. brain glycogen, which might protect against seizures induced by transient stimulation.

Note: It is active against both pentylenetetrazole seizures & maximal electroshock seizures.

Clinical Uses

(1) Absence seizures.
(2) Myoclonic seizures.
(3) Atonic seizures.
(4) Generalized tonic - clonic seizures.

Adverse Effects

(1) CNS: Sedation, tremor, ataxia.
(2) GIT: Nausea, vomiting, abd. pain, heartburn, inc. appetite, weight gain, pancreatitis.
(3) Liver: Hepatotoxicity.
(4) Blood: Thrombocytopenia.
(5) Hairs: Alopecia.
(6) Teratogenicity: Inc. incidence of spina bifida in offspring of women who take the drug during pregnancy.

Dosage

25 - 30 mg/kg/d.

Drug Interactions

(1) At low doses, inhibits its own metabolism.
(2) At higher doses, there is inc. free fraction of valproic acid.
(3) Displaces phenytoin from plasma proteins.
(4) Inhibits the metabolism of phenobarbital, phenytoin, & carbamazepine.

OXAZOLIDINEDIONES

Examples

Trimethadione, Paramethadione, Dimethadione.

Mechanism of Action

(1) Active against pentylenetetrazole - induced seizures.
(2) It causes reduction in synaptic transmission in spinal cord during repetitive stimulation without effecting single-impulse transmission thru monosynaptic pathways.
(3) Also causes an inc. in GABA level.

Adverse Effects

(1) CNS: Sedation, hemeralopia.
(2) Renal: Reversible nephrotic syndrome.
(3) Skin: Rashes, exfoliative dermatitis.
(4) Metabolic: Mild metabolic acidosis.

GENERIC & TRADE NAMES

(1) Hydantoin

Phenytoin: Di-Hydan, Dilantin, Fentin, Phenton-S.

(2) Iminostilbene

Carbamazepine: Carbanil, Epilepsin, Lexopine, Tegral.

(3) GABA Analogs

Gabapentin: Engaba, Gaba, Gabatin, Gabin.
Pregabalin: Gabica.

(4) Piracetams

Levetiracetam: Kepra.

(5) Succinimides

Ethosuximide: Emeside.

(6) Valproates

Valproic acid: Epival, Valep, Valpro.

(7) Benzodiazepines

See Unit I.

(8) Others

Oxcarbazepine: Oxalepsy.
Lamotrigine: Lamictal, Lamonil.
Topiramate: Epimate, Topamax, Topte.
Acetazolamide: Diamox.

Unit IV

Anti-Parkinsonian Drugs

PARKINSON'S DISEASE

Parkinsonism refers to 2 main disorders with similar clinical symptoms;

(1) Paralysis agitans or idiopathic Parkinson's disease, which accounts for 90% of the cases, &,
(2) Secondary or symptomatic parkinsonism, caused by past infection with the virus of lethargic encephalitis.

Clinical Features

(1) Tremor.
(2) Rigidity.
(3) Bradykinesia.
(4) Postural instability.

Role of Acetylcholine & Dopamine in Basal Ganglia

(1) Normally, dopaminergic neurons originating in substantia nigra exert an inhibitory effect on neurons, including cholinergic neurons, in corpus striatum.
(2) In Parkinson's disease, dopamine is selectively depleted in caudate nucleus, putamen & pallidum. This depletion can be correlated with the degree of degeneration of substantia nigra. In the presence of a dopamine deficiency, the normal balance b/w dopamine & acetylcholine is disturbed & cholinergic activity predominates.

DRUG CLASSIFICATION

(A) Dopaminergic Drugs

(1) Levodopa

(a) Levodopa (alone),
(b) Levodopa in combination with dopa-decarboxylase inhibitor
  (i) Levodopa + Carbidopa 2 Sinemet.
  (ii) Levodopa + Benserazide 2 Madopar, Prolopa.
  (iii) Levodopa + Carbidopa + Entacapone 2 Stalevo.

(2) Ergolines
Bromocriptine, Pergolide.

(3) Non-ergolines
Pramipexole, Ropinirole.

(B) Monoamine Oxidase 'B' Inhibitor
Deprenyl (Selegiline), Rasagiline

(C) Catechole-O-Methyltransferase Inhibitor
Tolcapone, Entacapone.

(D) Centrally - Acting Anticholinergic Drugs
Benzhexol (Trihexyphenidyl), Benztropine, Biperidine, Orphenadrine, Procyclidine.

(E) Others
(1) Amantadine (antiviral).
(2) Apomorphine.

LEVODOPA

MECHANISM OF ACTION

Levodopa is the immediate precursor of dopamine. When administered to pts, a small portion of the dose enters brain & is converted to dopamine by dopa decarboxylase.

Note: Dopamine can not be administered itself b/c it will not cross the blood - brain barrier.

PHARMACOLOGICAL EFFECTS

(1) It is the immediate precursor of dopamine, & converted to dopamine thru-out the body.
(2) Dopamine is a less potent sympathomimetic than epinephrine & norepinephrine.
(3) Effects of dopamine are due to stimulation of central & peripheral dopamine receptors, as well as α_1 & β_1 adrenoceptors.
(4) It causes release of norepinephrine from sympathetic nerve endings.
(5) Levodopa is effective in relieving all of the clinical features of parkinsonism particularly bradykinesia & any disability resulting from it.

CLINICAL USES

Treatment of moderate to severe parkinson's disease.

ADVERSE EFFECTS

(1) CNS

(a) Dyskinesias: Chorea, ballismus, athetosis, dystonia, myoclonus, tics, & tremor may occur individually or in any combination in face, trunk or limbs.

(b) Behavioral effects: Depression, anxiety, agitation, insomnia, somnolence, confusion, delusions, hallucinations, nightmares, euphoria.

(2) Eye
Mydriasis, precipitation of acute glaucoma.

(3) CVS
Tachycardia, ventricular extrasystoles, atrial fibrillation, orthostatic hypotension, hypertension (in the presence of MAO inhibitors, sympathomimetics, or overdosage).

(4) GIT
Anorexia, nausea, vomiting.

(5) Endo
Dec. prolactin secretion.

(6) Repro
Priapism (abnormal penile erection), brownish vaginal secretion.

(7) Renal
Brownish urine.

(8) Blood
Blood dyscrasias, positive coomb's test.

(9) Metabolic
Elevation of BUN, serum transaminase, alkaline phosphatase & bilirubin.

(10) Joints
Aggravation or precipitation of gouts.

(11) Skin
Hot flushes.

CONTRAINDICATIONS

(1) Psychosis.
(2) Angle - closure glaucoma.
(3) Pts. with a history of melanoma.

DRUG INTERACTIONS

(1) Pyridoxine inc. extracerebral conversion of levodopa to dopamine, & reduce its therapeutic effectiveness.
(2) MAO inhibitors impair dopamine & norepinephrine metabolism, & inc. both the central & peripheral effects of levodopa. As a result pts. may experience a hypertensive crisis or hyperpyrexia.
(3) Antipsychotics block dopamine receptors in the brain, & reduce or abolish the effects of levodopa.
(4) Concomitant use of tricyclic antidepressant can cause orthostatic hypotension.

SINEMET, MADOPAR, PROLOPA & STALEVO

MECHANISM OF ACTION

(1) Carbidopa & benserazide are dopa decarboxylase inhibitors.
(2) They do not cross the blood - brain barrier, so reduce only peripheral metabolism of levodopa to dopamine.
(3) Formation of dopamine in the brain is not affected.
(4) A higher percentage of administered levodopa is converted to dopamine in the brain.

(5) By using carbidopa or benserazide it is possible to administer lower doses of levodopa, thereby reducing its peripheral adverse effects.
(6) Entacapone prolong the action of levodopa by diminishing its peripheral metabolism.

CLINICAL USES
Replace levodopa as the most useful agents for parkinsonism.

DOSAGE
Sinemet contains carbidopa & levodopa in fixed proportion (1:10 or 1:4).
Treatment is started with sinemet 25 mg/100 mg 3 times daily, & gradually inc. the dose upto sinemet 25mg/250mg 3 or 4 times daily.

BROMOCRIPTINE

MECHANISM OF ACTION
Its anti-parkinsonian effect is due to its partial agonist activity at presynaptic dopamine D_2 receptors.

PHARMACOLOGICAL EFFECTS
(1) Stimulates D_2 receptors in corpus striatum.
(2) Inhibits synthesis & release of prolactin.
(3) Lowers elevated secretion of growth hormone in pts. with acromegaly.

CLINICAL USES
As an alternative to levodopa in parkinson's disease.

ADVERSE EFFECTS
(1) CNS
(a) Dyskinesias: Same as in levodopa.
(b) Mental disturbances: Confusion, hallucination, delusions & other psychiatric reactions.
(c) Headache, inc. arousal

(2) CVS
Orthostatic hypotension, cardiac arrhythmias, painless digital vasospasm.

(3) GIT
Anorexia, nausea, vomiting, constipation, dyspepsia, reflux esophagitis, bleeding from peptic ulcer.

(4) Resp. Tract
Nasal congestion.

(5) Erythromelalgia
It consists of red, tender, painful swollen feet & hands associated with arthralgia.

CONTRAINDICATIONS
(1) Pts. with recent myocardial infarction.
(2) Pts. with a history of psychotic illness.
(3) Peptic ulcer.
(4) Peripheral vascular disease.

DOSAGE
7.5 - 30 mg/day.

AMANTADINE

Mechanism of Action
(1) An antiviral agent, it is of some help in the treatment of parkinsonism.
(2) It releases dopamine from remaining intact neurons, delays re-uptake into these neurons, & exerts an anti-cholinergic action.

Pharmacological Effects
(1) Exerts an antiparkinsonian effect.
(2) Acts as a prophylactic against A2 influenza virus.

Clinical Uses
See Chapter 20.

Adverse Effects
See Chapter 20.

CENTRALLY-ACTING ANTICHOLINERGIC DRUGS

Examples
Benzhexol (Trihexyphenidyl), Benztropine, Biperidine, Chlorphenoxamine, Orphenadrine, Procyclidine.

Mechanism of Action
They block the central cholinergic receptors, & reduce excessive cholinergic stimulation in basal ganglia.

Clinical Uses
Parkinsonism, where it improves its tremor & rigidity.

Adverse Effects
(1) CNS: Drowsiness, mental slowness, inattention, restlessness, confusion, agitation, delusions, hallucinations, mood changes, dyskinesias.
(2) Eye: Blurred vision, mydriasis, inc. intraocular pressure.
(3) CVS: Tachycardia, palpitation, cardiac arrhythmias.
(4) Resp: Tachypnea.
(5) GIT: Dry mouth (which may cause acute suppurative parotitis), nausea, vomiting, constipation.
(6) Renal: Urinary retention.

Contraindications
(1) Prostatic hypertrophy.
(2) Pyloric stenosis.
(3) Paralytic ileus.
(4) Angle - closure glaucoma.

DRUGS CAUSING PARKINSONISM

(1) Reserpine, which depletes biogenic amines from storage sites.
(2) Haloperidol, which block dopaminergic receptors.
(3) Phenothiazine, which also block dopaminergic receptors.

GENERIC & TRADE NAMES

(1) Dopaminergic Drugs
Carbidopa + Levodopa: Sinedopa, Sinemet, Validopa.
Carbidopa + Benserazide: Madopar.
Bromocriptine: Brotin, Parlodel.
Pergolide: Celance.
Ropinirole: Requip.

(2) Centrally - Acting Anticholinergic Drugs
Benzhexol: Pacitane.
Orphenadrine: Norflex, Orphenalax.
Procyclidine: Kemadrin.

(3) Monoamine Oxidase 'B' Inhibitor
Selegiline: Jumex, Selgin.

(4) Others
Amantadine: PK-Merz, Virofral.

Unit V

Anti - Psychotic Drugs

[Neuroleptics, Major tranquilizers]

INTRODUCTION

Psychosis
It is a general term for any major mental disorder of organic &/or emotional origin, characterized by derangement of the personality & loss of contact with reality, often with delusions, hallucinations, or illusions.

Schizophrenia
It is a particular kind of psychosis characterized by a clear sensorium, but a marked thinking disturbance.

DRUG CLASSIFICATION

(A) Phenothiazine Derivatives
(1) Aliphatic derivatives: Chlorpromazine, Promazine, Promethazine, Trimeprazine.
(2) Piperadine derivatives: Thioridazine, Mesoridazine, Piperacetazine.
(3) Piperazine derivatives: Prochlorperazine, Trifluoperazine, Perphenazine, Fluphenazine, Thiopropazate.

(B) Thioxanthene Derivatives
Thiothixene, Chlorprothixene, Clopenthixol, Zuclopenthixol, Fluphenthixol.

(C) Butyrophenone Derivatives
Haloperidol, Droperidol, Benperidol, Trifluperidol.

(D) Miscellaneous
(1) Dibenzoxazepine: Loxapine.
(2) Dihydroindolone: Molindone, Ziprasidone.
(3) Dibenzodiazepine: Clozapine.
(4) Diphenylbutyl piperadine: Pimozide.
(5) Benzamides: Sulpiride, Remoxipiride.
(6) Thienobenzodiazepine: Olanzapine.
(7) Dibenzothiazepine: Quietiapine.
(8) Dihydrocarbostyril: Aripiprazole.
(9) Benzisoxazole: Risperidone.

MECHANISM OF ACTION OF ANTIPSYCHOTICS

(1) Block D_2 receptors in mesolimbic & mesofrontal systems, that accounts for its antipsychotic effects.
(2) Also blocks muscarinic cholinoceptors.
(3) At high doses, blocks α_1- adrenoceptors & histamine H_1 receptors.

PHARMACOLOGICAL EFFECTS OF ANTI-PSYCHOTICS

(1) Effects Due to D_2 Receptor Blockade
(a) Antipsychotic Effect
This is due to blockade of D_2 receptors in mesolimbic & mesofrontal systems.

(b) Other Effects
(i) D_2 receptors blockade in the nigrostriatal pathway results in unwanted parkinsonian effects.
(ii) D_2 receptor blockade in pituitary gland results in hypersecretion of prolactin.
(iii) D_2 receptor blockade in chemoreceptor trigger zone & stomach results in antiemetic effect.

(2) Other Effects
(a) Higher doses esp. of phenothiazines & thioxanthene produce pronounced sedation, due to blockade of H_1 receptors.
(b) Generalized inhibition of parasympathetic function, due to blockade of muscarinic cholinoceptors.
(c) Hypotension, most pronounced with high dose phenothiazines & thioxanthene, due to blockade of α_1-adrenoceptors.

CLINICAL USES OF ANTIPSYCHOTICS

(A) Psychiatric Uses
(1) Schizophrenia.
(2) Manic episode in bipolar affective disorder.
(3) Non - manic excited states.
(4) Tourette syndrome.
(5) For controlling disturbed behavior in pts. with senile dementia of Alzheimer type.
(6) Alcoholic hallucinosis.
(7) Paranoid states.

(B) Nonpsychiatric Uses

(1) As antiemetic (except thioridazine).
(2) As antipruritics (due to H_1 blocking effect).
(3) Neuroleptanesthesia (Droperidol).
(4) Hiccup (Chlorpromazine).

ADVERSE EFFECTS OF ANTIPSYCHOTICS

(1) CNS

(a) Neurologic effects: Extrapyramidal reactions include typical parkinson synd., akathisia, acute dystonic reactions (eg facial grimacing, torticollis); tardive dyskinesia, lethargy, drowsiness.

(b) Behavioral effects: Pseudo-depression due to akinesia; toxic-confusional states.

(c) Neuroleptic malignant synd: Characterized by muscle rigidity, impaired sweating, hyperpyrexia, altered BP & pulse rate, & raised creatinine phosphokinase level.

(2) Eye

Loss of accommodation, deposits in the cornea & lens (with chlorpromazine), retinal deposits (with thioridazine).

(3) CVS

Orthostatic hypotension, syncope, reflex tachycardia, arrhythmia, conduction block.

(4) GIT

Dry mouth, constipation.

(5) Endo

Hyperprolactinemia in women results in amenorrhea-galactorrhea synd, & in men gynecomastia.

(6) Repro

In women infertility & inc. libido; in men infertility, impotence & loss of libido.

(7) Renal

Urinary retention.

(8) Allergic Reactions

Cholestatic jaundice, agranulocytosis, skin eruption.

(9) Pregnancy

Dysmorphogenesis.

DOSAGE

(1) Chlorpromazine 2 100 -1000 mg/d.
(2) Thioridazine 2 100 - 800 mg/d.
(3) Trifluoperazine 2 5 - 60 mg/d.
(4) Fluphenazine 2 2 - 20 mg/d.
(5) Zuclopenthixol 2 20 - 150 mg/d.
(6) Haloperidol 2 2 - 20 mg/d.

DRUG INTERACTIONS

Additive effects occur when these drugs are used with sedative-hypnotics, alpha adrenoceptor blockers & anti-cholinergics.

GENERIC & TRADE NAMES

(1) Phenothiazine Derivatives

Chlorpromazine: Chlorotil, Largactil.
Fluphenazine: Fluphan, Flucate, Modrin*, Motival*.
Promethazine: Phenergan, Promazine, Semozin.
Prochlorperazine: Prochlor, Stemetil.
Trifluoperazine: Stelabid*, Stelazine.
Thioridazine: Melliril.

(2) Thioxanthene Derivatives

Zuclopenthixol: Clopenia, Clopixol.
Fluphenthixol: Fluanoxol.

(3) Butyrophenone Derivatives

Haloperidol: Halpol, Phrenia, Serenace.

(4) Miscellaneous

Clozapine: Clozaril, Glipin.
Olanzapine: Nozapin, Olanzin, Ozapine.
Aripiprazole: Aripip, Zedan.
Risperidone: Espidone, Risperal.

Unit VI

Anti - Manic Drugs

[Drugs Treatment of Bipolar Affective Disorder, Mood - Stabilizing Drugs]

BIPOLAR AFFECTIVE DISORDER

(1) Also called manic-depressive illness.
(2) It is a very serious emotional disorder. Pts have cyclic attacks of mania with symptoms of paranoid schizophrenia consisting of grandiosity, bellicosity, paranoid thoughts, & overactivity.
(3) Inc. catecholamine activity is found in bipolar affective disorder.

DRUGS FOR BIPOLAR AFFECTIVE DISORDER

(1) Lithium.
(2) Anti-epileptics: Valproic acid, Carbamazepine, Lamotrigine (see Unit III).
(3) Antipsychotics (see Unit V).

LITHIUM

MECHANISM OF ACTION

(1) Substitute for sodium in generating action potential.
(2) Enhances some of the actions of serotonin.
(3) Dec. norepinephrine & dopamine turnover, that may contribute to its antimanic action.

(4) Blocks the development of dopamine receptor super-sensitivity, that may accompany chronic therapy with antipsychotics.
(5) Enhance the synthesis of acetylcholine by inc. choline uptake into nerve terminals.
(6) Inhibits norepinephrine sensitive adenylate cyclase, contributing to its antidepressant & antimanic effects.
(7) Inhibits the conversion of IP_2 to IP_1 ↕ Depletion of phosphatidylinositol - 4, 5 - biphosphate (PIP_2 which is the memb. precursor of IP_3 & diacylglycerol).

CLINICAL USES

(1) Bipolar affective disorders.
(2) Acute mania.
(3) Recurrent endogenous depressions.
(4) Excited phase in schizo-affective disorders.
(5) Alcoholic mania & depression.
(6) Management of aggressive violent behavior in prisoners.

ADVERSE EFFECTS

(1) CNS: Tremor, choreoathetosis, ataxia, dysarthria, aphasia, confusion, withdrawal or bizarre motor movements, seizures.
(2) CVS: SA nodal depression, hypotension, arrhythmias.
(3) GIT: Anorexia, vomiting, diarrhea.
(4) Endo: Dec. thyroid function, goitre, hypothyroidism.
(5) Repro: Disturbed sexual function in men.
(6) Renal: Polydipsia, polyuria, nephrogenic diabetes insipidus, edema.
(7) Blood: Leukocytosis.
(8) Skin: Acneiform eruptions.
(9) Teratogenicity: Cardiovascular anomalies, esp. Ebstein's anomaly.
(10) Pregnancy: Lithium toxicity in newborn manifested by lethargy, cyanosis, poor suck, Moro reflexes, & hepatomegaly.

DOSAGE

600 to 3600 mg/day.

GENERIC & TRADE NAMES

Lithium
Lithium Carbonate: Camcolit, Carlit, Neurolith SR, Priadel.

Unit VII

Anti - Depressant Drugs

DEPRESSION

(1) It is a psychiatric syndrome consisting of dejected mood, psychomotor retardation, insomnia & weight loss, sometimes associated with guilt feelings & somatic preoccupations, often of delusional proportions.
(2) It is an alteration of mood characterized by sadness, worry, anxiety, & losses of weight, libido & enthusiasm.

Types

(1) Reactive (Secondary) Depression
It occurs in response to a real stimuli, eg grief, illness, etc or in response to drugs, eg antihypertensive, alcohol, hormones.

(2) Endogenous (Major Depressive) Depression
It is a genetically determined biochemical disorder manifested by inability to cope with ordinary stress.

(3) Bipolar Affective (Manic-Depressive) Depression
It is associated with bipolar affective disorder.

DRUG CLASSIFICATION

(A) Tricyclics
(1) Neutral: Imipramine, Dothiepin.
(2) Sedative: Amitriptyline, Clomipramine, Trimipramine, Doxepin.
(3) Stimulant: Desipramine, Nortriptyline, Protriptyline, Mianserin.

(B) Heterocyclics (2nd Generation Agents)
Amoxapine, Maprotiline, Trazodone, Bupropion.

(C) 3rd Generation Agents
Venlafaxine, Mirtazapine, Nefazodone, Duloxetine.

(D) Monoamine Oxidase Inhibitors
(1) Hydrazide derivatives: Phenelzine, Isorcarboxazid.
(2) Non-hydrazide derivatives: Tranylcypromine, Moclobemide.

(E) Sympathomimetic Stimulants
Dextroamphetamine, Methylamphetamine, Methylphenidate.

(F) Selective Serotonin Reuptake Inhibitors
Fluoxetine, Paroxetine, Sertraline, Fluvoxamine, Citalopram, Escitalopram.

TRICYCLIC ANTIDEPRESSANTS

MECHANISM OF ACTION

(1) They have both H_1-receptor blocking & α adrenergic properties.
(2) They potentiate the action of biogenic amines by blocking the inactivating re-uptake of amines after release from presynaptic neuron.
(3) They also possess antimuscarinic action, & block re-uptake of serotonin.
(4) Alpha-2 receptors which are found on adrenergic nerve terminals are blocked by tricyclics, resulting in inc. neurotransmitter release.

(5) One or more of the above mention action could contribute to elevation of mood in depressed pts.

CLINICAL USES

(1) Depression.
(2) Enuresis.
(3) Chronic pain.
(4) Obsessive compulsive phobic states.
(5) Cataplexy associated with narcolepsy.
(6) Acute pain attacks.
(7) School phobia.
(8) Attention deficit disorders in children.

ADVERSE EFFECTS

(1) CNS: Lassitude, fatigue, sleepiness, agitation, insomnia, aggravation of psychosis, tremor, delirium, confusion, paresthesias, seizures, neuropathy.
(2) Eye: Blurred vision, aggravation of glaucoma.
(3) CVS: Tachycardia, orthostatic hypotension, delayed cardiac conduction, arrhythmias.
(4) GIT: Constipation, paralytic ileus.
(5) Liver: Cholestatic jaundice.
(6) Endo: Sexual disturbances, gynecomastia, amenorrhea, weight gain.
(7) Renal: Urinary hesitancy, urinary retention.
(8) Blood: Agranulocytosis, hemolytic anemia.
(9) Skin: Sweating, rashes.

CONTRAINDICATIONS

(1) Prior sensitivity.
(2) Acute recovery phase of myocardial infarction.
(3) Concomitant use of MAO inhibitors.

DOSAGE

Amitriptyline 2 75 - 200 mg/day.
Desipramine 2 75 - 200 mg/day.
Doxepin 2 75 - 300 mg/day.
Imipramine 2 75 - 200 mg/day.
Protriptyline 2 20 - 40 mg/day.
Nortriptyline 2 75 - 150 mg/day.

MONOAMINE OXIDASE INHIBITORS

MECHANISM OF ACTION

(1) They form stable complex with the enzyme monoamine oxidase, irreversibly inactivating it & thereby preventing oxidative deamination of biogenic amines, eg norepinephrine, epinephrine, dopamine, serotonin & tyramine.
   (a) These biogenic amines are thus inc. significantly in brain, intestines, heart, & blood.
   (b) Inc. biogenic amine levels in brain is responsible for their antidepressant effects.
(2) Tranylcypromine also release norepinephrine centrally, which accounts for its relatively rapid action.

CLINICAL USES

Similar to tricyclics.

ADVERSE EFFECTS

Similar to tricyclics; except that it does not causes antimuscarinic adverse effect (blurred vision, aggravation of glaucoma, constipation, paralytic ileus, urinary hesitancy, urinary retention, delirium).

CONTRAINDICATIONS

(1) Hypersensitivity.
(2) Pheochromocytoma.

WHY MAO INHIBITORS CAUSES HYPERTENSIVE CRISIS OR CHEESE SYNDROME?

MAO inhibitors can interact with foods containing a high tyramine content, eg cheese, beer & chicken liver.
1) High conc. of tyramine absorbed form these foods cannot undergo oxidative deamination.
2) Tyramine can therefore induce release of large amounts of stored catecholamines from nerve terminals which can precipitate a hypertensive crisis or cheese syndrome.

(3) Congestive cardiac failure.
(4) Liver disease.
(5) Impaired renal function.
(6) Hypertension.

DOSAGE

Phenelzine 2 45 - 75 mg/day.
Isocarboxazid 2 20 - 50 mg/day.
Tranylcypromine 2 10 - 30 mg/day.

GENERIC & TRADE NAMES

(1) Tricyclics
Amitriptyline: Amitryp, Amyline, Tryptanol.
Clomipramine: Clomipril, Depramine.
Dothiepin: Prothiaden.
Imipramine: Imiprol, Tofranil.
Mianserin: Lantanon.
Nortriptyline: Notrilin, Sensival.
Trimipramine: Surmontil.

(2) Heterocyclics
Maprotiline: Ludiomil.
Bupropion: Zylexx SR.

(3) 3rd Generation Agents
Venlafaxine: Venaxin, Venalax, Vexor.
Mirtazapine: Mirtazep, Remeron.

(4) Monoamine Oxidase Inhibitors
Moclobemide: Aurorix.

(5) Sympathomimetic Stimulants
Methylphenidate: Phenida, Ritalin.

(6) Selective Serotonin Reuptake Inhibitors
Fluoxetine: Alert, Faxetine, Flux, Prozac.
Paroxetine: Froxtin, Paraxyl, Seroxat.

Sertraline: Pertral, Reline.
Fluvoxamine: Flomin, Voxamine.
Citalopram: Celesta, Cipramil, Citalo.
Escitalopram: Cipralex, Depram, Eslopram.

Unit VIII

CNS Stimulants

DRUG CLASSIFICATION

(A) Cerebral Cortex Stimulants
(1) Xanthines: Caffeine, Theophylline, Theobromine. (See Unit I, Chapter 13).
(2) Sympathomimetics: Amphetamine, Dextroamphetamine, Methamphetamine, Methylphenidate.
(3) Others: Atropine, Cocaine.

(B) Medullary Stimulants (Analeptics)
(1) Acting directly on medullary centre: Leptazol, Nikethamide, Ethamivan, Doxapran, Picrotoxin, Amiphenazole.
(2) Acting reflexly thru chemoreceptors in carotid body: Nikethamide, Bemigride.
(Note: For detail on Analeptics see Unit II, Chapter 13.)

(C) Spinal Cord Stimulants
Strychnine, Brucine.

(D) Antidepressant Drugs

(E) Hallucinogenic Drugs
Lysergic acid diethylamide, Mescaline, Psilocybin, Psilocin, Adrenochrome, Cannabis.

AMPHETAMINE

MECHANISM OF ACTION
(1) It stimulates both alpha - & beta - adrenoceptors thru an indirect mechanism (ie thru the release of catecholamines).
(2) It stimulates cerebral cortex, reticular activating system, medullary centre, & spinal cord.

PHARMACOLOGICAL EFFECTS
(1) Central Nervous System
(a) Psychic stimulation consisting of euphoria, wakefulness, alertness, & inc. mental & physical activity; usually followed by a sense of depression.
(b) Antifatigue action.
(c) Analeptic action.
(d) Mild analgesic properties of its own; enhances analgesic effect of morphine & meperidine, while dec. that of nitrous oxide.
(e) Depress appetite & reduce food intake thru a central action on hypothalamic feeding centre, & by reduction of acuity of smell & taste.
(f) Facilitates monosynaptic & polysynaptic transmission in the spinal cord.

(2) Eye
Mydriasis upon local application.

(3) Cardiovascular System
(a) Inc. both systolic & diastolic BP.
(b) Reflex slowing of heart rate.
(c) Large doses may produce cardiac arrhythmias.

(4) Gastrointestinal Tract
Relaxation in spastic states.

(5) Urinary Bladder
Relaxation of detrusor, & contraction of sphincter.

CLINICAL USES
(1) Narcolepsy.
(2) Hyperkinetic synd. in children.
(3) Nocturnal enuresis.
(4) As mydriatic (locally).
(5) As nasal decongestant (locally).

ADVERSE EFFECTS
(1) CNS: Dysphoria, headache, confusion, dizziness, fatigue, mental depression, delirium, psychosis, convulsions, coma.
(2) Eye: Mydriasis.
(3) CVS: Hypertension, arrhythmias.
(4) GIT: Dry mouth.
(5) Tolerance, psychic, & physical dependence

CONTRAINDICATIONS
(1) Pts with cardiovascular diseases.
(2) Pts receiving MAO inhibitors or guanethidine.
(3) Insomnia.
(4) Anorexia.
(5) Mentally unstable pts.

DOSAGE
5 - 10 mg orally, IM or IV.

GENERIC & TRADE NAMES

Caffeine: Amtalidin*, Panadol extra*.
Theophylline: Asthalin**,** Theograd.
Theobromine: Urodonal.
Methylphenidate: Phenida, Ritalin.
Atropin: Atrosol, Ethiatropin.

Unit IX

Anti - Migraine Drugs

MIGRAINE

(1) Migraine headache consists of periodic attacks of vascular headache, usually temporal & unilateral in onset, commonly associated with irritability, nausea, vomiting, constipation, or diarrhea, & often photophobia; attacks are preceded by constriction of cranial arteries, usually with resultant prodromal ocular symptoms, & is followed by vasodilation.
(2) Migraine headache, is characterized by a brief 'aura' that may involve visual scotomas or even hemianopia & speech abnormalities, followed by a severe throbbing unilateral headache that lasts for a few hrs to 1-2 days.
(3) The attacks are usually precipitated by stress & occur after stressful episodes.

Pathophysiology

(a) Some vascular mech. is involved b/c onset of headache is associated with inc. amplitude of temporal artery pulsations, & relief of pain by ergotamine is accompanied by dec. pulsation.
(b) Onset of migrainous aura is associated with an abnormally inc. release of serotonin from platelets.
(c) Arterial throbbing phase is associated with dec. of platelets & serum serotonin level below normal.
(d) Other chemical triggers include falling levels of estrogen in women whose headache is linked to menstrual cycle, & elevated levels of prostaglandin E_1.

DRUGS USED IN MIGRAINE

(A) In Acute Attacks

(1) Ergotamine tartarate.
(2) Dihydroergotamine.
(3) Aspirin.
(4) Paracetamol.
(5) Metoclopramide.

(B) For Prophylactic Use

(1) Beta - adrenoceptor blockers, eg propranolol, atenolol, timolol, metoprolol.
(2) Methysergide.
(3) Cyproheptadine.
(4) Pizotifen.
(5) Clonidine.
(6) Amitriptyline.
(7) Verapamil.
(8) Sandomigran.

ERGOTAMINE TARTARATE & DIHYDROERGOTAMINE

Mechanism of Action

(1) It is a strong serotonin antagonist, as well as a weak α - adrenoceptor blocker.
(2) It is also a partial agonist at β - adrenoceptors, & agonists at tryptaminergic & dopaminergic receptors.

Pharmacological Effects

(1) Anti - Migraine Effect

Vasoconstriction of cranial arteries induced by ergotamine, with consequent reduction in the amplitude of their pulsation is responsible for the relief of acute migraine attacks.

(2) Effect on Uterine Smooth Muscle

(a) In small doses, evokes rhythmic contraction & relaxation of uterus.
(b) At higher doses, induce powerful & prolonged contractions.

Clinical Uses

Acute migraine attacks.

Adverse Effects

(1) CNS: Drowsiness.
(2) CVS: Prolonged vasospasm resulting in gangrene, eg of arms, legs & bowel.
(3) GIT: Nausea, vomiting, diarrhea.
(4) Others: Fibroplastic changes in the retroperitoneal space, pleural cavity, & endocardial tissue of heart.

Contraindications

(1) Obstructive vascular disease.
(2) Collagen disease.

Dosage

(1) 6 mg, orally.
(2) 0.25 - 0.5 mg, intravenously or intramuscularly.

OTHER ANTIMIGRAINE DRUGS

(1) Aspirin & Paracetamol

See 'Chapter 9'.

(2) Metoclopramide

It is used in acute migraine attack for treating nausea & vomiting ; it also enhances aspirin absorption.
Note: For detail see 'Chapter 14'.

(3) Methysergide

Mechanism of Action

It is a strong antagonist of serotonin, inhibiting its vasoconstrictor & presser effect.

Clinical Uses

Prophylactic treatment of migraine.

Adverse Effects

Similar to ergotamine tartarate.

(4) Cyproheptadine

Mechanism of Action

It is a competitive antagonist of serotonin, blocking its vascular effects; also has weak anticholinergic activity.

Clinical Uses

(1) Prophylaxis of migraine.
(2) Pruritic dermatoses.

Adverse Effects

(1) CNS: Drowsiness.
(2) GIT: Dry mouth.

(5) Pizotifen

It blocks serotonin receptors, as well as have some H_1 - antihistamine & anticholinergic actions.

(6) Sandomigran

It is an antagonist of serotonin, histamine, bradykinin, & acetylcholine.

Clinical Uses

Prophylaxis of migraine.

Adverse Effects

CNS: Drowsiness.

GENERIC & TRADE NAMES

Ergotamine tartarate: Cafergot*.

Unit X

Self - Assessment (T/F)

(See answers on page no. 240)

(45) ***Following statements concerning benzo-diazepines are correct***
(A) Seizures occur with abrupt discontinuance after chronic use.
(B) Produces anxiety.
(C) In low doses, causes anesthesia.
(D) Contraindicated in psychoses.
(E) Has relatively high therapeutic index.

(46) ***Following statements concerning barbiturates are correct***
(A) Have a GABA - like action or enhances the effect of GABA.
(B) Induces hepatic microsomal drug metabolizing enzyme system.
(C) Acute barbiturate overdosage can be treated by acidification of urine.
(D) Phenobarbital is a short acting barbiturate.
(E) Contraindicated in advanced liver & renal disease.

(47) ***Concerning the clinical uses of sedative-hypnotics, following are correct***
(A) Diazepam is used for muscle spasticity in pts. with cerebral palsy.
(B) Chlordiazepoxide is useful in detoxification of alcoholic pts.
(C) Pentobarbital is used as IV adjuncts to surgical anesthetics.
(D) Chloral hydrate is used for hypnosis in young adults.
(E) Barbiturates are used for hyperbilirubinemia & kernicterus in neonate.

(48) ***Which one of the following best describes the mechanism of action of benzodiazepines***
(A) Blockade of excitatory actions of glutamic acid.
(B) Inhibition of GABA transaminase leading to inc. level of GABA.
(C) Activation of glycine receptors in spinal cord.
(D) Facilitation of GABA - mediated inc. in Cl ion conductance.
(E) Inc. in dopamine - stimulated adenyl cyclase activity.

(49) ***All of the following respond to treatment with benzodiazepines***
(A) Tetanus.
(B) Schizophrenia.
(C) Epileptic seizure.
(D) Insomnia.
(E) Anxiety.

(50) ***All of the following may occur after acute administration of ethanol***
(A) Myocardial depression.
(B) Sedation, slurred speech.
(C) Contraction of uterine smooth muscle.
(D) Alcoholic hepatitis.
(E) Hypothermia.

(51) ***All of the following are signs or symptoms of chronic ethanol use***
(A) Distal paresthesias.
(B) Gynecomastia & testicular atrophy.
(C) Fatty liver & hepatitis.
(D) Gastric irritation & bleeding.
(E) Dec. liver alcohol dehydrogenase levels.

(52) ***Drugs used in the treatment of partial seizures include***
(A) Valproic acid.
(B) Phenytoin.
(C) Ethosuximide.
(D) Carbamazepine.
(E) Primidone.

(53) ***Which of the following drugs is most likely to be effective in myoclonic seizures***
(A) Valproic acid.
(B) Phenobarbital.
(C) Phenytoin.
(D) Ethosuximide.
(E) Carbamazepine.

(54) ***Following drugs are effective in absence (petit mal) seizures***
(A) Clonazepam.
(B) Ethosuximide.
(C) Phenytoin.
(D) Valproic acid.
(E) Phenobarbital.

(55) ***All of the following statements concerning antiepileptic drugs are correct***
(A) Anticoagulants can displace phenytoin from its plasma protein binding sites.
(B) Carbamazepine induces hepatic microsomal drug - metabolizing enzyme system.
(C) Mechanism of action of carbamazepine involves block of Na ion channels in neuronal memb.

(D) Gastrointestinal distress is a common adverse effect of valproic acid.
(E) Sedation & development of physical dependence are serious problems with chronic use of ethosuximide in treatment of seizures states.

(56) ***All of the following statements concerning levodopa are correct***
(A) Choreoathetosis of face & distal extremities is an important adverse effect.
(B) Fluctuations in clinical response occur with increasing frequency as treatment continues.
(C) It effectively antagonizes akinesia & tremor caused by antipsychotic drugs.
(D) It should be avoided in pts with a history of melanoma.
(E) Pyridoxine increases its therapeutic effectiveness.

(57) ***Which of the following statements about carbidopa is accurate***
(A) It is dopa decarboxylase inhibitor.
(B) It cross the blood-brain barrier.
(C) It is converted to false transmitter, carbidopamine.
(D) When used with levodopa, it reduces the peripheral adverse effects of levodopa.
(E) It decreases the formation of dopamine in brain.

(58) ***All of the following statements about bromocriptine are accurate***
(A) It should not be administered to pts on anti-cholinergic drugs.
(B) It is contraindicated in pts with a history of psychosis.
(C) It has partial agonist activity at D_2 receptors.
(D) It inhibits synthesis & release of prolactin.
(E) It may cause dyskinesias.

(59) ***Clinical uses of antipsychotic drugs include***
(A) Schizophrenia.
(B) Manic episode in bipolar affective disorder.
(C) Epilepsy.
(D) Tourette syndrome.
(E) Amenorrhea - galactorrhea syndrome.

(60) ***Adverse effects of antipsychotic drugs include***
(A) Tardive dyskinesia.
(B) Orthostatic hypotension.
(C) Diarrhea.
(D) Altered endocrine function.
(E) Urinary retention.

(61) ***Regarding lithium, following statements are correct***
(A) It substitutes for Na in generating action potential.
(B) It stimulates norepinephrine sensitive adenyl cyclase.
(C) It is effective in bipolar affective disorders.
(D) Tremor is a common adverse effect.
(E) It may cause hypertension.

(62) ***Effects of tricyclic antidepressant drugs include all of the following***
(A) Sympathomimetic actions.
(B) Alpha - adrenoceptor blockade.
(C) Atropine - like effects.
(D) H_1 - receptor blockade.
(E) Elevation of seizure threshold.

(63) ***Clinical uses of antidepressant drugs include***
(A) Anxiety.
(B) Depression.
(C) Obsessive compulsive phobic states.
(D) School phobia.
(E) Bipolar affective disorders.

(64) ***Monoamine oxidase inhibitors include***
(A) Isocarboxazid.
(B) Imipramine.
(C) Nortriptyline.
(D) Tranylcypromine.
(E) Amoxapine.

(65) ***Which of the following statements about amphetamine is correct***
(A) It acts on alpha & beta adrenergic presynaptic terminals.
(B) It depresses hunger centre in hypothalamus.
(C) It is effective in narcolepsy.
(D) It causes miosis.
(E) It is contraindicated in pts. receiving MAO inhibitors.

(66) ***Following drugs are used for migraine prophylaxis***
(A) Ergotamine tartarate.
(B) Aspirin.
(C) Methysergide.
(D) Propranolol.
(E) Imipramine.

06 ANESTHETICS

Unit I

General Anesthetics

INTRODUCTION

General Anesthesia
It is a state which includes analgesia, amnesia, loss of consciousness, inhibition of sensory & autonomic reflexes, & skeletal muscle relaxation.

Balanced Anesthesia
It includes administration of medication preoperatively for sedation & analgesia, use of neuromuscular blocking drugs intra-operatively & use of both intravenous & inhaled anesthetic drugs.

Surgical Anesthesia
It is a degree of CNS depression sufficient to allow surgical operations to be performed.

Basal Anesthesia
It represents a degree of anesthesia short of surgical stage, ie, the pt. is unconscious but yet not sufficiently depressed for surgical operations.

Neuroleptanesthesia
It is a state of neuroleptanalgesia & unconsciousness, produced by the combined administration of a narcotic analgesic & a neuroleptic agent, together with the inhalation of nitrous oxide & oxygen.

Dissociative Anesthesia
It is a state of catatonia, amnesia & analgesia; pts feel totally dissociated from their surroundings.

SIGNS & STAGES OF ANESTHESIA

(A) Stage of Analgesia
It begins with administration of anesthetics & lasts till consciousness is lost.
(1) Initially there is analgesia without amnesia.
(2) Later, both analgesia & amnesia ensue.

(B) Stage of Excitement
It start after loss of consciousness & proceeds to the beginning of surgical anesthesia.
(1) Pt appears to be delirious & excited but is amnesic.
(2) Respiration is irregular both in volume & rate.
(3) Retching & vomiting may occur.
(4) Incontinence & struggling may occur.
(5) Pulse becomes rapid.
(6) BP inc. due to inc. level of circulating catecholamines.

(C) Stage of Surgical Anesthesia
It begins with recurrence of regular respiration & normal BP, & extends to complete cessation of spontaneous respiration. Subdivided into 4 planes ;

(1) Plane I
(a) Moving eyeballs.
(b) Pupils normal in size.
(c) Conjunctival reflex is abolished.
(d) Respiration is regular.

(2) Plane II
(a) Fixed eyeballs.
(b) Pupils constricted at first, but become dilated in lower plane II.
(c) Corneal reflex is abolished.
(d) Respiration is regular, but shallower than in plane I.

(3) Plane III
(a) Pupils are dilated.
(b) Light reflex is abolished.
(c) Lagging of thoracic respiration behind abdominal respiration.

(4) Plane IV
(a) Pupils are completely dilated.
(b) Light reflex is lost.
(c) At first, there is lagging of thoracic respiration behind the abdominal resp., & later cessation of respiration ensue.

(D) Stage of Medullary Depression
It starts by the cessation of respiration, & ends with the failure of circulation.

DRUG CLASSIFICATION

INHALATIONAL AGENTS

(1) Volatile liquids

(a) Ether
Diethylether, Divinylether.

(b) Halogenated Agents
Halothane, Desflurane, Sevoflurane Enflurane, Isoflurane, Methoxyflurane, Chloroform, Trichloroethylene, Ethyl chloride.

(2) Gases
Nitrous oxide, Cyclopropane.

INTRAVENOUS AGENTS

(1) Thiobarbiturates
Thiopental, Thiamylal, Methohexital.

(2) Benzodiazepines
Midazolam, Diazepam, Lorazepam.

(3) Opioid Analgesics
Fentanyl, Alfentanil, Remifentanil.

(4) Arylcyclohexylamines
Ketamine.

(5) Phenols
Disoprofol (Propofol).

(6) Imidazole
Etomidate.

(7) Miscellaneous
Dexmedetomidine, Propanidid.

MECHANISM OF ACTION OF GENERAL ANESTHETICS

(1) Inc. the threshold of cells to firing, resulting in dec. activity.
(2) Dec. the rate of rise of action potential by interfering with sodium influx.

HALOTHANE

PHARMACOLOGICAL EFFECTS

(A) Central Nervous System
(1) Cerebral blood vessels dilate, increasing cerebral blood flow & CSF pressure.
(2) As halothane anesthesia deepens, fast, low-voltage EEG waves are replaced by slow, high-voltage waves.
(3) Shivering occur during recovery.

(B) Cardiovascular System
(1) Dec. arterial blood pressure.
(2) Inc. cutaneous blood flow, as blood vessels dilate.
(3) Depressed myocardial contractility.
(4) Depressed cardiac sympathetic activity, resulting in bradycardia.
(5) Interferes with norepinephrine action, thus antagonizes the sympathetic response to arterial hypotension.
(6) Increases cardiac automaticity, esp. in the presence of adrenergic agonists, cardiac disease, hypoxia & electrolyte abnormalities.

Note: Surgical stimulation, hypercarbia & inc. anesthesia duration will lessen depressant effects of inhaled anesthetics.

(C) Respiratory System
(1) Respiration becomes rapid & shallow.
(2) Minute volume is reduced.
(3) Ventilatory response to CO_2 is dec. due to depression of central chemoreceptors.
(4) Bronchodilation occurs.
(5) Depresses airway mucociliary function, thus prolonged anesthesia may lead to pooling of mucus 2 Atelectasis & respiratory infections.

(D) Kidney
Dec. glomerular filtration rate & effective renal plasma flow, as renal vascular resistance is increased.

(E) Liver
(1) Dec. hepatic blood flow.
(2) Dec. hepatic function.

(F) Skeletal Muscle
(1) Relaxation occur by both central & peripheral mechanisms.
(2) Triggers malignant hyperthermia, in which in response to anesthesia, a sudden rapid rise in body temp. & signs of inc. muscle metabolism occur.

(G) Uterine Smooth Muscle
Relaxes uterine smooth muscle.

ADVERSE EFFECTS

(1) "Halothane hepatitis" can occur 2-5 days postoperatively, characterized by fever, anorexia, vomiting, eosinophilia & biochemical abnormalities.
(2) Postoperative jaundice.
(3) Hepatic necrosis.

ADVANTAGES

(1) Non-inflammable & non-explosive.
(2) Non-irritant to respiratory passages.
(3) Useful in pts. with asthma, due to its bronchodilating action.
(4) Useful in plastic surgery to produce a "bloodless area" thru inducing controlled hypotension.
(5) Safe for children.

DISADVANTAGES

(1) Inadequate muscle relaxation.
(2) CVS disturbances ie, hypotension, arrhythmias & bradycardia.
(3) Inhibition of uterus & dec. response to ergot & oxytocin; therefore, contraindicated during labor.
(4) Poor analgesics; so, commonly supplemented with nitrous oxide or ether.
(5) Expensive.
(6) Potential hepatotoxicity.
(7) Respiratory depression.

ENFLURANE

Pharmacological Effects

(A) Central Nervous System
(1) Cerebral blood vessels dilate, increasing cerebral blood flow & CSF pressure.

(2) Enflurane anesthesia lead to an EEG pattern characteristic of seizure activity or to frank seizures.

(B) Cardiovascular System

(1) Dec. arterial BP & dec. sympathetic response to arterial hypotension, similar to halothane.
(2) Depresses myocardial contractility, similar to halothane.
(3) Inc. in cardiac automaticity is less marked than with halothane.
(4) Tachycardia, either by altering sinus node depolarization or by shifting balance of ANS activity.

(C) Respiratory System

Similar to Halothane.

(D) Kidney

Similar to Halothane.

(E) Liver

(1) Lower incidence of liver impairment, usually reversible.
(2) Hepatic necrosis less commonly, esp. after repeated administration of enflurane.

(F) Skeletal Muscle

Similar to Halothane.

(G) Uterine Smooth Muscle

Similar to Halothane.

Advantages

(1) Non inflammable.
(2) Produces good muscle relaxation.
(3) Does not produce hepatotoxicity.
(4) Causes a lower incidence of arrhythmias.

Disadvantages

Causes seizure activity.

ISOFLURANE

Similar to Enflurane, except that it has no seizures activity.

METHOXYFLURANE

Advantages

(1) Non inflammable.
(2) Non irritant to respiratory passages.
(3) Excellent muscle relaxant & analgesic properties.
(4) Little or no postoperative vomiting.

Disadvantages

(1) Slow induction & recovery.
(2) Hypotensive action.
(3) Sensitization of myocardium to catecholamines.
(4) Postoperative diuresis, due to a specific nephrotoxicity affecting distal convoluted tubules.

CHLOROFORM

Advantages

(1) Non inflammable & non explosive.
(2) Non irritant to respiratory passages.
(3) Rapid pleasant induction.
(4) Good skeletal muscle relaxation.
(5) Cheap.

Disadvantages

(1) Narrow margin of safety.
(2) In induction stage, vagal bradycardia & cardiac arrest may occur.
(3) During excitement stage, myocardial sensitization to catecholamines may produce ventricular fibrillation.
(4) During surgical anesthesia, high conc. of chloroform in blood may directly depress myocardium with progressive fall in BP.
(5) During medullary paralysis, vasomotor centre is affected before the respiratory centre leading to circulatory insufficiency.
(6) Postoperatively vomiting, urinary retention & paralytic ileus may occur.
(7) Delayed chloroform poisoning occurs 24 hour after operation due to liver necrosis, characterized by vomiting, jaundice, acidosis & coma.

DIETHYL ETHER

Pharmacological Effects

(A) Central Nervous System

Dec. metabolic rate of brain, but inc. cerebral blood flow due to dec. cerebral vascular resistance.

(B) Cardiovascular System

(1) Depresses myocardium, directly.
(2) Cardiac output & arterial BP are maintained b/c of sympathetic stimulation.
(3) Tachycardia due to vagal blockade.

(C) Respiratory System

(1) Bronchodilation due to inc. sympathetic activity.
(2) Respiratory response to CO_2 is reduced, but is maintained spontaneously by reflex excitation at peripheral sites.

(D) Gastrointestinal Tract

(1) Nausea & vomiting during induction & recovery.
(2) Inhibition of tone & motility proportional to depth & duration of anesthesia.

(E) Kidney

Stimulate antidiuretic hormone release.

(F) Liver

Inc. glycogenolysis due to sympathetic stimulation.

(G) Skeletal Muscle

(1) Relaxation b/c it causes CNS depression at synaptic pathways in the spinal cord.
(2) Also has a curare-like action.

Advantages

(1) Wide safety margin.
(2) Good muscle relaxation.
(3) No significant CVS effects.
(4) Sufficiently potent to allow good oxygenation.
(5) Cheap.

Disadvantages

(1) Inflammable & explosive.
(2) Irritant to respiratory passages causing laryngospasm.

(3) Unpleasant slow induction & delayed recovery.
(4) Inc. salivation & vomiting.
(5) Pulmonary complications.
(6) Acidosis & hyperglycemia.
(7) Convulsions.

Contraindications

(1) Acute pulmonary disease or tuberculosis.
(2) Cautery of diathermy.
(3) Acidosis.
(4) Advanced renal or hepatic disease.
(5) Shock from trauma or hemorrhage.

NITROUS OXIDE

Alone, it is not effective as general anesthetic; so, usually supplement with opioids, thiopental & neuromuscular blockers.

Pharmacological Effects

(A) Cardiovascular System

Activation of symp. nervous system (when used with potent inhalational anesthetics) 2 Inc. total peripheral resistance & BP, & dec. cardiac output.

(B) Respiratory System

Similar to halothane except that, it causes dec. respiratory rate & inc. tidal volume.

Advantages

(1) Non explosive but supports combustion.
(2) Nonirritant to respiratory passages.
(3) Rapid induction & recovery.
(4) No adverse effects on circulation & respiration.
(5) Good general analgesic.

Disadvantages

(1) Not effective general anesthetic.
(2) Inadequate muscle relaxation.
(3) Diffusion hypoxia, during recovery.
(4) Distension of bowel, expansion or rupture of pulmonary cyst, rupture tympanic memb. in occluded middle ear, pneumocephalus.
(5) Air emboli.
(6) Post operative nausea & vomiting.

Contraindications

(1) Pregnancy.
(2) Immunosuppressed pts.
(3) Pernicious anemia.

CYCLOPROPANE

Advantages

(1) Rapid induction & recovery.
(2) Nonirritant to respiratory passages.
(3) Wide safety margin.
(4) Have little effect on CVS; so, it is the anesthetic of choice in shock.

Disadvantages

(1) Explosive & inflammable.
(2) Sensitizes myocardium to catecholamines.
(3) Postoperative hypotension.
(4) Atelectasis.
(5) Bronchospasm & respiratory centre depression leading to CO_2 accumulation.
(6) Nausea & vomiting.

NEUROLEPTANESTHETICS

Examples

(1) Droperidol & Fentanyl citrate.
(2) Innovar (a premixed combination of droperidol & fentanyl citrate).

Note: Nitrous oxide & Oxygen are added to these neuroleptanalgesics to produce neuroleptanesthesia.

Pharmacological Effects

(A) Cardiovascular System

(1) Droperidol produce mild α - adrenergic blockade 2 Hypotension.
(2) Fentanyl has parasympathomimetic effect 2 Bradycardia & hypotension.

(B) Respiratory System

(1) Droperidol dec. respiratory rate but inc. tidal volume.
(2) Fentanyl dec. both respiratory rate & tidal volume.
(3) Both has marked respiratory depressant effect.

Adverse Effects

(1) Post operative respiratory depression.
(2) Confusion & mental depression.
(3) Extrapyramidal symptoms.

KETAMINE

Produces dissociative anesthesia.

Pharmacological Effects

(A) Central Nervous System

(1) Inc. cerebral blood flow.
(2) Inc. cerebral oxygen consumption.
(3) Inc. intracranial pressure.

(B) Cardiovascular System

Heart rate, arterial BP & cardiac output are significantly inc. b/c of central symp. nervous system stimulation.

(C) Respiratory System

(1) Dec. respiratory rate slightly for 2-3 min.
(2) Upper airway muscle tone is well maintained.
(3) Upper airway reflexes are usually active.

Advantages

(1) Good analgesic & amnesic.
(2) No effect on laryngeal reflexes.
(3) Respiratory cycle is maintained near normal.
(4) Useful in pts with shock b/c of cardiostimulatory effect.
(5) Used in outpatient anesthesia.

Disadvantages

Recovery is accompanied by emergence delirium & psychomotor activity.

Contraindications

(1) Psychiatric disorders.

(2) Cerebrovascular disease.
(3) Respiratory infections.

ETOMIDATE

Advantages
(1) Rapid induction.
(2) Minimal cardiovascular & respiratory effects.

Disadvantages
(1) Myoclonia.
(2) Pain during injection.
(3) Postoperative nausea & vomiting.
(4) Embryocidal effect.

PROPANIDID

Advantages
Rapid induction & rapid recovery.

Disadvantages
(1) Hypotension, due to peripheral vasodilation & negative inotropic effect.
(2) Major epileptiform convulsion occur.

PROPOFOL

Advantages
Rapid induction & rapid recovery.

Disadvantages
(1) Causes nausea, vomiting, & dreaming.
(2) Muscle movement, hypotonus & tremors may occur.
(3) Hypersensitivity reactions, eg hypotension, flushing & bronchospasm may occur.

GENERIC & TRADE NAMES

(A) Inhalational Agents
Enflurane: Ethrane.
Halothane: Fluothane, Halothane.
Isoflurane: Forane.
Sevoflurane : Sevorane.

(B) Intravenous Agents
Benzodiazepines: See Chapter 5, Unit I.
Fentanyl: Durogesic TTS, Fentyl.
Ketamine: Calypsol, Ketasol.
Propofol: Diprivan, Propofol.
Thiopental: Pentothal Na.
Etomidate: Etomidate Lipuro.

Unit II

Local Anesthetics

DRUG CLASSIFICATION

(1) Esters
Cocaine, Procaine (Novocaine), Tetracaine (Amethocaine), Benzocaine, Chloroprocaine, Oxybuprocaine.

(2) Amides
Lidocaine (Xylocaine, Lignocaine), Mepivacaine, Bupivacaine, Levobupivacaine, Etidocaine, Prilocaine, Dibucaine, Ropivacaine, Proxymetacaine (Proparacaine).

(3) Both ester & amide
Articaine.

(4) Ethers
Pramoxine.

(4) Ketones
Dyclonine.

(5) Phenetidin Derivatives
Phenacaine.

(6) Alcohols
Ethyl alcohol, Benzyl alcohol.

(7) Miscellaneous
Ethylchloride, Eugenol (clove oil), Phenol.

MECHANISM OF ACTION OF LOCAL ANESTHETICS

Local anesthetics bind to receptors near intracellular ends of Na-channels 2 This result in blockade of Na current 2 Resulting in;
(1) Inc. threshold for excitation.
(2) Slow impulse conduction.
(3) Declining of rate of rise of action potential.
(4) Dec. action potential amplitude.
(5) Blockade of ability to generate action potential.

PHARMACOLOGICAL EFFECTS OF LOCAL ANESTHETICS

(1) Differential Nerve Block
(a) Fibres with smallest diameter are blocked first. Usual sequence is:
Type B (preganglionic fibres) 2 Type C (dorsal root pain fibres & sympathetic postganglionic fibres) 2 Type A delta (pain & temperature fibres) 2 Type A gamma (muscle spindle fibres) 2 Type A beta (touch & pressure fibres) 2 type A alpha (motor & proprioception fibres).
(b) Myelinated nerves blocked before unmyelinated nerves, eg, B fibres are blocked before the C fibres.
(c) In large nerve trunks, motor nerves are blocked first b/c they are located circumferentially.
(d) In extremities, proximal sensory fibres (located in mantle of nerve) are blocked before the distal sensory fibres (located in core).

(2) Effects on Other Excitable Membranes

(a) Weak neuromuscular blocker
(b) Similar depressant effect on cardiac cell memb.

CLINICAL USES OF LOCAL ANESTHETICS

(1) For Topical Anesthesia
Lidocaine, Tetracaine, Dibucaine, Procaine.

(2) For Infiltration Anesthesia
Lidocaine, Procaine, Prilocaine, Etidocaine, Mepivacaine, Articaine (specifically for dental local anesthesia).

(3) For Nerve Block Anesthesia
Lidocaine, Procaine, Mepivacaine, Chloroprocaine.

(4) For Spinal Anesthesia
Lidocaine, Procaine, Tetracaine, Prilocaine, Mepivacaine.

(5) For Epidural Anesthesia
Etidocaine.

(6) For Regional Anesthesia
Prilocaine, Etidocaine, Mepivacaine, Bupivacaine.

(7) For Treating Arrhythmias
Lidocaine.

ADVERSE EFFECTS OF LOCAL ANESTHETICS

(1) CNS
Euphoria, sleepiness, light headedness, visual & auditory disturbances, restlessness, nystagmus, shivering, convulsions, depression.

(2) CVS
Hypotension, cardiovascular collapse.
Note: Cocaine doesn't cause hypotension b/c it has vasoconstricting effect.

(3) Respiratory System
Respiratory failure secondary to CNS depression.

(4) Blood
Methemoglobinemia (prilocaine).

(5) Allergic Reactions

GENERIC & TRADE NAMES

(1) Procaine : Cardioplegia*.
(2) Benzocaine : Hitogen*.
(3) Oxybuprocaine: Medicaine, Novesin.
(4) Lidocaine: Anacaine, Epocain, Lignocain, Xylocaine.
(5) Bupivacaine: Abocain, Bupicain.
(6) Proparacaine : Alcaine.
(7) Ethylchloride : Ethylchloride spray.

Unit III

Self - Assessment (T/F)

(See answers on page no. 240)

(67) ***All of the following statements about halogenated anesthetics are accurate***
(A) All cause dec. hepatic & renal blood flow.
(B) All facilitate contraction of uterine smooth muscle.
(C) All cause dec. arterial pressure.
(D) All cause inc. in ventilatory response to CO_2.
(E) Halothane is useful in pts. with asthma.

(68) ***All of the following statements about inhalational agents are correct***
(A) Postoperative hepatitis is associated mostly with the use of isoflurane.
(B) Mild, generalized muscle twitching occurs with high doses of enflurane.
(C) Nitrous oxide is often used as a single agent in anesthesia.
(D) Induction & recovery are rapid with nitrous oxide.
(E) Methoxyflurane may causes postoperative diuresis.

(69) ***All of following statements concerning intravenous anesthetics are correct***
(A) Droperidol produces dissociative anesthesia.
(B) Ketamine is a cardiovascular depressant.
(C) Ketamine inc. cerebral blood flow.
(D) Propanidid may causes major epileptiform convulsions.
(E) Ketamine is used in outpatient anesthesia.

(70) ***Action of local anesthetics include***
(A) Blockade of voltage- dependent Na^+ channels.
(B) Preferential binding to resting channels.
(C) Slowing of axonal impulse conduction.
(D) Inc. in threshold for excitation.
(E) Blockade of slow Ca^{++} channels.

(71) ***Regarding the clinical uses of local anesthetics, following are correct***
(A) Lidocaine is useful for epidural anesthesia.
(B) Tetracaine is useful for topical anesthesia.
(C) Mepivacaine may be used for nerve block anesthesia.
(D) Lidocaine is useful for treating arrhythmias.
(E) Etidocaine is useful for spinal anesthesia.xcretion.

07 SKELETAL MUSCLE RELAXANTS

Unit I

Skeletal Muscle Relaxants

DRUGS CLASSIFICATION

(A) Neuromuscular Blockers

(1) Drugs Preventing Action of Released Acetylcholine

(a) Depolarizers
Suxamethonium (Succinylcholine), Decamethonium.

(b) Non - Depolarizers

(i) Isoquinoline derivatives: Tubocurarine, Atracurium, Cisatracurium, Metocurine, Doxacurium, Mivacurium.

(ii) Steroid derivatives: Pancuronium, Vecuronium, Pipecuronium, Rocuronium.

(iii) Others: Gallamine.

(2) Drugs Depressing Acetylcholine Output

(a) Inhibitors of Acetylcholine Synthesis
Hemicholinium, Triethylcholine.

(b) Inhibitors of Acetylcholine Release
Inc. Mg & PO_4 ions, lack of Ca^{++}, Procaine, Botulinum toxin.

(B) Spasmolytics (Central Muscle Relaxants)

(1) Diazepam (See Chapter 5, Unit I).
(2) Baclofen (GABA-mimetic at $GABA_B$ receptors).
(3) Tizanidine (α_2 agonist).
(4) Gabapentin & pregabalin (GABA analogs).
(5) Progabide ($GABA_A$ & $GABA_B$ agonists)
(6) Glycine (an inhibitory amino acid neurotransmitter).
(7) Idrocilamide & Riluzole (inhibitors of glutamatergic transmission).
(8) **Drugs used to treat acute local muscle spasm:** Chlorphenesin, Carisoprodol, Chlorzoxazone, Cyclobenzaprine, Metaxalone, Methocarbamol, Orphenadrine.

(C) Direct Skeletal Muscle Relaxants

(1) **Hydantoins**: Dantrolene.
(2) Botulinum toxin.

NEUROMUSCULAR BLOCKERS

MECHANISM OF ACTION

(A) Depolarizers

(1) Phase I Block (Depolarization)

The drug reacts with nicotinic receptors 2 Na-channels are opened causing endplate depolarization 2 This depolarization spreads causing fasciculations 2 B/c drugs is not metabolized rapidly, a flaccid paralysis results (b/c excitation- contraction coupling requires repolarization & repetitive firing to maintain muscle tension)

Note: Phase I block is potentiated by cholinesterase inhibitors & antagonized by tubocurarine.

(2) Phase II Block (Desensitization)

With continued drug exposure, memb. becomes repolarized again by acetylcholine as longs as blocking drug is present.

Reason: A nonexcitable area develops in investing muscle memb. which becomes repolarized shortly after drug arrival. This impedes centrifugal spread of impulses initiated by acetylcholine action on receptors.

Note: Phase II block is potentiated by tubocurarine & antagonized by cholinesterase inhibitors.

(B) Non-depolarizers

They act by competing with acetylcholine for nicotinic receptor sites at muscle end plate.

Note: Paralysis by nondepolarizers is potentiated by further administration of drug & antagonized by suxamethonium & cholinesterase inhibitors.

PHARMACOLOGICAL EFFECTS

(1) Skeletal Muscle

Skeletal muscle paralysis;

(a) Depolarizers

(i) Initially, transient muscle fasciculations occur esp. over the chest & abdomen.

(ii) This is followed by spreading paralysis. Arm, neck & leg muscles are involved before the facial & pharyngeal muscle. Respiratory muscle involvement occurs lastly.

(b) Non-depolarizers

Muscle are paralyzed in following order:

(i) Muscles innervated by cranial nerves.
(ii) Muscles of limbs & trunk.
(iii) Intercostal muscles.
(iv) Diaphragm.

Note : Recovery from muscle paralysis occurs in the reverse order.

(2) Cardiovascular System

(a) Depolarizers

Succinylcholine stimulates nicotinic receptors in both sympathetic & parasympathetic ganglia, & muscarinic receptors in SA-node. This causes;

(i) In low doses, negative inotropic & chrono-tropic effects.
(ii) With large doses, positive inotropic & chrono- tropic effects.

(b) Non-depolarizers

(i) Vecuronium, Doxacurium & Pipecuronium have no CVS effect.
(ii) Tubocurarine & to a much lesser extent Meto-curine, Atracurium & Mivacurium produce "hypotension." This result from histamine release & in larger doses from ganglionic blockade.
(iii) Gallamine & Pancuronium increases heart rate, primarily by vagolytic action & secondarily by sympathetic stimulation.

(3) Eye

Succinylcholine causes an inc. in intraocular pressure, which may be due to contraction of tonic myofibrils or transient dilatation of choroidal blood vessels.

(4) Gastrointestinal Tract

In muscular pts, fasciculations associated with succinylcholine cause an inc. in intragastric pressure. This may result in emesis.

(5) Histamine Release

Tubocurarine causes moderate while succinylcholine, metocurine, atracurium & mivacurium causes slight increase in histamine release.

(6) Hyperkalemia

Succinylcholine causes inc. release of K^+ into blood, that may result in cardiac arrest.

CLINICAL USES

(1) As surgical adjuvants to general anesthesia, for promoting skeletal muscle relaxation.
(2) For facilitation of endotracheal intubation, laryngo-scopy, bronchoscopy, & esophagoscopy.
(3) With electro-convulsant shock therapy, to prevent trauma.
(4) Treatment of tetanus & other convulsive states.
(5) Diagnosis of myasthenia gravis.
(6) For control of ventilation, in pts with ventilatory failure to eliminate chestwall resistance & ineffective spontaneous ventilation.

ADVERSE EFFECTS

(1) All Neuromuscular Blockers

(a) Resp: Prolonged apnea.
(b) Muscle: Skeletal muscle pain.

(2) Depolarizers

(a) Eye: Inc. intraocular pressure.
(b) CVS: Bradycardia, arrhythmias, cardiac arrest.
(c) Resp. tract: Inc. bronchial secretion.
(d) GIT: Inc. intragastric pressure, emesis.
(e) Temp: Malignant hyperthermia (when given with halothane).

(3) Tubocurarine, Metocurine, Atracurium & Mivacurium

(a) CVS: Hypotension.
(b) Resp. tract: Bronchospasm.

(4) Gallamine & Pancuronium

CVS: Tachycardia, hypertension.

DOSAGE

(1) Succinylcholine 2 0.5 - 1 mg/kg body weight, IV.
(2) Tubocurarine 2 0.12 - 0.4 mg/kg body weight, IV.
(3) Gallamine 2 Initially 80-120 mg by IV inj., & if necessary further doses of 20-40 mg may be given.
(4) Pancuronium 2 Initial doses 0.02-0.06 mg/kg, IV; incremental dose 0.01-0.02 mg/kg.
(5) Atracurium 2 0.3-0.6 mg/kg, IV.

BACLOFEN

Pharmacological Effects

(1) It is an active spasmolytic & acts as a GABA agonist at $GABA_B$ receptors.
(2) Also reduces pain in spasticity by inhibiting release of substance P in the spinal cord.

Adverse Effects

(1) CNS: Drowsiness, to which tolerance develops.
(2) CVS: Hypotension, CV depression.
(3) Resp: Respiratory depression.
(4) Muscle: Fatigue.
(5) Renal: Dysuria, frequency of micturition.

MEPHENESIN

Pharmacological Effects

(1) Skeletal muscle relaxation without inducing, sleep or loss of consciousness, by depressing transmission thru spinal & supraspinal polysynaptic pathways.
(2) Local anesthetic action preceded by local irritation.

Adverse Effects

(1) CNS: Dizziness, lassitude, muscle weakness, ataxia.
(2) Eye: Nystagmus, diplopia.
(3) GIT: Nausea, vomiting.
(4) Blood: Hemolysis.
(5) Renal: Hemoglobinuria.

DANTROLENE

Mechanism of Action

It reduces skeletal muscle strength by interfering with excitation-contraction coupling in muscle fibre, by inhibiting the release of activator Ca^{++} from sarcoplasmic reticulum.

Note: Motor units that contract rapidly are more sensitive to drug.

Clinical Uses

(1) To reduce spasticity.
(2) In malignant hyperthermia.

Adverse Effects

(1) CNS: Sedation.
(2) Skeletal muscle: Generalized muscle weakness.
(3) Liver: Hepatitis.

Dosage

Begin with 25 mg daily as a single dose orally, increasing to max. of 100 mg QID.

GENERIC & TRADE NAMES

(1) Neuromuscular Blockers

Succinyl choline: Leptosuccine, Muscolax, Pantolax, Suxamethonium.
Atracurium: Atrelax, Tracrium.
Pancuronium: Pancron, Pavulon.
Vecuronium: Norcuron, Veronium.
Rocuronium: Esmeron.
Procaine: Cardioplegia*.

(2) Spasmolytics

Diazepam: See Chapter 5, Unit I.
Baclofen: Baclorax, Lioresal.
Tizanidine: Azanid, Movax, Tizadin.
Gabapentin: Engaba, Entin, Gabin.
Pregabalin: Gabica.
Orphenadrine: Duragesic*, Flexar*, Medigesic*, Norflex, Norgesic*, Samerol N*.

Unit II

Self - Assessment (T/F)

(See answers on page no. 240)

(72) ***Characteristics of phase I depolarizing neuromuscular blockade include***
(A) Well- sustained tetanic tension.
(B) Marked muscarinic blockade.
(C) Muscle fasciculations in later stages of block.
(D) Potentiation by cholinesterase inhibitors.
(E) Antagonization by tubocurarine.

(73) ***All of the following may cause histamine release***
(A) Tubocurarine.
(B) Pancuronium.
(C) Atracurium.
(D) Succinylcholine.
(E) Vecuronium.

(74) ***Regarding adverse effects of neuromuscular blockers, following are correct***
(A) Tubocurarine causes hypertension.
(B) All causes skeletal muscle pain.
(C) Succinylcholine causes arrhythmias.
(D) Atracurium causes bronchodilation.
(E) All causes prolonged apnea .

08 OPIOID ANALGESICS & ANTAGONISTS

Unit I

Opioid Analgesics

DRUG CLASSIFICATION

OPIOID AGONISTS

(1) Natural Opium Alkaloids

(a) Phenanthrene Group

Morphine, Codeine.

(b) Benzylisoquinoline Group

Papaverine, Narcotine (Noscapine).

(2) Semi-Synthetic Opium Derivatives

(a) Morphine Derivatives

Hydromorphone, Oxymorphone, Heroin (Diacetyl morphin).

(b) Codeine Derivatives

Hydrocodone, Oxycodone, Dihydrocodeine, Pholcodine.

(3) Synthetic Opium Substitutes

(a) Phenylpiperidines

(i) **Strong agonists:** Meperidine, (Pethidine), Fentanyl, Sufentanil, Alfentanil, Remifentanil.

(ii) **Mild to moderate agonists:** Diphenoxylate, Loperamide,

(b) Phenylheptylamines

Methadone, Propoxyphene, Levomethadyl acetate.

(c) Morphinans

Levorphanol, Dextromethorphan.

OPIOID AGONIST - ANTAGONISTS & PARTIAL AGONISTS

(1) Phenanthrenes

Nalbuphine, Buprenorphine.

(2) Morphinans

Butorphanol.

(3) Benzomorphans

Pentazocine, Dezocine.

(4) Miscellaneous

Tramadol.

OPIOID AGONISTS

MECHANISM OF ACTION

Opioid analgesics bind with & stimulate specific opioid receptors in brain (ie, they mimic actions of endogenous chemicals, known as opiopeptins) 2 This results in inhibition of release of excitatory neurotransmitters from terminals of nerves containing nociceptive stimuli.

Neurotransmitters Showing Depressed Release

Acetylcholine, norepinephrine, dopamine, 5- hydroxy-tryptamine & substance P.

Endogenous Opioid Peptides

Methionine-enkephalin, leucine-enkephalin, dynorphine, neo-endorphins, dynorphine B, & β -endorphin

Opioid Receptor Types

(1) Mu («)

Mediates supraspinal analgesia, respiratory depression, euphoria & physical dependence, & is associated with morphine-like analgesia & euphoria.

Subtypes: μ_1 & μ_2

(2) Kappa (©)

Mediates analgesia, miosis & sedation, & is associated with pentazocine-like analgesia, sedation & miosis.

(3) Delta (¢)

Associated with alteration in effective behavior

(4) Sigma (±)

Associated with dysphoric, hallucinogenic & cardiac stimulant effects

Opioid Receptor Distribution

(1) Limbic system including amygdaloid nucleus & hypo-thalamus.
(2) Medial & lateral thalamus, & area postrema.
(3) Nucleus of tractus solitarius.
(4) Substantia gelatinosa, & other areas of spinal cord.

PHARMACOLOGICAL EFFECTS

(1) Central Nervous System

(a) Analgesia

(i) By raising threshold for pain sensation.
(ii) By changing pain perception, & reaction of pt. to pain.

(b) Euphoria

(i) Pt. in pain or addict experiences a pleasant floating sensation, & freedom from anxiety & distress.
(ii) Normal subjects experience dysphoric effects.

(c) Sedation

It consists of drowsiness, clouding of mentation, & some impairment of reasoning ability.

(d) Respiratory Depression

(i) It results from reduced responsiveness of respiratory centre in brainstem to blood levels of CO_2.

(ii) Inc. arterial CO_2 retention causes cerebral vasodilation resulting in inc. intracranial pressure.

(e) Cough Suppression

It results from suppression of cough centre located in nucleus of tractus solitarius.

(f) Miosis

It results from stimulation of Edinger-Westphal nucleus, causing pin-point pupils.

(g) Truncal Rigidity

Intensification of tone in large trunk muscles occur as a result of opioids' stimulating action at spinal cord level 2 Dec. thoracic compliance, & interference with respiration.

(h) Emesis

Stimulation of brainstem chemoreceptor trigger zone results in nausea & vomiting.

(2) Neuroendocrine

(a) Stimulate release of ADH, prolactin & somatotropin.

(b) Inhibit release of luteinizing hormone.

(3) Cardiovascular System

(a) No significant direct effect on CVS.

(b) Hypotension may occur if CVS is already stressed. This is due to peripheral arterial & venous dilation resulting from histamine release & central depression of vasomotor centre.

(c) Cerebral vasodilation due to respiratory depression causes inc. intracranial pressure.

(4) Gastrointestinal Tract

(a) Dec. intestinal propulsive peristalsis & stomach motility 2 Constipation.

(b) Spasmodic nonpropulsive contractions of gastrointestinal smooth muscle.

(c) Dec. gastric HCl secretion.

(5) Biliary Tract

(a) Constriction of biliary smooth muscles 2 Biliary colic.

(b) Constriction of sphincter of Oddi 2 Inc. biliary pressure, reflux of biliary & pancreatic secretions, & elevated plasma amylase & lipase levels.

(6) Urinary Tract

(a) Dec. renal plasma flow 2 Depressed renal function.

(b) Inc. ureteral & bladder tone.

(c) Inc. urethral sphincter tone 2 Urinary retention esp. in postoperative pts.

(7) Uterus

Dec. uterine tone 2 Prolong labor.

(8) Skin

Opioids produce flushing & warming of skin, sometime accompanied by sweating & itching. These effects results from opioids central effects as well as histamine release causing cutaneous vasodilation.

CLINICAL USES

(1) Analgesia

Used for relief of pain resulting from myocardial infarction, terminal illness, surgery, obstetrical procedures, cancer &, biliary & renal colics.

Note: For Biliary & renal colics strong agonist in inc. dose is used.

(2) For relief of dyspnea from pulmonary edema associated with left ventricular failure.

(3) Cough.

(4) Diarrhea.

(5) As premedicant drugs before anesthesia & surgery.

ADVERSE EFFECTS

(1) CNS

Inc. intracranial pressure, behavioral restlessness, tremulousness, hyperactivity (in dysphoric reaction).

(2) CVS

Postural hypotension esp. in hypovolemia.

(3) GIT

Nausea, vomiting, constipation.

(4) Resp

Respiratory depression.

(5) Renal

Urinary retention.

(6) Skin

Urticaria, itching (around nose).

(7) Tolerance

Manifests clinically after 2-3 weeks of frequent therapeutic doses:

(a) High degree of tolerance occur for analgesia, euphoria, dysphoria, mental clouding, sedation, resp. depression, antidiuresis, nausea, vomiting, & cough suppression.

(b) No tolerance occur for miosis & constipation.

(c) Cross-tolerance may occur among different opioid analgesics.

(8) Physical dependence

It results in withdrawal (abstinence) syndrome, if there is failure to continue administer drug.

Symptoms & signs: Rhinorrhea, lacrimation, yawning, chills, goose pimples, hyperventilation, hyperthermia, mydriasis, muscular aches, vomiting, diarrhea, anxiety, & hostility.

(9) Psychologic dependence

Effects such as euphoria, indifference to stimuli, sedation & a peculiar abdominal experience linked to intense sexual orgasm, leads to psychologic dependence.

CONTRAINDICATIONS

(1) With mixed agonist-antagonists opioids.

(2) Pts with head injuries.

(3) Pregnancy.
(4) Pts with impaired pulmonary function
(5) Liver disease.
(6) Pts with endocrine disease eg Addison's disease, myxedema.

DOSAGE

(1) Morphine 2 10 mg; SC, IM.
(2) Oxymorphone 2 1.5 mg; SC, IM.
(3) Methadone 2 120 mg; Orally, SC.
(4) Meperidine 2 60-100 mg; oral, SC, IM, IV.
(5) Fentanyl 2 0.1 mg; I M, IV.
(6) Levorphanol 2 2-3 mg; oral, IM.
(7) Codeine 2 30-60 mg; oral, IM.
(8) Oxycodone 2 4.5 mg; oral, IM.

OPIOID AGONIST – ANTAGONISTS & PARTIAL AGONIST

Examples

Pentazocine, Butorphanol, Buprenorphine, Nalbuphine, Tramadol.

Mechanism of Action

They competitively block mu receptors &, act as agonists on kappa & sigma receptors.

(1) Produce analgesia in the absence of opioid agonists.
(2) In the presence of agonists, they block many of the actions of latter drugs.

PENTAZOCINE

(1) It is kappa-agonist, with mu-antagonist properties.
(2) Pharmacological effects are nearly similar to morphine but has one-fifth analgesic properties.
(3) Produce psychomimetic effects eg, anxiety & hallucination.
(4) Cause less nausea & constipation.
(5) Unlike opioid agonists, it inc. pulmonary artery pressure & cardiac work, & causes hypertension & tachycardia.
(6) Respiratory depression is less pronounced.
(7) Due to its antagonistic activity, it is capable of precipitating withdrawal in agonist addicts.
(8) Tolerance to analgesia can develop.
(9) Both physical & psychological dependence can occur, but less than with agonists.

BUTORPHANOL

(1) It is kappa agonist.
(2) Pharmacological effects similar to Pentazocine.
(3) Unlike Pentazocine, it does not ppt. withdrawal synd. in opioid addicts.
(4) Unlike pentazocine & butorphanol, it does not cause adverse cardiac effects.
(5) Both physical & psychological dependence can occur.

NALBUPHINE

(1) It is kappa-receptor agonist, & mu-receptor antagonist.
(2) Produce analgesia equal to morphine.
(3) Produce withdrawal state in opioid addict.

TRAMADOL

(1) It is a centrally acting analgesic, predominantly via blockage of serotonin reuptake.
(2) Also a weak mu-receptor agonist.
(3) No clinically significant effect occurs on respiratory or cardiovascular systems.
(4) Used as an adjunct with pure opioid agonists in the treatment of chronic neuropathic pain.
(5) Adverse effects include nausea & dizziness.
(6) Contraindicated in epileptics.

HEROIN

(1) It is diacetylated morphine.
(2) It has more rapid onset & shorter duration of action than morphine.
(3) Its analgesic potency is greater than morphine.
(4) It is the most potent of all dependence producing drugs.

SIGNS & SYMPTOMS OF HEROIN POISONING

(1) Sleepiness, lethargy, or coma, depending on dose.
(2) Bradycardia & hypotension.
(3) Hypoventilation or apnea.
(4) Pin-point pupils.
(5) Skin cool; may show signs of IV or IM drug abuse with associated infectious disease complications.
(6) Dec. bowel sounds.
(7) Muscle tone flaccid; occasionally twitching, & rigidity.

TREATMENT OF HEROIN POISONING

(1) Administration of antagonist Naloxone; 1- 2 mg by IV, IM or SC inj., & repeated every 2-3 min. for 2-3 doses.
(2) Airway support.

TREATMENT OF HEROIN ADDICTS

(1) Drug Treatment

(a) Stop heroin & start giving methadone. Methadone suppress withdrawal symptoms which occur after stopping heroin, & it also satisfy craving for heroin without producing euphoria or somnolence.
(b) Then gradually reduce the dose of methadone, & finally withdraw it.

(2) Psychiatric Treatment

(a) Effects are made to remove the causes responsible for addiction.
(b) Contacts of addict with his antisocial associates should be stopped.
(c) He should be engaged in some job to keep him busy &, divert his mind to useful occupations.
(d) He is informed about the harmful effect of addiction on his health & the ruin it brings to his

family besides entailing risk of going to jail for his criminal acts.

GENERIC & TRADE NAMES

(1) Opioid Agonists

Papaverine: Spasmogin*.
Noscapine, Dextromethorphan, & Pholcodine: See Chapter 13, Unit III.
Fentanyl: Durogesic, Fentyl.
Diphenoxylate, & Loperamide: See Chapter 14, Unit III.
Dextropropoxyphene: Draphene, Paradecaphen, Algaphan*, Analphene*, Darvin*, Diagesic*, Distalgesic*, Femidol*, Jalgesic*.
Morphine: Magnus Mr, Morphine inj.
Codeine: Codar, Codogesic, Tempol C.
Pethidine: Pethidine inj.

(2) Opioid Agonist- Antagonists

Nalbuphine: Nalbine, Nalbinor, Nubain.
Buprenorphine: Buepron, Bunorfin, Bupregesic, Dorfene, Temgesic.
Butorphanol: Deocalm.
Pentazocine: Fortagesic*, Panto, Pentagesic, Pentazogon, Penzocine, Sosegon.
Tramadol: Nopa, Tamadol, Tradol, Tramal.

Unit II

Opioid Antagonists

OPIOID ANTAGONISTS

DRUG CLASSIFICATION

(1) Phenanthrene
Nalorphine, Naloxone, Naltrexone, Nalmefene.

(2) Morphinans
Levallorphan.

PHARMACOLOGICAL EFFECTS

(1) When given in absence of opioid agonists, they are almost inert at therapeutic doses; however, at higher dose antagonizes endogenous opiopeptins.
(2) When given to opioid-treated subject, they completely reverse opioid effects within 1-2 min.
(3) In acute opioid overdosage, they effectively normalize respiration, level of consciousness, pupil size, bowel activity, etc.
(4) In dependent subjects who appear normal while taking opioids, they almost instantaneously ppt. withdrawal synd.
(5) There is no tolerance to their antagonistic actions.

CLINICAL USES

(1) Acute opioid overdosage.
(2) As maintenance drug for addicts in treatment programs.
(3) Cerebrovascular disease, eg stroke.

DOSAGE

Naloxone 2 0.1-0.4 mg IV, which can be repeated as necessary.

GENERIC & TRADE NAMES

Naloxone: Nalox, Narcan.
Naltrexone: Trexan.

Unit III

Self - Assessment (T/F)

(See answers on page no. 240)

(75) ***All of the following statements about opioid analgesics are correct***
(A) They have no significant direct effects on heart
(B) They stimulate chemoreceptor trigger zone
(C) They relax the smooth muscle of bladder
(D) They dec. intestinal peristalsis
(E) They produce flushing & warming of skin

(76) ***Interaction of opioid analgesic with kappa receptors leads to all of the following***
(A) Sedation
(B) Cerebral vascular dilatation
(C) Euphoria
(D) Spinal analgesia
(E) Miosis

(77) ***With continued use of strong opioid analgesics, tolerance develops to all of the following effects***
(A) Constipation
(B) Analgesia
(C) Sedation
(D) Cough suppression
(E) Miosis

(78) ***Which of the following statements about pentazocine is incorrect***
(A) It is a mixed agonist-antagonist
(B) It precipitates withdrawal in agonist addicts.
(C) It produces less euphoria than morphine.
(D) It is often combined with morphine for maximal analgesic effects.
(E) High doses of pentazocine causes hypertension.

(79) ***Opioid antagonists include***
(A) Naloxone.
(B) Nalorphine.
(C) Levallorphan.

(D) Levorphanol.
(E) *Nalbuphine.*

09 NONSTEROIDAL ANTI-INFLAMMATORY DRUGS, NONOPIOID ANALGESICS, & ANTI-RHEUMATOID & ANTI-GOUT DRUGS

Unit I

NSAIDs

DRUG CLASSIFICATION

(A) Nonselective COX Inhibitors

(1) Salicylates
Acetyl salicylic acid (Aspirin), Salicylic acid, Na salicylate, Methyl salicylate, Choline salicylate, Mg salicylate, Na thiosalicylate.

(2) Propionic Acid Derivatives
Ibuprofen, Fenoprofen, Ketoprofen, Flurbiprofen, Indoprofen, Fenbufen, Carprofen, Tiaprofen, Naproxen, Oxaprozin.

(3) Substituted Anthranilic Acids
Meclofenamate, Mefenamic acid, Flufenamic acid, Tolfenamic acid.

(4) Phenylacetic Acids
Diclofenac Na, Diclofenac K.

(5) Acetic Acid Derivatives
Ketorolac, Etodolac.

(6) Indole Acetic Acids
Indomethacin.

(7) Sulfoxides
Sulindac.

(8) Pyrrolealkanoic Acid
Tolmetin.

(9) Pyrazolone Derivatives
Phenylbutazone, Apazone, Oxyphenbutazone, Dipyron (Metamizol).

(10) Oxicams
Piroxicam,Tenoxicam.

(11) Difluorophenyl Derivatives
Diflunisal.

(12) Naphthylacetic Acid Prodrug
Nabumetone.

(B) COX-2 Selective Inhibitors

(1) Sulfonamide
Celecoxib, Nimesulide.

(2) Bipyridine Derivatives
Etoricoxib.

(3) Enolcarboxamide
Meloxicam.

(4) Isoxazole
Valdecoxib.

ASPIRIN

MECHANISM OF ACTION

It irreversibly blocks both isoforms of cyclooxygenase (COX-1 & COX-2), thereby decreasing prostaglandin & thromboxane synthesis thru-out the body.

Note: COX-1 is primarily expressed in non-inflammatory cells, whereas COX-2 is expressed in activated lymphocytes, polymorphs & other inflammatory cells.

PHARMACOLOGICAL EFFECTS

(1) Anti-inflammatory

(a) Inhibits prostaglandin biosynthesis by irreversibly blocking 'cyclooxygenase' which catalyzes reaction of arachidonic acid to endoperoxide compounds.
(b) In high dose, also inhibits thromboxane A2 formation, by the same enzyme (cyclooxygenase) inhibition.
(c) Inhibits granulocyte adherence to damaged vasculature, stabilizes lysosomes, & inhibits migration of polymorphonuclear leukocytes & macrophages into inflammation site.
(d) Interferes with chemical mediators of kallikrein system.

(2) Analgesic

Aspirin reduces mild to moderate pain of varying cause, eg, of muscular, vascular & dental origin, postpartum states, arthritis & bursitis.

Mechanism

(a) Due to its anti-inflammatory effects.
(b) Due to depression of pain stimuli at subcortical site.

(3) Antipyretic

Aspirin reduces only elevated temperature.

Mechanism

(a) Inhibition of PGE_2 synthesis.
(b) Blockade of CNS response to interleukin-1.
(c) Vasodilation of superficial blood vessels causing inc. dissipation of heat.

(4) Platelets

Inc. bleeding time due to inhibition of platelet aggregation secondary to thromboxane synthesis inhibition.

(5) Cardiovascular System

(a) Peripheral vasodilation, at large doses.
(b) Vasomotor paralysis, at toxic doses.

(6) Respiration

(a) Inc. depth of respiration due to inc. in alveolar ventilation, resulting from inc. oxygen consumption, & CO_2 production in skeletal muscle.
(b) At higher doses, hyper-ventilation leading to respiratory alkalosis; however, compensation occur thru kidneys.
(c) At toxic doses, medullary respiratory centre depression resulting in uncompensated respiratory acidosis.

(7) Gastrointestinal Tract

(a) Aspirin stimulate chemoreceptor trigger zone in CNS, causing emesis.
(b) Produce dose-related gastric ulceration & hemorrhage.
(c) Inhibits gastric mucus secretion.
(d) Inc. gastric acid secretion, as it inhibits synthesis of PGI_2.

(8) Renal

(a) Inc. excretion of Na-urate resulting in uricosuria, at dosage above 5 g.
(b) Dec. excretion of Na-urate resulting in hyper-uricemia, at dosage below 2 g.

(9) Endocrine

(a) In very large doses, stimulates adrenal cortex steroid secretion, thru an action on hypothalamus.
(b) Causes competitive displacement of thyroxin & triiodothyronine from prealbumin leading to their enhanced rate of disappearance.
(c) Prolong gestational period during pregnancy, due to delay in onset of labor b/c of prostaglandin synthesis inhibition.

(10) Metabolic

(a) Aspirin uncouple oxidative phosphorylation.
(b) Large doses produce hyperglycemia & glycosuria.
(c) Reduce lipogenesis by blocking incorporation of acetate into fatty acids.

CLINICAL USES

(1) Mild to moderate pain eg, headache, arthritis, dysmenorrhea.
(2) Rheumatoid arthritis & other inflammatory joint conditions.
(3) Fever esp. acute rheumatic fever.
(4) Unstable angina (as prophylactic agent).
(5) Cataract.
(6) Gout.

ADVERSE EFFECTS

(1) CNS

(a) With higher doses 'Salicylism' occur characterized by tinnitus, dec. hearing, vertigo, headache, confusion, lassitude, drowsiness, hyperthermia, sweating, thirst.
(b) Still higher doses, causes hypernea.
(c) At toxic doses, respiratory alkalosis & later acidosis.

(2) CVS

Depressed cardiac function & peripheral vasodilation at toxic doses.

(3) GIT

Gastric intolerance, gastritis, upper gastrointestinal bleeding, vomiting (of central origin).

(4) Renal

Dec. glomerular filtration rate.

(5) Liver

Hepatitis.

(6) Hypersensitivity Reactions

Bronchoconstriction & shocks, occur in pts with asthma & nasal polyps.

Treatment of Salicylate Poisoning

(1) Induce emesis with ipecac syrup, or perform gastric lavage.
(2) Correct abnormal electrolyte imbalance & dehydration.
(3) Urine alkalinization.
(4) Dialysis.

CONTRAINDICATIONS

(1) Hemophilia.
(2) Pregnancy.
(3) Peptic ulcer.

DOSAGE

(1) Analgesic or antipyretic dose 2 300-600 mg, every 4 hours orally.
(2) Anti-inflammatory dose 2 4 g daily, orally, in 3 divided doses taken after meal.

DRUG INTERACTION

(1) Acetazolamide, NH_4CL & alcohol enhance salicylate intoxication.
(2) Aspirin displaces drugs from protein binding sites, eg, tolbutamide, chlorpropamide, NSAIDs, phenytoin, probenecid.
(3) It reduces pharmacologic activity of spironolactone, & antagonize effects of heparin.
(4) It competes with penicillin G for renal tubular secretion.

PROPIONIC ACID DERIVATIVES

Examples

Ibuprofen, Fenoprofen, Ketoprofen, Naproxen, Flurbiprofen, Indoprofen, Fenbufen, Carprofen, Oxaprozin..

Pharmacological Effects

(1) Anti-inflammatory (non-selective reversible blockage of cyclooxygenase).

(2) Analgesic (non-selective reversible blockage of cyclooxygenase).
(3) Antipyretic (non-selective reversible blockage of cyclooxygenase).
(4) Inhibits platelet aggregation.
(5) Inhibits prothrombin synthesis.

Clinical Uses
(1) Mild rheumatoid arthritis.
(2) Ankylosing spondylitis.
(3) Osteoarthrosis.
(4) Seronegative arthropathies.
(5) Periarticular disorders eg, bursitis, capsulitis of shoulder, tenosynovitis, sprains, strains & low back pain.
(6) Soft tissue injuries.
(7) Mild to moderate pain eg, dental pain, dysmenorrhea.
(8) Acute gout (Naproxen).

Adverse Effects
(1) CNS: Headache, dizziness, tinnitus, anxiety, aseptic meningitis.
(2) GIT: Gastrointestinal irritation and bleeding (less severe than with aspirin).
(3) Renal: Acute renal failure, interstitial nephritis, nephrotic syndrome.
(4) Skin: Rash, pruritus.
(5) Blood: Agranulocytosis, aplastic anemia.

Contraindications
(1) Active peptic ulcer.
(2) Nasal polyps.
(3) Angioedema.
(4) Bronchospastic reactivity to aspirin.

Dosage
(1) Ibuprofen 2 1200 - 1800 mg daily, orally in divided doses; max. 2400 mg.
(2) Fenoprofen 2 300 - 600 mg orally, TDS or QID; max. 3 g
(3) Naproxen 2 250 - 500 mg orally, BD.

INDOMETHACIN

Pharmacological Effects
Similar to propionic acid derivatives.

Clinical Uses
(1) Patent ductus arteriosus (Indomethacin).
(2) Acute gouty arthritis.
(3) Ankylosing spondylitis.
(4) Osteoarthritis of hip.
(5) Pericarditis.
(6) Rheumatoid arthritis.
(7) Bartter's syndrome.
(8) Not routinely used for analgesia or antipyresis.

Adverse Effects
(1) CNS: Headache, dizziness, confusion, depression, psychosis, hallucinations.
(2) CVS: Coronary vasoconstriction.
(3) GIT: Abd. pain, diarrhea, GI bleeding, pancreatitis.
(4) Blood: Thrombocytopenia, aplastic anemia.

Contraindications
(1) Nasal polyps.
(2) Angioedema.
(3) Asthma.
(4) Pregnancy.
(5) Psychiatric disorders.
(6) Peptic ulcer.

Dosage
(1) Indomethacin 2 Initially 200 μg BD, IM or IV; then 200 μg either daily or every other day in chronic cases.
(2) Sulindac 2 200 mg BD, orally.

PHENYLBUTAZONE

Pharmacological Effects
Similar to propionic acid derivatives.

Clinical Uses
(1) Rheumatoid arthritis.
(2) Ankylosing spondylitis.
(3) Acute gouty arthritis.
(4) Musculoskeletal disorders.
(5) Osteoarthritis.

Adverse Effects
(1) Eye: Optic neuritis.
(2) Ear: Deafness.
(3) Renal: Nephrotic synd., renal tubular necrosis.
(4) Liver: Hepatic necrosis.
(5) Skin: Exfoliative dermatitis.
(6) Blood: Agranulocytosis, aplastic anemia, hemolytic anemia.
(7) Allergic reactions

Dosage
100 - 200 mg, TDS.

KETOROLAC

Mechanism Of Action
Like most NSAIDs, ketorolac is a non-selective COX inhibitor.

Pharmacological Effects
Similar to propionic acid derivatives.

Clinical Uses
Short-term management of pain (up to five days maximum).

Adverse Effects
Similar to other NSAIDs.

Contraindications
(1) Hypersensitivity to ketorolac.
(2) In patients with nasal polyps, angioedema, bronchospastic reactivity or other allergic manifestations to aspirin or other NSAIDs.
(3) Renal dysfunction.

CELECOXIB

Mechanism Of Action

It is a highly selective COX-2 inhibitor (inhibition of prostaglandin production).

Pharmacological Effects

COX-2 selectivity allows celecoxib (& other COX-2 inhibitors) to reduce inflammation & pain, while minimizing gastrointestinal adverse effects that are common with non-selective NSAIDs.

Clinical Uses

(1) Osteoarthritis.
(2) Rheumatoid arthritis.
(3) Acute pain.
(4) Painful menstruation and menstrual symptoms.
(5) To reduce the number of colon & rectal polyps in patients with familial adenomatous polyposis.

Adverse effects

(1) Significantly lower incidence of gastrointestinal ulceration than traditional NSAIDs.
(2) Allergic reactions
(3) Increased risk for heart attack & stroke

Dosage

100 to 200 mg once or twice a day.

Unit II

Nonopioid Analgesics

DRUG CLASSIFICATION

(A) Aniline Derivatives

Acetaminophen (Paracetamol), Phenacetin.

(B) Nonsteroidal Anti-inflammatory Drugs

(1) Salicylates.
(2) Propionic acid derivatives.
(3) Indole acetic acids.
(4) Substituted anthranilic acids.
(5) Pyrrolealkanoic acids.
(6) Pyrazolone derivatives.
(7) Oxicams.
(8) Difluorophenyl derivatives.
(9) Carbazole derivatives.
(10) Phenylacetic acids.

Note: For detail of each drug group see previous unit.

ACETAMINOPHEN

Pharmacological Effects

(1) It is an effective analgesic & antipyretic agent.
Mechanism: Thru inhibition of prostaglandin synthesis in brain.
(2) It has no anti-inflammatory effect.

Clinical Uses

(1) Mild to moderate pain eg, headache, myalgia, post-partum pain.
(2) For analgesia in aspirin allergic pts.
(3) Fever.

Adverse Effects

(1) CNS
Dizziness, excitement, disorientation.

(2) Renal
Acute tubular necrosis.

(3) Liver
(a) At therapeutic doses, a mild inc. in hepatic enzymes.
(b) Ingestion of 15 g or more causes severe hepato-toxicity with central lobular necrosis. Early symptoms of hepatic damage include nausea, vomiting, diarrhea & abd. pain.

(4) Endocrine
Hypoglycemic coma.

(5) Hypersensitivity Reactions
Skin rashes, drug fever.

Treatment of Overdosage

(a) Stomach wash & administering activated charcoal.
(b) Hemodialysis, if begun within first 12 hrs of ingestion.
(c) Paracetamol antidote eg, Methionine, Acetylcysteine, Cysteamine HCI.

Contraindications

(1) Hypersensitivity to acetaminophen.
(2) Impaired hepatic functions.

Dosage

325 - 500 mg QID, orally.

GENERIC & TRADE NAMES (NSAIDS & NONOPIOID ANALGESICS)

(1) Nonselective COX Inhibitors

Aspirin: Anaprin, Ascard, Aspirin, Aspro, Dispirin, Empirin-S, Empirin comp, Epalcin*, Irzapyrin*, Lopirin, Meprogesic, Trigesic*.....
Methyl salicylate: Methyl salicylate, Wintogeno.
Choline salicylate: Bonjela*.
Ibuprofen: Anglofen, Brufen, Dolofen, Ibugen, Ibu-slow, Inflam, Profen, Ruberin, Rumafen.....
Ketoprofen: Ketonal, Mobifen, Oruvail, Profenid.
Flurbiprofen: Ansaid, Froben, Lubifen, Ocufen.
Tiaprofen: Surgam.
Naproxen: Aproxen, Flexin, Naprosyn, Naprox, Naptrol, Nepexen, Proxen, Synflex, Xenar CR.
Oxaprozin: Daypro.
Meclofenamate: Meclomen.
Mefenamic acid: Befenac, Dologin, Dolor, Doloran, Mefenamic acid, Mefgesic, Ponstan.....
Diclofenac K: Cataflam, Caflam, Deflam, Dolo K.
Diclofenac Na: Alcazar, Almiral, Artifen, Diclofen, Diclogesic, Dicloran, Diclozaf, Phlogin, Voltaren, Voren, Vurdon.....
Ketorolac: Toradol, Torapan.
Indomethacin: Anglocid, Camcocid, Elmetacin, Incin, Indocin, Indobid, Liometacen.
Phenylbutazone: Pharmazone, Wilzolid.
Dipyron: Dipyron, Elkopyron, Fibrex, Javalgin.

Piroxicam: Brexin, Feldene, Limbar, Paldon, Riacen, Rosiden, Roxicam.
Tenoxicam: Tenoxam, Tenoxim, Tenoxitil.
Nabumetone: Relifex.

(2) COX-2 Selective Inhibitors

Celecoxib: Articoxib, Celoxib, Nuzib, Osteoxib.
Nimesulide: Amsolide, Mesulid, Nimsulid, Nise.
Meloxicam: Articam,Melocam, Mobex, Synlox.
Valcecoxib: Vorteil.

(3) Aniline Derivatives

Acetaminophen: Anamol, Calpol, Coldene*, Coldrex*, Diagesic*, Disprol, Duragesic*, Kaypol, Medigesic*, Panadol, Panaram, Paracetamol, Samerol*.....

Unit III

Disease Modifying Anti-Rheumatic Drugs (DMARDs)

DRUG CLASSIFICATION

(1) Immunosuppressive Drugs

Methotrexate, Mechlorethamine, Chlorambucil, Cyclophosphamide, Cyclosporine, Azathioprine, Mycophenolate mofetil.

(2) 4- Aminoquinolines

Chloroquine, Hydroxychloroquine.

(3) Gold

Aurothiomalate, Aurothioglucose, Auranofin.

(4) Penicillin Metabolite

Penicillamine.

(4) TNF-~ Blockers

Adalimumab, Infliximab, Etanercept.

(5) Others

Sulfasalazine, Abatacept, Rituximab, Leflunomide, Anakinra.

GOLD

Examples

Aurothiomalate, Aurothioglucose, Auranofin.

Pharmacological Effects

(1) Alter morphologic & functional capabilities of macro-phages.
(2) Inhibit lysosomal enzyme activity.
(3) Reduces histamine release from mast cells.
(4) Inactivates first component of complement.
(5) Suppress phagocytic activity of polymorphs.
(6) Inhibits Shwartzman phenomenon.
(7) Aurothiomalate reduces number of circulating leukocytes.
(8) Auranofin inhibits release of PGE_2 from synovial cells &, release of leukotriene B_4 & C_4 from polymorphs.

Clinical Uses

Active progressive rheumatoid arthritis inadequately controlled by other NSAIDs.

Adverse Effects

(1) CNS: Nitritoid reactions characterized by headache, faintness, sweating & flushing; peripheral neuropathy.
(2) Eye: Corneal deposits of gold.
(3) GIT: Stomatitis, metallic taste in mouth, diarrhea, neuropathy.
(4) Resp. Tract: Pulmonary infiltrates.
(5) Renal: Proteinuria, nephrotic synd.
(6) Liver: Cholestatic jaundice.
(7) Skin: Pruritic dermatitis, skin pigmentation.
(8) Blood: Thrombocytopenia, leukopenia, pancytopenia, eosinophilia, aplastic anemia.

Contraindications

(1) Previous toxicity.
(2) Pregnancy.
(3) Serious liver impairment.
(4) Serious renal impairment.
(5) Blood dyscrasias.

Dosage

(1) Aurothiomalate & aurothioglucose 2 50 mg IM weekly until a total of 1000 mg has been injected.
(2) Auranofin 2 6 mg orally daily, increasing to 9 mg/d if a response is not seen after 3 months.

INFLIXIMAB

It is known as a "chimeric monoclonal antibody" (the term "chimeric" refers to the use of both mouse & human components of the drug i.e. murine binding F_{ab} domains & human constant F_c domains).

Mechanism Of Action

It blocks the action of the pleiotropic proinflammatory TNFα (tumor necrosis factor alpha) by binding to it & preventing it from signaling the receptors for TNFα on the surface of cells.
Note: TNFα is one of the key cytokines that triggers & sustains the inflammation response.

Pharmacological Effects

COX-2 selectivity allows celecoxib (& other COX-2 inhibitors) to reduce inflammation & pain, while minimizing gastrointestinal adverse effects that are common with non-selective NSAIDs.

Clinical Uses

(1) Rheumatoid arthritis.
(2) Ankylosing spondylitis.
(3) Juvenile chronic arthritis.
(4) Psoriatic arthritis.
(5) Psoriasis.
(6) Ulcerative colitis.
(7) Crohn's disease.
(8) Wegener's granulomatosis.
(9) Giant cell arteritis.

(10) Sarcoidosis.

Adverse effects

(1) CNS: Headache, demyelinating syndromes.
(2) CVS: Vaculitis.
(3) Resp: Upper respiratory tract infections, sinusitis, cough.
(4) GIT: Nausea, hepatitis.
(5) Blood: Leukopenia, activation of latent tuberculosis.
(6) Skin: Rash, infusion site reaction.

Dosage

3-5 mg/kg every 8 weeks, as an intravenous infusion.

GENERIC & TRADE NAMES

Immunosuppressive drugs: See Chapter 23.
4- Aminoquinolines: See Chapter 21.
Penicillamine: Vistamin.
Infliximab: Remicade.
Sulfasalazine: Salazine, Salazodine, Salazopyrin.
Rituximab: Mabthera.
Leflunomide: Ariva, Flunomid, Lenomide.

Unit IV

Anti - Gout Drugs

GOUT

It is a familial metabolic disease characterized by recurrent episodes of acute arthritis due to deposits of monosodium urate in joints & cartilages. It is associated with high serum level of uric acid & formation of uric acid calculi in kidneys.

DRUG CLASSIFICATION

(1) Colchicum Alkaloid
Colchicine.

(2) Nonsteroidal Anti-inflammatory Drugs
Aspirin, Naproxen, Indomethacin, Phenylbutazone, Ibuprofen.

(3) Uricosuric Agents
Probenecid, Sulfinpyrazone.

(4) Urate Synthesis Inhibitor
Allopurinol, Febuxostat.

COLCHICINE

Pharmacological Effects

(1) It relieves pain & inflammation of gouty arthritis in 12-24 hrs without altering metabolism or excretion of urates, & without other analgesic effects.
(2) It produces anti-inflammatory effects by binding to micro-tubular protein 'tubulin', thereby preventing its polymerization & leading to inhibition of leukocyte migration & phagocytosis.
(3) It also inhibits leukotriene B_4 formation.

Clinical Uses

(1) For prophylaxis & treatment of acute gouty arthritis.
(2) Mediterranean fever.
(3) Sarcoid arthritis.

Adverse Effects

(1) GIT: Nausea, vomiting, abd. pain.
(2) Appendages: Hair loss (alopecia).
(3) Bone marrow: Bone marrow depression.
(4) Skeletal muscle: Myopathy.
(5) Acute intoxication: Results from over dosage, & characterized by burning throat pain, bloody diarrhea, shock, hematuria, oliguria & CNS depression.

Dosage

(1) For treatment of acute attack 2 Initially 0.5 - 1 mg, followed by 0.5 mg every 2 hrs until pain is relieved or nausea & diarrhea appear.
(2) For prophylaxis 2 0.5 mg 1-3 times/d.

URICOSURIC AGENTS

Examples

Probenecid, Sulfinpyrazone.

Pharmacological Effects

(1) They lowers serum levels of uric acid by inhibiting proximal tubular reabsorption of uric acid.
(2) As a general inhibitor of tubular secretion of organic acids, probenecid will also inc. serum levels of other organic acids, eg penicillin.
(3) Sulfinpyrazone also inhibits prostaglandin synthesis & interferes with a number of platelet functions, including adherence to subendothelial cells.

Clinical Uses

(1) Chronic gout.
(2) To prolong effects of penicillin. (probenecid).
(3) As antithrombotic agent. (Sulfinpyrazone).

Adverse Effects

(1) GIT: Gastrointestinal irritation.
(2) Renal: Nephrotic synd. (probenecid).
(3) Blood: Aplastic anemia.
(4) Allergy: Rash, dermatitis.

Contraindications

Oliguria.

Dosage

(1) Probenecid 2 Started at 0.5 g orally daily in divided doses, progressing to 1 g daily after 1 week.
(2) Sulfinpyrazone 2 Started at 200 mg orally daily, progressing to 400 - 800 mg daily.

ALLOPURINOL

Mechanism of Action

Allopurinol & its metabolite alloxanthine, prevents terminal steps in uric acid synthesis by inhibiting xanthine oxidase, which converts xanthine or hypoxanthine to uric acid. Hyperuricemia is thus reversed by blockade of uric acid production.

Clinical Uses

(1) Chronic gout.
(2) Chronic myelogenous leukemia.
(3) Chronic lymphogenous leukemia.
(4) As antiprotozoal.

Adverse Effects

(1) CNS: Peripheral neuritis.
(2) Eye: Cataracts.
(3) GIT: Nausea, vomiting, diarrhea.
(4) Liver: Hepatotoxicity.
(5) Renal: Interstitial nephritis.
(6) Blood: Aplastic anemia.
(7) Skin: Pruritic maculopapular rash, exfoliative dermatitis, necrotizing vasculitis.
(8) Bone marrow: Bone marrow depression.
(9) Acute attacks of gout: Occur during initial therapy with allopurinol, due to active dissolution of microcrystalline deposits of sodium urate within subcutaneous tissue, resulting in transient periods of hyperuricemia & crystal deposition in joint tissue.
Note: To prevent this, colchicine is given simultaneously.

Dosage

100-300 mg/day, orally.

GENERIC & TRADE NAMES

Colchicine: Colchicine.
Allopurinol: Progout, Zyloric, Zynol.
NSAIDs: See Unit II.

Unit V

Self - Assessment (T/F)

(See answers on page no. 240)

(80) ***Important effects of aspirin includes***
(A) Reduction of fever.
(B) Reduction of prostaglandin synthesis in inflamed tissue.
(C) Medullary respiratory centre depression at toxic doses.
(D) Reduction of bleeding tendency.
(E) Tinnitus & vertigo.

(81) ***All of the following statements concerning ibuprofen are correct***
(A) It increases prothrombin synthesis.
(B) It is useful in ankylosing spondylitis.
(C) It relieves dental pain & dysmenorrhea.
(D) Agranulocytosis may occur as an adverse reaction.
(E) It is contraindicated in active peptic ulcer.

(82) ***Drugs that are useful in dysmenorrhea includes***
(A) Colchicine.
(B) Chloroquine.
(C) Ibuprofen.
(D) Aspirin.
(E) Naproxen.

(83) ***Drugs used in treatment of gout includes***
(A) Indomethacin.
(B) Allopurinol.
(C) Colchicine.
(D) Probenecid.
(E) Auranofin.

(84) ***Acetaminophen has all of the following properties***
(A) It has anti-inflammatory effect similar to aspirin.
(B) It reduces fever..
(C) It is useful for analgesia in pts. with hepatic disease.
(D) It may cause acute tubular necrosis .
(E) *It is an aspirin substitute in pts. with peptic ulcer.*

10 DRUGS AFFECTING BLOOD

Unit I

Anti - Anemics

ANEMIA

DEFINITION

It is a reduction in O_2 transporting capacity of blood, due to a reduction below normal limits of total circulating red cell mass & hemoglobin concentration.

CAUSES OF ANEMIA (CLASSIFICATION)

(A) Blood Loss
(1) Acute, eg due to trauma.
(2) Chronic, eg due to GIT lesions.

(B) Inadequate RBCs Production

(1) Deficiency of essential factors:
(a) Iron deficiency 2 Hypochromic microcytic anemia.
(b) Intrinsic factor deficiency 2 Pernicious anemia.
(c) Vit B_{12} or Folic acid deficiency 2 Megaloblastic anemia.

(2) Endocrine deficiency:
Dec. erythropoietin production

(3) Bone marrow invasion:
(a) Leukemia.
(b) Secondary carcinoma.

(4) Stem cells failure:
Aplastic anemia.

(5) Drugs:
(a) Chloramphenicol.
(b) Thiouracil.

(C) Increased RBCs Destruction (Hemolytic Anemia)

(1) Intra - erythrocytic defects:
(a) Hereditary spherocytosis.
(b) Thalassemias.

(2) Extra - erythrocytic abnormalities:
(a) Erythroblastosis fetalis.
(b) Transfusion reactions.
(c) Malaria.

CLASSIFICATION OF ANTI - ANEMICS

(A) Drugs for Iron - Deficiency Anemia

(1) Oral Iron Preparations
Ferrous sulfate, Ferrous gluconate, Ferrous fumarate, Ferric ammonium citrate, Ferric choline citrate, Ferrous succinate, Ferric pyrophosphate, Sodium iron edetate, Iron polymaltose,

(2) Parenteral Iron Preparations
Iron dextran, Iron-sorbitol-citric acid complex, Iron sorbitol, Iron polysaccharide complex, Iron protein succinylate, Iron sucrose.

(B) Drugs for Megaloblastic Anemia
(1) Vit B_{12} (Cyanocobalamin & Hydroxocobalamin).
(2) Folic acid.

(C) Hematopoietic Growth Factors
(1) Erythropoietin.
(2) Darbepoetin alfa.

IRON (Fe)

DAILY IRON REQUIREMENTS

(1) Men: 0.5 - 1 mg.
(2) Menstruating women: 2 mg.
(3) Pregnant women: 5 - 6 mg.

PHARMACOKINETICS

(A) Absorption

(1) Form
Ferrous (Fe^{+2}) is more readily absorbed than ferric (Fe^{+3}).

(2) Site
Duodenum & proximal jejunum.

(3) Process
By active transport across the intestinal mucosal cells.
Note: In the intestinal mucosal cells Fe^{+2} is converted into Fe^{+3}.

(4) Fate
(a) Transported to plasma via transferrin.
(b) Converted to ferritin & stored in mucosal cells.

(B) Distribution
(1) Iron is transported in the plasma bound to transferrin, from intestinal mucosal cells or from

storage sites in liver or spleen, to developing erythroid cells in bone marrow.

(2) Transferrin receptors present on proliferating erythroid cells, bind the transferrin-iron complex & internalize iron, releasing it within the cells.

(C) Storage

(1) Forms

(a) Ferritin.
(b) Hemosiderin.

(2) Sites

Macrophages in liver, spleen, & bone marrow.

(D) Elimination

(1) About 1 mg Fe is lost by exfoliation of intestinal mucosal cells into stool.
(2) Trace amounts are excreted in bile, urine, & sweat.

(E) Regulation of Pharmacokinetics

(1) By the amount of storage Fe present (inversely related).
(2) By the rate of erythropoiesis (directly related).

MECHANISM OF ACTION

Fe combines with protoporphyrin IX & forms heme 2 4 heme combines with polypeptide (globin) to form hemoglobin chain (α or β) 2 2α combines with 2β chains to form hemoglobin A.

CLINICAL USES

Treatment or prevention of iron deficiency anemia.

(A) Oral Iron Preparations

Used for Fe deficiency in;

(1) Infants.
(2) Children during rapid growth periods.
(3) Pregnant & lactating women.

(B) Parenteral Iron Preparations

Reserved for;

(1) Pts with documented Fe def., unable to tolerate or absorb oral Fe.
(2) Pts with extensive chronic blood loss, due to;
  (a) Postgastrectomy conditions.
  (b) Small bowel resection.
  (c) Inflammatory bowel disease involving proximal small bowel.
  (d) Malabsorption syndromes.
  (e) Hereditary hemorrhagic telangiectasia.

ADVERSE EFFECTS

(A) Adverse Effects With Usual Dosage

(1) Oral Iron Preparations

GIT: Nausea, epigastric discomfort, abdominal cramps, constipation, diarrhea.

(2) Parenteral Iron Preparations

(a) CNS: Headache, light-headedness.
(b) Resp tract: Bronchospasm.
(c) GIT: Nausea, vomiting.
(d) Musculo-skeletal: Local pain & tissue staining, arthralgia, back pain.
(e) Skin: Fever, flushing, urticaria.
(f) Hypersensitivity: Anaphylaxis.

(B) Acute Iron Toxicity

Seen in young children who have accidently ingested iron tablets.

Fatal Dose

10 tablets.

Clinical Features

(1) Necrotizing gastroenteritis, with vomiting, abdominal pain, & bloody diarrhea.
(2) Followed by shock, lethargy, & dyspnea.
(3) Followed by improvement or, severe metabolic acidosis, coma, & death.

Treatment

(1) Gastric aspiration.
(2) Gastric lavage with carbonate solution.
(3) **Antidote:** Deferoxamine, parenterally.
(4) Supportive therapy for GIT bleeding, metabolic acidosis, & shock.

(C) Chronic Iron Toxicity

Occur in pts with hemochromatosis or, with many red cell transfusions.

Clinical Features

Hemochromatosis & Hemosiderosis

Excess iron deposition occur in heart, liver, pancreas & other organs 2 Organ failure & death.

Treatment

(1) Intermittent phlebotomy.
(2) **Drugs:** Deferasirox, Deferoxamine.

DOSAGE

(1) Oral Preparations

Ferrous sulfate (325 mg tab), Ferrous gluconate (320 mg tab), or Ferrous fumarate (200 mg tab) 2 3-4 tab per day.

(2) Parenteral Preparations

Iron-sorbitol-citric acid complex 2 1.5 mg/Kg IM as single daily dose; max. 100 mg per inj.

VITAMIN B_{12}

DAILY B_{12} REQUIREMENTS

2 μg in both sexes.

PHARMACOKINETICS

(A) Absorption

(1) Vit. B_{12} binds with intrinsic factor, a glycoprotein secreted by parietal cells of gastric mucosa.
(2) Intrinsic factor- B_{12} complex is absorbed in distal ileum by a highly specific receptor-mediated transport system.

(B) Distribution

Vit. B_{12} is transported to various body cells bound to a plasma glycoprotein, transcobalamin II.

(C) Storage

Excess vit. B_{12} (upto 300-500 μg) is stored in liver.

(D) Elimination

(1) Only trace amounts of vit. B_{12} are normally lost in urine & stool.
(2) Significant amount of vit. B_{12} are excreted in urine, when large amounts are given parenterally.

MECHANISM OF ACTION

(1) Act as a cofactor in the conversion of methylmalonyl-CoA to succinyl -CoA by the enzyme methylmalonyl-CoA mutase.
Effects of B_{12} Deficiency
Methylmalonyl -CoA accumulates 2 Abnormal fatty acid synthesis & incorporation into cell memb. 2 Demyelination of neurons.
(2) Act as a cofactor in the conversion of 5 - CH_3 - H_4 folate & homocysteine, to H_4 folate & methionine, by the enzyme 5 - CH_3 - H_4 folate - homocysteine methyl-transferase.
Effect of B_{12} Deficiency
5 - CH_3 - H_4 folate accumulates 2 Deficiency of folate cofactors 2 Dec. DNA synthesis 2 Megaloblastic anemia.

CLINICAL USES

Box 10.1 CAUSES OF VIT B12 DEFICIENCY

1) Deficiency of intrinsic factor (as in gastric atrophy) 2 Pernicious anemia
2) Defects in absorption of intrinsic factor - B_{12} complex in distal ileum
3) Partial or total gastrectomy
4) Malabsorption syndromes
5) Inflammatory bowel disease
6) Small bowel resection
7) Nutritional deficiency (seen in strict vegetarian)
8) Congenital absence of transcobalamin II

Treatment or prevention of vit B_{12} deficiency conditions, eg
(1) Megaloblastic anemia.
(2) Pernicious anemia.
(3) Neuropathy.

ADVERSE EFFECTS

No; b/c large doses are promptly excreted in urine.

DOSAGE

(1) Initially 2 100 - 1000 µg 1M, daily or every other day for 1-2 weeks.
(2) Maintenance therapy 2 100-1000 µg 1M, once a month (for life).
(3) In neuropathy 2 Injections should be given every 1-2 weeks for 6 months before switching to monthly inj.

FOLIC ACID

DAILY FOLIC ACID REQUIREMENTS

50 µg in both sexes.

PHARMACOKINETICS

(A) Absorption

(1) Form

Dietary folates in polyglutamte forms, first undergo hydrolysis by conjugase (present in brush border of intestinal mucosa) &, form monoglutamate 5 - CH_3 - H_4 folate that is readily & completely absorbed.

(2) Site

Proximal jejunum.

(B) Distribution

Widely distributed thru-out the body via blood stream.

(C) Storage

Normally, 5 - 20 mg is stored in liver & other tissues.

(D) Elimination

Excreted in urine & stool, & also destroyed by catabolism.

MECHANISM OF ACTION

Folic acid (H_4 folate) is a precursor of several folate cofactors, which are essential for one-carbon transfer reactions necessary for DNA synthesis, eg:
(1) Synthesis of thymidylic acid from deoxyuridylate.
(2) Synthesis of purine.

CLINICAL USES

Treatment or prevention of folic acid deficiency, which causes megaloblastic anemia.

ADVERSE EFFECTS

No; b/c it is promptly excreted in urine.

Box 10.2 CAUSES OF FOLIC ACID DEFICIENCY

1) Inadequate dietary intake
2) Liver disease
3) Pregnancy
4) Hemolytic anemia
5) Sprue & other malabsorption syndrome
6) Cancer , leukemia, & myeloproliferative disorders
7) Pts on renal dialysis
8) Drugs eg, Phenytoin, isoniazid, oral contra-ceptives, methotrexate

DOSAGE

1 mg orally, daily.

ERYTHROPOIETIN

Pharmacological Effects

Erythropoietin stimulates erythroid proliferation & differentiation, by interacting with specific erythropoietin receptors on red cell progenitors in bone marrow.

Note: Endogenously it is secreted by kidney in response to hypoxia.

Clinical Uses
Treatment of renal failure pts with significant anemia.

Adverse Effects
(1) CVS: Hypertension, thrombotic complications.
(2) Allergic reactions

TREATMENT OF OTHER ANEMIAS

Blood Loss Anemia
(1) Acute Loss
Blood volume replacement by transfusion of whole blood, red cell concentrates, plasma, or plasma substitutes.
(2) Chronic Loss
Iron supplements.

Aplastic Anemia
(1) Bone marrow transplantation
(2) Replacement therapy
  (a) Red cell concentrates
  (b) Platelet transfusion
  (c) Antibiotic
(3) Androgenic steroids or erythropoietin
(4) Prednisolone

Hemolytic Anemias
(1) Removal of causative agents
(2) Blood transfusion
(3) Folic acid supplements
(4) Prednisolone
(5) Splenectomy
(6) Bone marrow transplantation
(7) Antimalarials

GENERIC & TRADE NAMES

(A) Iron
Ferrous Sulfate: Blissferon, Fer-in-sol, Ferrous Sulfate, Iberet, Unifer.
Ferrous Gluconate: Ferrous Gluconate, Feglone.
Ferrous Fumarate: Ferovis, Givitol.
Na Iron Edetate: Sytron.
Iron-Sorbitol-Citric Acid Complex : Iprafer forte, Jectosol.
Iron polymaltose: Apofer, Biofer, Fermalose, Indofer.
Iron polysaccharide complex: Ferricure.
Iron protein succinylate: Ferplex, Succiron.
Iron sucrose: Ivefer, Venofer.

(B) Vit B_{12}
Cyanocobalamin: Cyanoplex, Cyanovit, Cyomin, Cytacon, Cytamen, Elkomin, Vit B_{12}.

(C) Folic Acid
Delfol, Folitab, Folic Acid, Folacin.

(D) Iron- Vit B_{12} Combinations
Iberet-500, Incremin.

(E) Iron-Folic Acid Combinations
Apofer F, Ferlip-F, Ferrum FA, Ferry F, Giofer F, Maltofer Fol, Iberet Folic-500 Gradumet*.

(F) Iron - B_{12} - Folate Combinations
Iberol-F*, Theragran-H*, Tri-Hemic 600*.

(G) Erythropoietin
Epokine, Eprex, Hemax.

Unit II

Anti - Coagulants

INTRODUCTION TO HEMOSTASIS

HEMOSTASIS
It is the spontaneous arrest of bleeding from a damaged vessel.

Hemostatic Response
(1) Vasospasm
Occur immediately following damage to a vessel.
(2) Formation of Platelet Plug
(a) Within seconds, platelets stick to exposed collagen of damaged endothelium & to each other 2 Platelet plug.
(b) Platelets releases several factor eg, ADP, TXA_2 & serotonin, which cause further platelets aggregation & vasoconstriction.
(c) Aggregated platelet plug make available platelet factor 3 for coagulation sequence to take place.
(3) Fibrin Reinforcement of Platelet Plug
Coagulation system, activated by intrinsic or extrinsic pathway, leads to cascade of reactions that causes conversion of proenzymes (inactive coagulation factors) into activated enzymes (activated coagulation factors or proteases) 2 Finally Xa (activated factor X) is produced 2 Xa converts prothrombin (factor II) into thrombin (factor IIa) 2 Thrombin converts fibrinogen (factor I) into fibrin 2 Fibrin molecules polymerize to form fibrin threads which cement platelet plug.

NATURAL ANTICOAGULANTS OF BODY
(A) Fibrin Inhibition System
Plasma contains protease inhibitors that rapidly inactivate coagulation proteins as they escape from site of vessel injury; include,
(1) Antithrombin III
(2) α_1 - antiprotease
(3) α_2 - macroglobulin
(4) Protein C & S
(B) Fibrinolysin System

Plasminogen is activated by factor XII - dependent pathway or by plasminogen activator (eg urokinase - like PA & tissue - type PA) into plasmin 2 Plasmin breaks down fibrin (fibrinolysis).

CLASSIFICATION OF ANTI - COAGULANTS

These are drugs that prevent coagulation of blood.

(1) Oral Anti-Coagulants
Warfarin Na, Dicumarol, Phenindione.

(2) Indirect Thrombin Inhibitors
Antithrombotic effect is exerted via antithrombin; eg , Unfractionated heparin, Low-molecular-weight heparin (Dalteparin, Enoxaparin), Fondaparinux, Tinzaparin.

(3) Direct Thrombin Inhibitors
Antithrombotic effect is exerted by direct binding to the active site of thrombin; eg , Hirudin, Bivalirudin, Lepirudin, Argatroban, Ximelagatran.

(4) Fibrinolytic (Thrombolytic) Drugs
Drugs that lyse fibrin or thrombi; eg , Streptokinase, Urokinase, Anistreplase, Tissue plasminogen activator (t - PA), Reteplase, Tenecteplase.

(5) Anti-Thrombotic Drugs
Drugs that inhibits platelet aggregation; eg , Aspirin, Clopidogrel, Dipyridamole, Ticlopidine, Abciximab, Eptifibatide, Tirofiban, Cilostazol.

WARFARIN

MECHANISM OF ACTION

It blocks γ - carboxylation of several glutamate residues in prothrombin & factors VII, IX, X, & endogenous anticoagulant protein C 2 This results in incomplete molecules that are biologically inactive in coagulation.

CLINICAL USES

Secondary prophylactic treatment of venous thrombosis & pulmonary embolism.

ADVERSE EFFECTS

(1) CVS
Bleeding, purpura, fall in hematocrit.

(2) GIT
Diarrhea.

(3) Skin
- **(a) Warfarin necrosis:** It is a painful erythematous patch on skin, which can progress to gangrene; occur during 1st week of therapy.
  Note: Same process may causes frank infarction of breast, fatty tissues, intestine, & extremities.
- **(b) Purple toe syndrome:** It is caused by cholesterol emboli from atheromatous plaques, following bleeding into plaques; occur 3-8 weeks after starting therapy.
- **(c) Rash, alopecia**

(4) Pregnancy
Warfarin readily crosses placenta, & causes hemorrhagic disorders & bony abnormalities in fetus.

Treatment

(1) Stop the drug.
(2) **Antidote:** Vit K_1 (Phytonadione).
(3) Fresh - frozen plasma (FFP), or factor IX concentrates.

CONTRAINDICATIONS

(1) Hemorrhagic conditions.
(2) Impaired renal or hepatic function.
(3) Within 24 hours of surgery or labor.
(4) Pregnancy.
(5) Bacterial endocarditis.
(6) Active tuberculosis.
(7) Recent head trauma.
(8) Neurosurgery.

DRUG INTERACTIONS

(A) Drugs that Inc. Warfarin Effect

(1) Pharmacokinetically
Amiodarone, Cimetidine, Disulfiram, Metronidazole, Miconazole, Phenylbutazone, Sulfinpyrazone, Trimethoprim - sulfamethoxazole.

(2) Pharmacodynamically
Aspirin, Cephalosporins (3rd generation), Heparin.

(B) Drugs that Dec. Warfarin Effect

(1) Pharmacokinetically
Barbiturates, Cholestyramine, Rifampin.

(2) Pharmacodynamically
Diuretics, Vit K.

DOSAGE

(1) Initially: 2-5 mg daily for about 1 week.
(2) Maintenance dose: 5-7 mg/day.

HEPARIN

MECHANISM OF ACTION

Heparin bind tightly to plasma protease inhibitor antithrombin III & cause a conformational change in it 2 This results in exposure of antithrombin's active site, for more (about 1000 - fold) rapid interaction with clotting factor proteases, which forms equimolar stable complexes with proteases 2 This causes inhibition of clotting factor proteases (thrombin, factor IXa, Xa, XIa & XIIa) 2 Fibrin formation is abolished.

CLINICAL USES

(1) Prophylaxis of venous thrombosis in;
  (a) Pts undergoing elective surgery.
  (b) Acute phase of myocardial infarction.
(2) Treatment of established venous thrombosis or pulmonary embolism.

ADVERSE EFFECTS

(1) CVS: Bleeding, paradoxical thromboembolism.
(2) Blood: Transient thrombocytopenia.
(3) Bone: Osteoporosis, spontaneous fractures.
(4) Skin: Transient alopecia.
(5) Hypersensitivity reactions: Chills, fever, urticaria, anaphylaxis.

Antidote

Protamine sulfate.

CONTRAINDICATIONS

(1) Pts hypersensitive to heparin.
(2) Pts with active bleeding.
(3) Hemophilia.
(4) Thrombocytopenia.
(5) Purpura.
(6) Severe hypertension.
(7) Intracranial hemorrhage.
(8) Infective endocarditis.
(9) Active tuberculosis.
(10) Ulcerative lesions of GIT.
(11) Threatened abortion.
(12) Visceral carcinoma.
(13) Advanced hepatic or renal disease.
(14) During or after surgery of brain, spinal cord, or eye.
(15) Pts undergoing lumbar puncture or regional anesthesia.

DOSAGE

(1) For Established Disease

(a) Initial IV bolus inj. of 5000 - 10,000 units.
(b) Followed by continuous infusion of 900 units/hr or 10 - 15 units/Kg/hr,
or
Intermittent IV administration of 75-100 units/kg every 4 hours.

Note: This therapy is continued for 7-10 days, with a 3-5 day overlap with warfarin; then warfarin is continued for 6 weeks to 6 months.

(2) For Prophylaxis

5000 units SC, TDS or BD.

FIBRINOLYTIC (THROMBOLYTIC) DRUGS

EXAMPLES

Streptokinase, Urokinase, Anistreplase, t - PA.

MECHANISM OF ACTION

They act either directly or indirectly (thru proactivator plasminogen) to convert endogenous plasminogen to plasmin (a protease) 2 Plasmin cleaves fibrin, & thus thrombus is dissolved.

CLINICAL USES

(1) Multiple pulmonary emboli.
(2) Central deep vein thrombosis, eg superior vena caval synd. & ascending thrombophlebitis of iliofemoral vein.
(3) Acute myocardial infarction.
(4) Acute peripheral arterial thrombosis & emboli.
(5) For unclotting catheters & shunts.

ADVERSE EFFECTS

(1) CVS: Bleeding complications (hematoma, intracranial hemorrhage, GIT bleeding), reperfusion atrial or ventricular dysarrhythmias, hypotension.
(2) Hypersensitivity Reactions: Minor bronchospasm to anaphylaxis.
(3) Body Temp: Fever.

CONTRAINDICATIONS

(1) Recent stroke.
(2) Craniotomy.
(3) Head trauma.
(4) Brain tumor .

DOSAGE

Streptokinase

Loading IV dose of 250,000 units, followed by continuous infusion of 100,000 units/hr for 24 - 72 hours.

GENERIC & TRADE NAMES

Warfarin: Coumadin, Warfarin, Werifrin.
Heparin: Ecfast, Mediparine, Pine.
Dalteparin: Fragmin.
Enoxaparin: Clexan.
Tinzaparin: Innohep.
Streptokinase: Amikase, Durakinase, Streptase.
Aspirin: Anapirin, Ascard, Lopirin.
Clopidogrel: Clogrel, Clopeg, Lowplat.
Dipyridamole: Damopres, Persantin.
Ticlopidine: Clopidine, Ticlid, Ziclodin.
Abciximab: Reopro.
Eptifibatide: Integrilin.
Tirofiban: Aggrastat.
Cilostazol: Lostaz, Pletaal.

Unit III

Coagulants

(Anti-Hemorrhagics)

DRUGS CLASSIFICATION

These are drugs that promote coagulations & prevent hemorrhage.

(1) Vitamin K

(a) Natural

Vit. K_1 (Phytonadione), & K_2.

(b) Synthetic
Acetomenaphthone.

(2) Fibrinolytic Inhibitors
Aminocaproic acid, Tranexamic acid.

(3) Serine Protease Inhibitors
Aprotinin.

(4) Plasma Fractions

(a) Factor VIII
Cryoprecipitate, Lyophilized factor VIII concentrates.

(b) Factor IX

(c) Fibrinogen

(d) Fresh frozen plasma (FFP)

VITAMIN K

Mechanism of Action
It confers biologic activity upon prothrombin & factors VII, IX, & X by participating in their post-ribosomal modification.

Clinical Uses
(1) Administered to all newborn, to prevent hemorrhagic diseases of vit. K deficiency (which is esp. common in premature infants).
(2) As antidote of warfarin.

Adverse Effects
Rapid infusion can produce;
(1) Dyspnea
(2) Chest & back pain
(3) Death

FIBRINOLYTIC INHIBITORS

Examples
Aminocaproic acid, Tranexamic acid.

Mechanism of Action
They competitively inhibits plasminogen activator.

Clinical Uses
(1) Adjunct therapy in hemophilia.
(2) Bleeding from fibrinolytic therapy.
(3) Prophylaxis for rebleeding from intracranial aneurysms.
(4) Postsurgical GIT bleeding .
(5) Postprostatectomy bleeding.
(6) Bladder hemorrhage secondary to radiation & drug-induced cystitis.

Adverse Effects
(1) CVS: Intravascular thrombosis, hypotension.
(2) Resp Tract: Nasal stuffiness.
(3) GIT: Abdominal discomfort, diarrhea.
(4) Muscles: Myopathy.

Dosage
Tranexamic Acid
Loading dose of 15 mg/kg orally, followed by 30 mg/kg QID.

GENERIC & TRADE NAMES

Vitamin K: Vitamin K.
Tranexamic acid: Tranex, Transamin.
Aprotinin: Trasylol.

Unit IV

Other Hematological Drugs

ANTI-METHEMOGLOBINEMICS

Methemoglobinemia
It refers to the presence of methemoglobin in blood that results in cyanosis.
Note: Methemoglobin is formed from hemoglobin by oxidation of its ferrous iron to ferric (Fe^{+3}) state.

Causes
(1) Drug induced (see unit V)
(2) Defect in NADH methemoglobin reductase.

ANTI-METHEMOGLOBINEMICS
Reducing Agents
(1) Ascorbic acid
(2) Methylene blue
Note: Excess methylene blue may itself cause methemoglobinemia.

ANTI-HYPERLIPIDEMICS

Hyperlipidemias
It refers to elevations in plasma lipoproteins & triglycerides levels.

Clinical Sequelae
(1) Atherosclerosis, & its complications.
(2) Acute pancreatitis.
(3) Xanthomas.

CLASSIFICATION OF ANTI-HYPERLIPIDEMICS
(1) Bile Acid Sequestrants
Cholestyramine, Colestipol, Colesevelam.

(2) HMG CoA Reductase Inhibitors
Lovastatin, Atorvastatin, Pravastatin, Mevastatin, Simvastatin, Fluvastatin, Rosuvastatin.

(3) Niacin (Nicotinic Acid)

(4) Fibric Acid Derivatives
Clofibrate, Gemfibrozil, Fenofibrate, Bezafibrate.

(5) Inhibitors Of Intestinal Sterol Absorption
Ezetimibe.

ANTI-ANAPHYLACTICS

Anaphylaxis

It refers to an exaggerated IgE-mediated allergic reaction to foreign protein or other substances, in a sensitized individual.

Clinical Features

(1) Pruritus, urticaria, angioedema.
(2) Respiratory distress (due to laryngeal edema, laryngospasm, or bronchospasm).
(3) Hypotension & shock.
(4) Abdominal pain.

ANTI-ANAPHYLACTICS

(1) Epinephrine
(2) Inhaled beta-agonists, eg albuterol or metaproterenol.
(3) Aminophylline
(4) Antihistamines, eg diphenhydramine.
(5) Glucocorticoids, eg hydrocortisone.
(6) Glucagon.

Unit V

Drugs Causing Blood Dyscrasias

DRUGS CAUSING HEMOLYTIC ANEMIA

(A) Due to Hypersensitivity

- ***(1) Antimicrobials***
  Penicillins, Cephalosporins, Rifampin, Aminoglycosides.
- ***(2) Anti - Hypertensives***
  Methyldopa.
- ***(3) Anti - Migraine***
  Methysergide.
- ***(4) Anti - Parkinsonism***
  Levodopa.
- ***(5) NSAIDs***
  Mefenamic acid.

(B) Due to G6PD Deficiency

- ***(1) Analgesics***
  Acetylsalicylic acid, Phenacetin, Acetanilide.
- ***(2) Anti - Bacterials***
  Sulfonamides, Dapsone, Nitrofurantoin, Nitrofurazone, Furazolidine, Chloramphenicol, Isoniazid.
- ***(3) Anti - Malarials***
  Chloroquine, Primaquine, Pamaquin, Pyrimethamine, Quinine.
- ***(4) Others***
  Vit K, Probenecid, Nalidixic acid, Quinidine, Dimercaprol, Phenylhydrazine, p-Aminosalicylic acid.

DRUG CAUSING APLASTIC ANEMIA

- ***(1) Anti - Cancer Drugs***
  Mercaptopurine, Busulphan, Cyclophosphamide, Doxorubicin, Methotrexate.
- ***(2) Anti - Inflammatory & Anti - Rheumatic Drugs***
  Phenylbutazone, Oxyphenbutazone, Gold compounds, Indomethacin.
- ***(3) Anti - Epileptics***
  Phenytoin, Troxidone, Primidone.
- ***(4) Anti - Diabetics***
  Tolbutamide, Chlorpropamide.
- ***(5) Anti - Thyroid Drugs***
  Carbimazole, Methythiouracil, Propylthiouracil, Potassium Perchlorate.
- ***(6) Psychotropics***
  Chlorpromazine, Prochlorperazine, Promazine, Mianserin.
- ***(7) Anti - Histamines***
  Chlorpheniramine.
- ***(8) Antibiotics***
  Chloramphenicol, Sulfonamides.

DRUGS CAUSING MEGALOBLASTIC ANEMIA

- ***(1) Anti - Epileptics***
  Phenytoin, Primidone.
- ***(2) Others***
  Methotrexate, Pyrimethamine, Trimethoprim.

DRUGS CAUSING SIDEROBLASTIC ANEMIA

- ***(1) Anti - Tuberculous Drugs***
  Isoniazid, Cycloserine, Pyrazinamide.
- ***(2) Antibiotics***
  Chloramphenicol.
- ***(3) Analgesics***
  Phenacetin.

DRUGS CAUSING METHEMOGLOBINEMIA

- ***(1) Analgesics***
  Phenacetin, Acetanilide.
- ***(2) Antimicrobials***
  Sulfonamides, Trimethoprim.
- ***(3) Antimalarials***
  Primaquine.
- ***(4) Anti - Anginal Drugs***
  Nitrites & nitrates.

DRUGS CAUSING ACUTE INTERMITTENT PORPHYRIA

(1) Sedative - Hypnotics
Thiopentone, Meprobamate, Alcohol.
(2) Oral Contraceptives
(3) Others
Sulfonamides, Pentazocine, Griseofulvin, Methyldopa.

DRUGS CAUSING NEUTROPENIA & AGRANULOCYTOSIS

(1) Antibiotics
Chloramphenicol, Penicillin, Sulfonamides, Co - trimoxazole.
(2) Anti - Epileptics
Phenytoin.
(3) Antithyroid Drugs
Propylthiouracil.
(4) Antidiabetics
Chlorpropamide.
(5) Phenothiazines
Chlorpromazine.
(6) Antimalarials
Maloprim.

DRUGS CAUSING ANAPHYLAXIS

(1) Penicillins.
(2) Cephalosporins.
(3) Amphotericin B.
(4) Ketoconazole.
(5) Local anesthetics.

Unit VI

Self - Assessment (T/F)

(See answers on page no. 240-241)

(85) ***Optimal treatment of mild iron deficiency anemia associated with pregnancy is***
(A) A high-fibre diet.
(B) Parenteral iron dextran injections.
(C) Iron dextran tablets.
(D) Ferrous sulfate tablets.
(E) Folic acid supplements.

(86) ***Regarding toxicity of iron, following are correct***
(A) Acute oral ingestion of a large overdose causes constipation.
(B) Chronic iron overload, as in hemochromatosis, causes liver disease.
(C) Acute overdose may cause metabolic acidosis.
(D) Chronic toxicity is treated by phlebotomy .
(E) In acute toxicity, deferoxamine may be used as an antidote.

(87) ***Anticoagulant activity of warfarin can be potentiated by***
(A) Rifampin.
(B) Aspirin.
(C) Phenylbutazone.
(D) Cimetidine.
(E) Disulfiram.

(88) ***Concerning anticoagulants, all of the following are correct***
(A) Parenteral administration of heparin provides immediate anticoagulation.
(B) Oral administration of warfarin provide delayed anticoagulation.
(C) Anticoagulant action of heparin require the presence of antithrombin III.
(D) Warfarin is the preferred anticoagulant in pregnant women.
(E) Heparin overdose can be reversed with basic protein protamine.

(89) ***Anti - hyperlipidemic agents include***
(A) Clofibrate.
(B) Cholestyramine.
(C) Aspirin.
(D) Lovastatin.
(E) Prednisone.

11 CARDIOVASCULAR SYSTEM DRUGS

Unit I

Anti-Hypertensive Drugs

HYPERTENSION

Persistently elevated arterial pressure is called hypertension.

Threshold for Hypertension

(1) Systolic Pressure
Ranges from 140 to 200 mm Hg.

(2) Diastolic Pressure
Ranges from 90 to 110 mm Hg.

DRUG CLASSIFICATION

DRUGS THAT ALTER SYMPATHETIC NERVOUS SYSTEM

(1) Centrally Acting Sympathoplegic Drugs
Methyldopa, Clonidine, Guanabenz, Guanfacine.

(2) Ganglionic Blocking Drugs
Mecamylamine, Hexamethonium.

(3) Adrenergic Neuron Blocking Drugs
Reserpine, Guanadrel, Guanethidine, Bethanidine, Debrisoquin.

(4) Adrenoceptor Blocking Drugs

(a) ~ - Receptor Blockers
Prazosin, Doxazosin, Terazosin, Phenoxybenzamine, Phentolamine.

(b) - Receptor Blockers
Atenolol, Acebutolol, Betaxolol, Bisoprolol, Carteolol, Carvedilol, Esmolol, Metoprolol, Nadolol, Penbutolol, Propranolol, Pindolol, Timolol.

(c) ~: - & : - Blockers
Labetalol.

CALCIUM CHANNEL BLOCKERS

(1) Dihydropyridines
Nifedipine, Nicardipine, Nisoldipine, Amlodipine, Felodipine, Isradipine.

(2) Miscellaneous
Diltiazem, Verapamil.

ANGIOTENSIN BLOCKERS

(1) Angiotensin Receptor Blockers
Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan.

(2) Angiotensin Converting Enzyme Inhibitors
Benzapril, Captopril, Enalapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolapril.

(3) Competitive Inhibitors of Angiotensin II
Saralasin

DIURETICS

(1) Thiazide Diuretics
Chlorothiazide, Chlorthalidone.

(2) Loop Diuretics
Furosemide, Ethacrynic acid.

(3) K^+ Sparing Diuretics
Spironolactone, Amiloride.

(4) Nonthiazide Sulfonamide Diuretics
Indapamide.

Note: For detail on diuretics, see chapter 12.

DIRECT ACTING VASODILATORS

Diazoxide, Fenoldopam, Hydralazine, Minoxidil, Na nitroprusside.

CENTRALLY ACTING SYMPATHOLYTICS

METHYLDOPA

Mechanism of Action

(1) Converted into α -methylnorepinephrine which is stored in adrenergic nerve granules, where it stoichiometrically replaces norepinephrine &, is released by nerve stimulation to interact with presynaptic central α_2 adrenoceptors 2 Dec. sympathetic outflow 2 Dec. arterial pressure.

(2) Inhibit dopa decarboxylase 2 Dec. stores of norepinephrine in the sympathetic nervous system 2 Dec. BP.

(3) Reduces renal vascular resistance, probably α-methylnorepinephrine being a weaker vasoconstrictor than norepinephrine in renal beds

Clinical Uses

Mild to moderately severe hypertension.

Adverse Effects
(1) CNS: Sedation, lassitude, nightmares, depression, vertigo, extrapyramidal signs.
(2) CVS: Orthostatic hypotension, rebound hypotension on sudden withdrawal.
(3) GIT: GI disturbances.
(4) Blood: Hemolytic anemia, positive Coombs test.
(5) Endo: Lactation.
(6) Liver: Hepatitis.
(7) Metabolic: Drug fever.

Contraindications
(1) Pheochromocytoma.
(2) Acute hepatic disease.
(3) During MAO inhibitor administration..

Dosage
1-2 g orally in divided doses.

CLONIDINE

Mechanism of Action
It stimulates presynaptic α_2 receptors in vasomotor center of brain 2 Dec. sympathetic outflow to the peripheral vessels.

Pharmacological Effects
(1) Cardiovascular System
(a) I/V inj. causes an initial transient inc. in both systolic & diastolic pressure due to direct stimulation of peripheral α - adrenoceptors.
(b) This is followed by a fall in BP, resulting from a dec. in cardiac output & heart rate.
(c) Vagal discharge is inc. in association with inc. baroreceptor reflex sensitivity.

(2) Kidney
(a) Dec. plasma renin activity.
(b) Dec. renal vascular resistance but with no alteration in renal blood flow.

Adverse Effects
(1) CNS: Sedation, drowsiness.
(2) CVS: Rebound hypertensive crisis from sudden withdrawal of clonidine characterized by nervousness, tachycardia, headache & sweating.
(3) GIT: Dry mouth
(4) Renal: Fluid retention.

Dosage
0.2 - 1.2 mg /d.

ADRENERGIC NEURON BLOCKERS

RESERPINE

Mechanism of Action
(1) Reserpine blocks the ability of adrenergic transmitter vesicles to take up & store biogenic amines by interfering with an uptake mechanism that depends on Mg^{++} & ATP 2 Depletion of norepinephrine, dopamine & serotonin in both central & peripheral neurons.
(2) Also exerts a direct vasodilating effect on vascular smooth muscle when administer intraarterially.

Pharmacological Effects
(1) Central Nervous System
Sedation due to depletion of biogenic amines centrally.

(2) Cardiovascular System
(a) Dec. heart rate, cardiac output & BP, & may dec. peripheral vascular resistance.
(b) Inhibits cardiovascular reflexes only partially.

Clinical Uses
Mild to moderate hypertension.

Adverse Effects
(1) CNS: Sedation, lassitude, nightmares, depression, extrapyramidal signs.
(2) CVS: Postural hypotension, bradycardia.
(3) GIT: Diarrhea, abd. cramps, inc. gastric acid secretion.
(4) Resp. tract: Nasal congestion.

Contraindications
(1) Pheochromocytoma
(2) Peptic ulcer
(3) Depression.
(4) During MAO inhibitors administration.
(5) Parkinsonism.

GUANETHIDINE

Mechanism of Action
(1) It is transported across the sympathetic nerve memb. by a mech. that transports norepinephrine itself 2 Concentrated in transmitter vesicles, where it replaces norepinephrine 2 Causing a gradual norepinephrine depletion in nerve endings.
(2) It inhibits norepinephrine release from sympathetic nerve endings.

Pharmacological Effects
(1) Central Nervous System
No effect, b/c it does not cross the BBB.

(2) Cardiovascular System
(a) Initially, it displaces & releases enough unchanged norepinephrine to cause mild transient hypertension & cardiac stimulation.
(b) Followed by hypotension & bradycardia.
(c) Orthostatic hypotension, b/c it depresses vasoconstrictor reflexes.
(d) Inc. sensitivity of tissues to catecholamines.

(3) Skeletal Muscle
It has a direct inhibitory effect on skeletal muscle contraction.

Clinical Uses
Moderate to severe hypertension (usually with a diuretic & a vasodilator).

Adverse Effects
(1) CVS: Orthostatic hypotension & syncope esp. during exercise.
(2) GIT: Diarrhea.
(3) Sk. muscles: Aching, weakness.
(4) Repro: Delayed or retrograde ejaculation.

Contraindications
(1) Pheochromocytoma.
(2) Severe coronary artery disease.

(3) Cerebrovascular insufficiency.
(4) During MAO inhibitor administration.

ANGIOTENSIN BLOCKERS

SARALASIN

Mechanism of Action

It acts by competitive inhibition of angiotensin II at its receptors.

Pharmacological Effects

(1) It blocks the presser & aldosterone releasing effects of angiotensin II, & lowers BP in high renin states eg in renal artery stenosis.
(2) It also has weak agonist activity so that rapid administration to persons without high circulating angiotensin II may inc. BP.

ACE INHIBITORS

Mechanism of Action

They inhibit the converting enzyme peptidyl dipeptidase that hydrolyzes angiotensin I to angiotensin II, & inactivates bradykinin (a potent vasodilator).

Pharmacological Effects

(1) They cause a reduction in total peripheral resistance & mean arterial BP, & either no change or an inc. in cardiac output.
(2) They do not cause reflex sympathetic activation & can be used safely in pts. with ischemic heart disease.

Clinical Uses

(1) Mild to moderate hypertension.
(2) Chronic congestive cardiac failure

Adverse Effects

(1) CNS: Headache, dizziness & fatigue (enalapril).
(2) CVS: Severe hypotension in hypovolemic pts.
(3) Renal: Acute renal failure, hyperkalemia, proteinuria, angioedema.
(4) Resp. tract: Dry cough, wheezing.
(5) Blood: Neutropenia.
(6) Skin: Skin rashes.
(7) Special senses: Alteration in taste.

Contraindications

(1) Aortic stenosis.
(2) Bilateral renal artery stenosis.
(3) Renal impairment.
(4) Pregnancy.
(5) Lactation.

ANGIOTENSIN RECEPTOR BLOCKERS

Examples

Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan.

Mechanism of Action

They are selective, competitive antagonists of Angiotensin II type 1 (AT_1) receptor, reducing the end organ responses to angiotensin II.

Pharmacological Effects

(1) Decrease in total peripheral resistance (afterload) & venous return (preload).
(2) Reduction in blood pressure occurs independently of the status of the renin-angiotensin system. As a result, plasma renin activity increases due to removal of the angiotensin II feedback.

Clinical Uses

(1) Mild to moderate hypertension.
(2) Diabetic nephropathy.

DIRECT ACTING VASODILATORS

DIAZOXIDE

Mechanism of Action

Relaxes smooth muscle of the arterioles 2 Dec. systemic vascular resistance 2 Dec. BP.

Pharmacological Effects

(1) Cardiovascular System

It causes a fall in both systolic & diastolic pressure, accompanied by an inc. in heart rate & cardiac output.

(2) Smooth Muscles

It relaxes other smooth muscle in addition to vascular one.

(3) Endocrine

It inhibits release of insulin.

Clinical Uses

(1) I/V in hypertensive emergencies.
(2) Orally in hypoglycemia caused by hyperinsulinemia.

Adverse Effect

(1) CVS

(a) Severe hypotension which may result in stroke & myocardial infraction.
(b) Angina.
(c) Cardiac failure in pts. with ischemic heart disease.

(2) Endo

Hyperglycemia.

(3) Renal

Edema.

Contraindications

(1) Congestive cardiac failure.
(2) Diabetes mellitus.

Dosage

Initially 75 - 100 mg; if necessary 150 mg every 5 min. until BP is lowered to normal.

SODIUM NITROPRUSSIDE

Pharmacological Effects

(1) Cardiovascular System

(a) It directly relaxes both arterial & venous smooth muscles.
(b) It dec. BP in both supine & upright positions.
(c) It causes dec. myocardial oxygen demand due to inc. venous capacitance.
(d) Causes a slight inc. in heart rate & dec. in cardiac output except in heart failure.

(e) In heart failure, heart rate may dec. & cardiac output inc.

(2) Kidney

Renal blood flow is maintained, & renin secretion is increased.

Clinical Uses

(1) Hypertensive emergencies.
(2) To minimize bleeding during surgery by producing controlled hypotension.
(3) Acute myocardial infarction.
(4) Acute congestive cardiac failure.

Adverse Effects

(1) CNS: Headache, restlessness.
(2) CVS: Excessive hypotension, arrhythmias, palpitation, retrosternal pain.
(3) Endo: Delayed hypothyroidism.
(4) Blood: Methemoglobinemia, metabolic acidosis.
(5) GIT: Nausea.
(6) Thiocynate Poisoning: Manifested as weakness, disorientation, psychosis, muscle spasms & convulsions.

Dosage

0.5 - 10 µg / kg /min, IV.

HYDRALAZINE

Mechanism of Action

Same as diazoxide. It may reduce diastolic BP more than systolic BP.

Clinical Uses

(1) Moderate to severe hypertension.
(2) Acute & chronic congestive cardiac failure.

Adverse Effects

(1) CNS: Headache, dizziness, peripheral neuropathy.
(2) CVS: Palpitation, flushing, reflex tachycardia, angina, ischemic arrhythmias.
(3) GIT: Anorexia, nausea.
(4) Skin: Sweating; lupus erythematosus like synd. characterized by arthralgia, myalgia, skin rashes, & fever.

Contraindications

(1) Coronary artery disease.
(2) Lupus Erythematosus.

Dosage

40 - 200 mg /d.

MINOXIDIL

Mechanism of Action

Same as diazoxide.

Clinical Uses

(1) Severe hypertension.
(2) Severe hypertension coupled with renal functional impairment.
(3) Topically used as a stimulant of hair growth for correction of baldness.

Adverse Effects

(1) CNS: Headache.
(2) CVS: Tachycardia, palpitations, angina, pericardial effusion, tamponade.
(3) Endo: Hirsutism (hypertrichosis).
(4) Skin: Sweating.

OTHER ANTI- HYPERTENSIVE DRUGS

Ganglion Blockers

See chapter 3, Parasympathetic nervous system drugs.

Adrenoceptor Blockers

See chapter 2, Sympathetic nervous system drugs.

Ca^{++} Channel Blockers

See Unit II of this chapter.

GENERIC & TRADE NAMES

(1) Diuretics

See Chapter 12.

(2) Centrally Acting Sympathoplegic Drugs

Methyldopa: Aldomet, Hyergen, Normet.

(3) Alpha Adrenoceptor Blockers

Prazosin: Minipress.
Doxazosin: Cardura.
Terazosin: Hytrin.

(4) Beta Adrenoceptors Blockers

Atenolol: Atelor, Atenovid, Atenolol, Blokium, Cardiolite, Coxalol, Normitab, Nortenalol, Pulse, Tenolol, Tenoret-50*, Tenormin.
Betaxolol: Betaxen, Betoptic.
Bisoprolol: Bison, Concor.
Carteolol: Carteol, Mikelan.
Carvedilol: Carveda, Vadil.
Esmolol: Brevibloc.
Metoprolol: Betalock Zok, Mepresor, Metocard.
Nadolol: Corgard.
Pindolol: Vikaldix.
Propranolol: Beta Prograne, Blockonol, Cardinol, Inderal, Oprinol.
Timolol: Betalol, Timosol.

(5) Ca^{++} Channel Blockers

Nifedipine: Adalat, Cardipine, Nidipine, Nifedicor.
Nicardipine: Nicapress R.
Amlodipine: Amlocard, Norvasc, Sofvasc.
Felodipine: Plendil.
Isradipine: Dynacirc.
Diltiazem: Angizem, Calcard, Calzem, Cardiazem, Deltazem, Dilzem, DTZ, Herbesser, Lacerol, Tiazem.
Verapamil: Calan, Isocardin, Zavera.

(6) ACE Inhibitors

Candesartan: Advant, Canaxit, Canditensin, Treatan.
Eprosartan: Eveten.
Irbesartan: Aprovel, Coaprovel.
Losartan: Bepsar, Cosartan, Eziday, Co-Eziday*, Losartan.
Valsartan: Diovan, Varlan.
Captopril: Acetropil, Capoten, Capozide*, Capril, Katopril, Ropril, Vasotone.

Enalapril: Cardace, Co-Renitec*, Cortec, Ranitec, Stadelant.
Fosinopril: Monopril.
Lisinopril: Lace, Novotec, Zestril.
Perindopril: Coversyl, Dopril.
Quinapril: Accupril.
Ramipril: Hiace, Tritace.
Trandolapril: Gopten.

(7) Vasodilators

Na Nitroprusside: Nipride.

Unit II

Anti - Anginal Drugs

ANGINA PECTORIS

It is the strangling chest pain often radiating to the left shoulder & arm that occurs when coronary blood flow is inadequate to supply the oxygen required by the heart.

Types

(1) Classic (Atherosclerotic) Angina
Caused by atheromatous obstruction of the large coronary vessels.

(2) Variant (Angiospastic or Prinzmetal's) Angina
Caused by transient spasm of localized portions of large coronary vessels.

DRUG CLASSIFICATION

CORONARY VASODILATORS

(A) Nitrites & Nitrates

(1) According to Chemical Nature

(a) Nitrites
(i) **Inorganic nitrites:** Sodium nitrite.
(ii) **Organic nitrites:** Amylnitrite, Ethyl-nitrite.

(b) Nitrates
Glyceryl trinitrate (Nitroglycerine), Erythrityl tetranitrate, Pentaerythritol tetranitrate, Isosorbide dinitrate, Isosorbide mononitrate.

(2) According to Duration of Action

(a) Short Acting
(i) Amyl nitrite 2 Inhalant (duration 3-5 min).
(ii) Nitroglycerine 2 Sublingual (10-30 min).
(iii) Isosorbide dinitrate 2 Sublingual (10-60 min).

(b) Intermediate Acting
(i) Isosorbide dinitrate 2 Sublingual ($1^1/_2$ - 2 hr).
(ii) Isosorbide dinitrate 2 Chewable (2-3 hrs).
(iii) Nitroglycerine 2 2% ointment (3-6 hrs).
(iv) Nitroglycerine 2 Slow release buccal preparation (3-6 hrs).
(v) Isosorbide dinitrate 2 Oral (4-6 hrs).

(c) Long Acting
(i) Pentaerythritol tetranitrate 2 Oral (6-8 hrs).
(ii) Erythrityl tetranitrate (6-8 hrs).
(iii) Nitroglycerine 2 Oral sustained- action (6-8 hrs).
(iv) Isosorbide mononitrate 2 Oral (6-10 hrs) .
(v) Nitroglycerine 2 Slow release trans-cutaneous preparation (8-10 hrs).

(B) Miscellaneous Vasodilators

Nicorandil.

BETA ADRENOCEPTOR BLOCKERS

Propranolol, Atenolol, Metoprolol, Nadolol, Pindolol.

CALCIUM CHANNEL BLOCKERS

(A) Dihydropyridines

Nifedipine, Nicardipine, Nisoldipine, Amlodipine, Felodipine, Isradipine.

(B) Miscellaneous

Diltiazem, Verapamil, Bepridil.

NEWER ANTIANGINAL DRUGS

Ranolazine, Trimetazidine, Ivabradine.

NITRATES & NITRITES

MECHANISM OF ACTION

Nitroglycerine is denitrated into nitric oxide 2 NO reacts with sulfhydryl-containing receptors associated with guanyl cyclase 2 Guanyl cyclase is activated 2 Inc. cGMP level 2 Smooth muscle relaxation.

PHARMACOLOGICAL EFFECTS

(A) Cardiovascular System

Relaxation occur in all segments of vascular system:
(1) Arterioles & precapillary sphincters are dilated less, due to reflex responses.
(2) Inc. venous capacitance due to dec. venous tone 2 Dec. ventricular preload 2 Dec. cardiac output.
(3) Arterial dilation 2 Dec. mean systemic arterial pressure 2 Dec. after load of the heart 2 Dec. Cardiac oxygen requirement.
(4) Venous dilation 2 Dec. preload 2 Dec. myocardial wall tension 2 Dec. myocardial oxygen requirement.
(5) Dec. left ventricular end-diastolic volume reduces tissue pressure around subendocardial vessels 2 Inc. coronary blood flow to this area.
(6) Selective dilation of large epicardial & collateral coronary arteries occurs.

(7) Vasodilation of cerebral vessels 2 Inc. intracranial pressure & headache.
(8) Cutaneous vasodilation 2 Flushing.

(B) Other Smooth Muscle Organs

Relaxation of smooth muscles occur in the bronchi, GIT including biliary system, & genitourinary system. These effects has little clinical value b/c of short duration of drugs' action.

(C) Blood

Nitrite ion reacts with hemoglobin to produce methemoglobin which result in pseudocyanosis & tissue hypoxia.

CLINICAL USES

(1) Classic angina pectoris.
(2) Variant angina pectoris.
(3) Paroxysmal nocturnal dyspnea.
(4) Cyanide poisoning.

ADVERSE EFFECTS

(1) CNS: Throbbing headache, dizziness, weakness, cerebral ischemia.
(2) CVS: Orthostatic hypotension, reflex tachycardia.
(3) Blood: Hypoxia, pseudocyanosis, methemoglobinemia.
(4) Skin: Flushing.

CONTRAINDICATIONS

(1) Elevated intracranial pressure.
(2) Severe anemia.

DOSAGE

(1) Nitroglycerine (SL) 2 0.15-1.2 mg.
(2) Nitroglycerine (SRBP) 2 6.5-13 mg/4 hrs.
(3) Isosorbide dinitrate (SL) 2 2.5-10 mg/2 hr.
(4) Isosorbide dinitrate (oral) 2 10-60 mg/4-6 hrs.
(5) Pentaerythritol tetranitrate (oral) 2 40 mg/6-8 hrs.

Why Given Sublingually?

These drugs are inactivated by the hepatic nitrate reductase, so sublingual route is preferred for achieving a therapeutic blood level rapidly.

BETA - ADRENOCEPTOR BLOCKERS

BENEFICIAL EFFECTS IN ANGINA

(A) Thru its β-blocking effect, it decreases sympathetic stimulation of heart, resulting in;
(1) Dec. heart rate.
(2) Dec. contractility.
(3) Dec. cardiac output.
(4) Dec. arterial pressure.
These effects dec. myocardial oxygen requirement at rest & during exercise.
(B) Dec. heart rate causes an inc. diastolic perfusion time that inc. the myocardial perfusion.

UNDESIRABLE EFFECTS IN ANGINA

(A) Inc. end-diastolic volume, due to dec. heart rate.
(B) Inc. ejection time, also due to dec. heart rate.
These results in inc. myocardial oxygen requirement.

USES IN ANGINA

(1) Used only in classic angina.
(2) Used concomitantly with nitrates to balance its undesirable effects

CALCIUM CHANNEL BLOCKERS

MECHANISM OF ACTION

Bind to receptors on voltage-gated calcium channels 2 This results in blocking of Ca^{++} channels 2 This results in inhibition of Ca^{++} influx into cardiac & smooth muscle cells.

PHARMACOLOGICAL EFFECTS

(A) Vascular Smooth Muscle

Relaxation occur, more in the arterioles than in the veins;
(1) Dilation of main coronary arteries & coronary arterioles, & inhibition of coronary artery spasm 2 Inc. myocardial oxygen delivery in pts. with variant angina.
(2) Dilation of peripheral arterioles decreases total peripheral vascular resistance 2 Dec. BP (esp. with nifedipine) 2 Dec. myocardial oxygen requirement.

(B) Cardiac Muscle

Dec. oxygen requirement in pts. with angina, due to;
(1) Dec. impulse generation in SA node.
(2) Dec. conduction in AV node.
(3) Dec. cardiac contractility.
(4) Dec. cardiac output.
Note: Verapamil & diltiazem, have greater cardiac effects.

(C) Other Smooth Muscles

Relaxation occurs in bronchiolar, gastrointestinal & uterine smooth muscles, but these are less sensitive than vascular smooth muscle.

(D) Other Effects

(1) Interfere with stimulus-couple secretion in glands & nerve endings.
(2) Verapamil has slight local anesthetic action (due to less effective blockade of sodium channels).
(3) Verapamil inhibits insulin release.

CLINICAL USES

(1) Classic angina pectoris.
(2) Variant angina pectoris.
(3) Hypertension.
(4) Supraventricular tachyarrhythmias.
(5) Hypertrophic cardiomyopathy.
(6) Migraine.
(7) Raynaud's phenomenon.
(8) Atherosclerosis.

ADVERSE EFFECTS

(1) CNS: Dizziness.
(2) CVS: Cardiac arrest, bradycardia, AV-block, congestive cardiac failure, hypotension, peripheral edema.
(3) GIT: Nausea, constipation.
(4) Skin: Flushing.
(5) Verapamil inc. serum level of digitalis during the first week of therapy, & thus can cause digitalis toxicity.

CONTRAINDICATIONS

(1) Severe hypotension.
(2) Cardiogenic shock.
(3) Sick sinus syndrome.
(4) Digitalized patients.

MISCELLANEOUS VASODILATORS

DIPYRIDAMOLE

Pharmacological Effects

(1) Inhibits uptake of adenosine (a coronary vasodilator) into erythrocytes & other tissues, to inc. its plasma level.
(2) Dec. coronary vascular resistance, & inc. coronary blood flow.
(3) Inhibits platelet aggregation, so used to prevent formation of thromboemboli in pts with prosthetic cardiac valves.

PAPAVERINE

Pharmacological Effects

(1) It is a potent inhibitor of phosphodiesterase enzyme.
(2) It relaxes smooth muscle of large blood vessels, & decreases total peripheral vascular resistance thru an effect on arterioles.
(3) If given IV, it produces a quinidine-like effect that results in sudden death.

GENERIC & TRADE NAMES

(1) Nitrates & Nitrites

Isosorbide dinitrate: Carsodil, Isobid, Isoday, Isoket, Isordil, Sorbid.
Glyceryl trinitrate: Angised, Deponit, Glytrin, Nitrocine, Nitromint, Nitronal, Sustac.
Isosorbide mononitrate: Corlet, Elantan, Ismo-20, Monis, Monosor, Vasocord.

(2) - Adrenoceptor Blockers

See Unit I.

(3) Ca^{++} Channel Blockers

See Unit I.

Unit III

Drug Treatment of CCF

CONGESTIVE CARDIAC FAILURE (CCF)

It refers to failure of the heart to pump enough blood to meet the needs of the tissues, following myocardial damage.

Causes

(1) Diseases of myocardium, mainly ischemic.
(2) Excessive workload due to arterial hypertension.
(3) Valvular disease.
(4) Arteriovenous shunt.

Clinical Features

(1) Tachycardia.
(2) Dec. exercise tolerance.
(3) Shortness of breath.
(4) Peripheral & pulmonary edema.
(5) Cardiomegaly.

DRUG CLASSIFICATION

(A) Drugs Having Positive Inotropic Effects

(1) Cardiac Glycosides (Digitalis)

Digoxin, Digitoxin, Deslanoside, Lanatoside C.

(2) Bipyridines

Inamrinone, Milrinone.

(3) $_1$ - Adrenoceptor Agonists

Dobutamine.

(B) Drugs Without Positive Inotropic Effects

(1) Angiotensin Blockers

(a) Angiotensin Converting Enzyme Inhibitors

Benzapril, Captopril, Enalapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolapril.

(b) Angiotensin Receptor Blockers

Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan.

(2) Direct Vasodilators

Hydralazine, Nitroprusside, Isosorbide dinitrate, Nesiritide, Bosentan.

(3) ~:- Adrenoceptor Blocker

Prazosin.

(4) -Adrenoceptor Blockers

Bisoprolol, Carvedilol, Metoprolol.

(5) Diuretics

DIGITALIS

PHARMACOLOGICAL EFFECTS

(A) Cardiac Effects

(1) Mechanical Effects

(a) Digitalis increases myocardial contractility, both by increasing velocity of cardiac muscle

contraction & by increasing the max. force that is developed.

(b) Cardiac output is inc., with dec. in cardiac filling pressure, heart size, & venous & capillary pressure.

Mechanism

Digitalis inhibits Na^+ - K^+ -ATPase resulting in intracellular accumulation of Na^+ (& loss of intracellular K^+) 2 Influx of Ca^{++} secondary to activation of memb. Na^+ - Ca^{++} carrier 2 Inc. amount of free intracellular Ca^{++} 2 Ability of sarcoplasmic reticulum to bind Ca^{++} is dec. leading to more intracellular Ca^{++} available 2 Inc. intensity of interaction of actin & myosin filaments.

(2) Electrical Activity

(a) Inc. refractory period of AV node.
(b) Dec. conduction velocity thru AV node.
(c) Inc. vagal tone of heart (indirect effect).

(3) Heart Rate

Digitalis has negative chronotropic effect, due to direct slowing of SA node as well as due to indirect stimulation of vagal tone.

(4) Myocardial Oxygen Consumption

(a) Inc. contractility causes an inc. myocardial O_2 consumption.
(b) Dec. ventricular volume due to inc. muscle tone & cardiac output, decreases myocardial O_2 consumption.
(c) Net consumption depends upon which of the above two factor is dominant.

(B) Extracardiac Effects

These are due to inhibition of Na^+ - K^+ -ATPase & an inc. in intracellular Ca^{++}.

(1) Central Nervous System

Inc. spontaneous activity of neurons, due to depolarization.

(2) Cardiovascular System

(a) Dec. peripheral vascular resistance & venomotor tone in congestive cardiac failure; however, in normal persons, digitalis produces venous & arterial constriction).
(b) Inc. systolic BP, due to inc. stroke volume.
(c) Dec. diastolic BP, due to improved circulation & dec. reflex vasoconstriction.

(3) Gastrointestinal Tract

Inc. spontaneous activity of smooth muscle of GIT.

(4) Renal

Diuresis occur due to improved myocardial contractility & dec. sympathetic activity, which results in inc. renal blood flow promoting excretion of salt & water.

(C) Interactions With K^+, Ca^{++} , & Mg^{++}

(1) K^+ & digitalis interacts in 2 ways;
(a) They inhibit each other's binding to Na^+ - K^+ ATPase; therefore, hyperkalemia decreases enzyme-inhibiting actions of digitalis, whereas hypokalemia facilitates these actions.
(b) Abnormal cardiac automaticity is inhibited by hyperkalemia, thus moderately inc. extracellular K^+ decreases toxic effects of digitalis.
(2) Ca^{++} facilitates toxic actions of digitalis by accelerating the overloading of intracellular Ca^{++} stores.
(3) Mg^{++} effect is opposite to that of Ca^{++}.

CLINICAL USES

(1) Congestive cardiac failure.
(2) Atrial flutter.
(3) Atrial fibrillation.
(4) Paroxysmal atrial tachycardia.
(5) AV-nodal tachycardia.

ADVERSE EFFECTS

(1) CNS

Headache, fatigue, malaise, neuralgias, disorientation, hallucination, delirium, visual disturbances, convulsions.

(2) CVS

Premature ventricular beats, ventricular tachycardia, ventricular fibrillation, AV block, sinus arrhythmias, SA block, paroxysmal & nonparoxysmal atrial tachycardia.

(3) GIT

Anorexia, nausea, vomiting, diarrhea.

(4) Endo

Gynecomastia, galactorrhea.

Treatment

(1) Discontinuation of digitalis & K- depleting diuretics.
(2) KCI is given, if hypokalemia is present.
(3) Phenytoin is given, for ventricular & atrial arrhythmias.
(4) Lidocaine & procainamide, for ventricular tachyarrhythmias.
(5) Propranolol, to treat ventricular & supraventricular tachycardia.
(6) Atropine, to control sinus bradycardia & AV block.
(7) Digitalis immune fab (a digitalis antibody).

CONTRAINDICATIONS

(1) Cardiac tamponade.
(2) Constrictive pericarditis.
(3) Idiopathic hypertrophic subaortic stenosis.
(4) Wolff- Parkinson - White pts, with atrial fibrillation.
(5) Ventricular fibrillation.
(6) Ventricular tachycardia.

DIGITALIZATION

If there is no urgent need for a desired effect, an oral "digitalizing dose" is first administered &, then the "maintenance dose" is adjusted on the basis of clinical & laboratory assessment. This is called digitalization.

(1) Digoxin

Digitalizing dose is 0.5 to 0.75 mg every 8 hours for 3 doses, while the maintenance daily dose is 0.125 to 0.5 mg.

(2) Digitoxin

Digitalizing dose is 0.2 to 0.4 mg every 12 hours for 3 doses, while the maintenance daily dose is 0.05 - 0.2 mg.

BIPYRIDINES

Mechanism of Action

It inhibits phosphodiesterase enzyme 2 Inc. cAMP conc. 2 Inc. Ca^{++} influx.

Pharmacological Effects

(1) A positive inotropic effect.
(2) A vasodilating effect, which reduces both pulmonary & systemic vascular resistance.

Clinical Uses

Congestive cardiac failure.

Adverse Effects

(1) CVS: Ventricular tachycardia in pts. with atrial flutter or fibrillation.
(2) GIT: Nausea, vomiting.
(3) Blood: Thrombocytopenia.

GENERIC & TRADE NAMES

(1) Digitalis

Digoxin: Digox, Digoxin, Doxin.

(3) $_1$ Agonists

Dobutamine: Dobuject, Dobutamine, Dobutrex.

(4) ACE Inhibitors

See Unit I.

(5) Vasodilators

See Unit I.

(6) ~ & Blockers

See Chapter 2, Unit III.

(7) Diuretics

See Chapter 12.

Unit IV

Drug Treatment of Cardiac Arrhythmias

CARDIAC ARRHYTHMIAS

It refers to abnormalities in rate, regularity, or site of origin of cardiac impulse, or a disturbance in conduction of impulse such that the normal sequence of activation of atria & ventricles is altered.

Causes

(1) Faulty impulse initiation.
(2) Faulty impulse conduction.
(3) Combination of both.

Factors Precipitating Arrhythmias

(1) Hypoxia, & ischemia.
(2) Acidosis or alkalosis.
(3) Electrolyte abnormalities.
(4) Excessive catecholamine exposure.
(5) Autonomic influences.
(6) Drug toxicity (eg digitalis).
(7) Overstretching of cardiac fibres.
(8) Presence of scarred or diseased cardiac tissue.

DRUG CLASSIFICATION

(1) Class 'I' Agents (Na-Channel Blockers)

(A) Group 'I A'

Increases the duration of action potential; eg, Quinidine, Procainamide, Disopyramide, Amiodarone.

(B) Group 'I B'

Decreases the duration of action potential; eg, Lidocaine, Tocainide, Mexiletine, Moricizine,

(C) Group 'I C'

eg Flecainide, Encainide, Propafenone, Moricizine.

(II) Class 'II' Agents (= blockers)

Propranolol, Esmolol, Atenolol, Sotalol, Amiodarone.

(III) Class 'III' Agents

Includes drugs that prolong effective refractory period by mech. other than or in addition to Na- channel blocking eg,
Bretylium, Amiodarone, Sotalol, Dofetilide, Ibutilide.

(IV) Class 'IV' Agents (Ca Channel Blockers)

Verapamil, Diltiazem, Amiodarone.

(V) Miscellaneous Antiarrhythmics

Adenosine, Magnesium, Potassium.

QUINIDINE

MECHANISM OF ACTION

It blocks activated as well as inactivated sodium channels.

PHARMACOLOGICAL EFFECTS

(A) Cardiac Effects

At high conc., it has direct effect on most cells of heart; while at lower conc., indirect (anticholinergic) effects may significantly contribute to effects on heart.

(1) Dec. pacemaker rate, esp. that of ectopic pacemaker.
(2) Dec. conduction velocity, & inc. effective refractory period in atrial, ventricular & purkinje fibres.
(3) Dec. excitability, esp. in depolarized tissue.
(4) In low doses AV conduction is inc. due to anti-cholinergic effect, & pts. with atrial flutter or fibrillation may experience an inc. in ventricular rate.

(5) Lengthens action potential duration which along with inc. effective refractory period reduces the maximum reentry frequency.

(6) ECG changes

(a) Prolongation of QRS complex.
(b) Prolongation of Q-T interval.
(c) Prolongation of P-R interval.
(d) Alterations in T waves (due to delayed repolarization).

(B) Extracardiac Effects

(1) Quinidine has α - adrenoceptor blocking properties which causes vasodilation & a reflex inc. in SA nodal rate.
(2) It also has antimalarial, antipyretic & oxytocic properties.

CLINICAL USES

(1) Premature atrial contractions.
(2) Paroxysmal atrial fibrillation & flutter.
(3) Intra-atrial & atrioventricular nodal reentrant arrhythmias.
(4) Wolff-Parkinson-White tachycardia.
(5) Premature ventricular contractions.
(6) Ventricular tachycardias.

ADVERSE EFFECTS

(1) CNS

Cinchonism occur characterized by;
Tinnitus, hearing loss, headache, diplopia, photophobia, altered color perception, confusion, psychosis, vomiting, diarrhea.

(2) CVS

(a) Quinidine syncope characterized by recurrent light headedness, & episodes of fainting.
(b) AV block, ventricular tachyarrhythmias, depression of myocardial contractility.
(c) Precipitate digitalis toxicity as it inc. plasma digitalis level.
(d) Angioneurotic edema, hypotension.

(3) GIT

Anorexia, nausea, vomiting, diarrhea.

(4) Skin

Rashes.

(5) Blood

Thrombocytopenia.

(6) Liver

Hepatitis.

(7) Metabolic

Fever.

CONTRAINDICATIONS

(1) Complete AV block with an AV nodal or idioventricular pacemaker.
(2) History of embolism.
(3) Old standing atrial fibrillation.
(4) Subacute bacterial endocarditis.
(5) Heart failure.
(6) Arrhythmias due to digitalis toxicity.

PROCAINAMIDE

Mechanism of Action

Same as that of quinidine.

Pharmacological Effects

(A) Cardiac Effects

Nearly similar to quinidine;

(1) Suppresses abnormal ectopic pacemaker activity, & lengthens the duration of action potential & refractory period in the atria & ventricles.
(2) Slows conduction in atrium, AV node & ventricles.
(3) Unlike quinidine, it has less prominent antimuscarinic action.
(4) Ganglionic blocking properties results in more potent negative inotropic effects than quinidine.
(5) Induces severe CCF in pts. with preexisting ventricular dysfunction.

(B) Extracardiac Effects

Reduces peripheral vascular resistance, & cause hypotension due to ganglionic blocking effects.

Clinical Uses

(1) Atrial & ventricular arrhythmias.
(2) Ventricular arrhythmias associated with acute myocardial infraction.

Adverse Effects

(1) CNS: Mental confusion, psychosis.
(2) Eye: Precipitation of acute glaucoma.
(3) CVS: Ventricular arrhythmias, ventricular fibrillation, cardiac depression, hypotension, pericarditis.
(4) Resp. tract: Pleuritis, parenchymal pulmonary disease.
(5) GIT: Anorexia, nausea, vomiting, diarrhea.
(6) Liver: Hepatitis.
(7) Renal: Urinary retention.
(8) Blood: Agranulocytosis.
(9) Skin: Lupus erythematosus-like syndrome consisting of arthralgia & arthritis, rashes.
(10) Body temp: Fever.

Contraindications

(1) AV block.
(2) Systemic lupus erythematosus.

Dosage

Up to 50 mg/ kg daily in divided doses every 3 to 6 hours.

DISOPYRAMIDE

Mechanism of Action

Similar to quinidine.

Pharmacological Effects

Similar to quinidine, but it has even more marked anti-muscarinic effects.

Clinical Uses

Ventricular arrhythmias.

Adverse Effects

(1) Eye: Blurred vision, worsening of pre-existing glaucoma.
(2) CVS: CCF, hypotension, depressed myocardial contractility, conduction disturbances.
(3) GIT: Dry mouth, constipation.
(4) Renal: Urinary retention in pts. with prostatic hypertrophy.

Contraindications
(1) 2nd or 3rd degree AV block.
(2) Cardiogenic shock.
(3) Severe uncompensated cardiac failure.

Dosage
300-800 mg daily in divided doses.

AMIODARONE

Mechanism of Action
(1) It is an effective blocker of Na^+ channels, but only the channels in the inactivated state.
(2) It is a weak Ca^{++} channel blocker.
(3) It is also a non-competitive inhibitor of α - & β - adrenoceptors.

Pharmacological Effects
(1) Inc. action potential duration, & effective refractory period in atrial & ventricular muscles.
(2) Inc. P-R, QRS, & Q-T intervals.
(3) Dec. sinus rate, & AV conduction.
(4) Causes both systemic & coronary vasodilation.
(5) Also has an antianginal effect.

Clinical Uses
(1) Premature ventricular contractions.
(2) Ventricular tachycardia.
(3) Supraventricular arrhythmias.
(4) Arrhythmias in pts. with Wolff- Parkinson-White syndrome.

Adverse Effects
(1) CNS: Paresthesias, tremor, ataxia, headache, dizziness, peripheral neuropathy.
(2) Eye: Yellowish brown micro-crystalline deposits on cornea.
(3) CVS: Bradycardia, AV block, paradoxical ventricular arrhythmias.
(4) Resp. tract: Pulmonary fibrosis & inflammation.
(5) GIT: Anorexia, nausea, vomiting, constipation.
(6) Liver: Hepatocellular necrosis.
(7) Blood: Inc. in serum levels of digitalis, diltiazem, quinidine, procainamide.
(8) Endo: Hypo-or Hyperthyroidism.
(9) Skin: Photodermatitis.

Dosage
200 - 400 mg/d.

LIDOCAINE

Mechanism of Action
It blocks the activated & inactivated Na^+ channels, but shorten the action potential duration.

Pharmacological Effects
(1) It is a potent suppressor of abnormal cardiac activity.
(2) It prolonged diastole, due to shorten action potential duration.
(3) It has little effect on atria.
(4) It shortens effective refractory period of Purkinje fibres.
(5) It is an amide local anesthetic.

Clinical Uses
(1) Ventricular arrhythmias during
  (a) Open cardiac surgery
  (b) Digitalis toxicity
  (c) Acute myocardial infarction
(2) For local anesthesia

Adverse Effects
(1) CNS: Paresthesias, tremor, nausea of central origin, lightheadedness, hearing disturbances, slurred speech, convulsions, respiratory arrest.
(2) CVS: Circulatory collapse, SA nodal standstill, hypo-tension.

Dosage
IV loading dose of 150 - 200 mg in 15 min. followed by maintenance infusion of 2 - 4 mg/min.

PHENYTOIN

Antiarrhythmic Effect
(1) Effects are very similar to lidocaine.
(2) It depresses spontaneous automaticity in atrial & ventricular tissues without altering intraventricular conduction.
(3) Inc. conduction thru damaged purkinje fibers.
(4) It is especially useful for ventricular arrhythmias associated with digitalis toxicity or acute myocardial infarction.

Note: For more detail, see Chapter 5, Unit III.

FLECAINIDE

Mechanism of Action
Na^+ channel blocker.

Pharmacological Effects
(1) Dec. automaticity of ectopic pacemaker.
(2) Dec. conduction & excitability, & inc. refractory period (more in the depolarized tissue).

Clinical Uses
(1) Premature ventricular contractions.
(2) Ventricular tachycardia.

Adverse Effects
(1) CNS: Dizziness, blurred vision, nervousness.
(2) CVS: Aggravate arrhythmias or induce new ones, SA nodal depression, AV block in pts. with conduction disturbances.
(3) GIT: Anorexia, nausea, vomiting.
(4) Repro: Impotence.

PROPRANOLOL

Antiarrhythmic Effects

Effects are primarily due to β - adrenoceptor blockade but also result from a direct memb. effect;

(1) Depresses SA nodal firing.
(2) Dec. automaticity in purkinje fibres.
(3) A substantial inc. in effective refractory period of AV node.

Antiarrhythmic Uses

(1) Atrial flutter & fibrillation.
(2) Paroxysmal supraventricular tachycardia.
(3) Ventricular arrhythmias, due to;
  (a) Enhanced adrenergic stimulation.
  (b) Digitalis toxicity.

BRETYLIUM

Mechanism of Action

(1) It is an adrenergic neuronal blocking agent. It accumulates in postganglionic adrenergic nerve terminals, where it initially stimulates norepinephrine release but then inhibits the release of norepinephrine in response to neuronal stimulation.
(2) It also has direct electrophysiologic effects on heart.

Pharmacological Effects

Cardiac Effects

(1) Inc. ventricular action potential duration & effective refractory period, more pronounced in ischemic cells.
(2) Also inc. action potential duration & effective refractory period of atrial muscle & AV node.
(3) Some positive inotropic effect, due to initial release of norepinephrine.

Clinical Uses

Life-threatening ventricular arrhythmias refractory to other therapy.

Adverse Effects

(1) CVS: Hypotension esp. orthostatic.
(2) GIT: Nausea, vomiting.

GENERIC & TRADE NAMES

(1) Na^+ Channel Blockers

Quinidine: Quinidine bisulphate.
Procainamide: Pronestyl.
Disopyramide: Norpace.
Amiodarone: Cordarone, Sedacoron.
Lidocaine: Anacaine, Xylocaine, Xyles.

(2) Beta Blockers

See Chapter 2, Unit III.

(3) Class III Agents

Bretylium: Bretylol.

(4) Ca^{++} Channel Blockers

See Unit I.

Unit V

Self-Assessment (T/F)

(See answers on page no. 241)

(90) ***Regarding methyldopa & clonidine, following are correct***
(A) Both stimulates pre-synaptic central alpha-2 receptors.
(B) Both causes rebound hypertension on sudden withdrawal.
(C) Orthostatic hypotension is a common adverse effect.
(D) Both causes sedation.
(E) Both increases renal vascular resistance.

(91) ***Captopril & enalapril do all of the following***
(A) Competitively inhibit angiotensin at its receptor.
(B) Inhibit angiotensin converting enzyme peptidyl-dipeptidase.
(C) Dec. angiotensin II conc. in blood.
(D) Reflex sympathetic activation.
(E) Acute renal failure.

(92) ***Following are correct, regarding direct acting vasodilators***
(A) Diazoxide is a venodilator.
(B) Na nitroprusside is used intravenously in hypertensive emergencies.
(C) Hydralazine is an arteriolar dilator.
(D) Minoxidil is used topically for correction of baldness.
(E) Hydralazine reduces diastolic BP more than systolic BP.

(93) ***Postural hypotension is a common adverse effect of***
(A) Na nitroprusside.
(B) Propranolol.
(C) Phenoxybenzamine.
(D) Methyldopa.
(E) Reserpine.

(94) ***Nitroglycerine, either directly or thru reflexes, results in***
(A) Tachycardia.
(B) Inc. venous capacitance.
(C) Dec. afterload.
(D) Dec. myocardial wall tension.
(E) Inc. cardiac output.

(95) ***Antianginal effect of propranolol is attributed to***
(A) Dec. heart rate.
(B) Dec. arterial pressure.
(C) Inc. end-diastolic ventricular volume.
(D) Inc. in ejection time.
(E) Dec. contractility.

(96) ***Nitroglycerin in moderate doses may produce***
(A) Cerebral vasodilation.

(B) Reflex tachycardia.
(C) Methemoglobinemia.
(D) Flushing.
(E) Sympathetic discharge.

(97) ***Regarding Ca channel blockers, following are correct***
(A) They inhibit influx of Ca^{++} into cardiac & smooth muscle cells.
(B) They dilate main coronary arteries & coronary arterioles.
(C) Nifedipine has greater effect on heart.
(D) Used clinically in classic as well as in variant angina pectoris.
(E) Constipation may occur.

(98) ***Primary mechanism of action of digitalis involves***
(A) An inc. of action potential amplitude.
(B) An inc. in ATP synthesis.
(C) A modification of actin molecule.
(D) An inc. in intracellular Ca^{++} levels.
(E) A block of Na^{+}-Ca^{++} exchange.

(99) ***Important effects of digitalis on heart include***
(A) Inc. force of contraction.
(B) Dec. AV conduction velocity.
(C) Inc. heart rate.
(D) Prolonged refractory period of AV node.
(E) Inc. ectopic automaticity.

(100) ***All of the following are therapeutically useful in treatment of congestive cardiac failure***
(A) A vasodilator such as hydralazine.
(B) A cardiac glycoside such as digoxin.
(C) A beta-agonist such as norepinephrine.
(D) A diuretic such as hydrochlorothiazide.
(E) A beta-blocker such as propranolol.

(101) ***All of the following are useful in treatment if digitalis overdose***
(A) Quinidine.
(B) Digoxin immune FAB fragment.
(C) Dietary potassium supplements for pts. being treated concomitantly with diuretics.
(D) Lidocaine.
(E) Phenytoin.

(102) ***All of the following pairs correctly match a drug with its action***
(A) Quinidine 2 Blocks Na^{+} channels.
(B) Bretylium 2 Blocks K^{+} channels.
(C) Verapamil 2 Blocks Ca^{++} channels.
(D) Propranolol 2 Blocks β-adrenoceptors.
(E) Procainamide 2 Blocks K^{+} channels.

(103) ***Cardiac effects of quinidine includes***
(A) Dec. pacemaker rate esp. of ectopic pacemaker.
(B) Dec. conduction velocity in atrial, ventricular, & purkinje fibres.
(C) Dec. refractory period in atrial, ventricular, & purkinje fibres.
(D) Shortening of action potential duration.
(E) Dec. excitability.

(104) ***Recognized adverse effects of quinidine include***
(A) Cinchonism.
(B) Constipation.
(C) Thrombocytopenic purpura.
(D) Displacement of digoxin from its binding site with possible digoxin toxicity.
(E) *Angioneurotic edema.*

12 RENAL DRUGS

Unit I

Diuretics

DRUG CLASSIFICATION

DIURETICS

Drugs inducing a state of increase urine flow are called diuretics. These agents are ion transport inhibitors that dec. Na^+ reabsorption at different sites in nephron. As a result, Na^+ & other ions eg $C1^-$ enter urine in greater amounts than normal, along with water, which is carried passively to maintain osmotic equilibrium.

CLASSIFICATION OF DIURETICS

(A) Drugs Acting on Proximal Tubule

(1) Osmotic Diuretics
Mannitol, Urea, Isosorbide.

(2) Carbonic Anhydrase Inhibitors
Acetazolamide, Brinzolamide, Dorzolamide, Methazolamide, Dichlorphenamide.

(3) Acidifying Salts
Ammonium chloride.

(4) Xanthine Diuretics
Aminophylline, Tea, Coffee, Soda.

(B) Drugs Acting on Ascending Limb of Henle's Loop

(1) Loop (High - Ceiling) Diuretics
Furosemide, Bumetanide, Ethacrynic acid, Torsemide, Muzolimine, Piretanide.

(2) Mercurial Diuretics
Mercaptomerin.

(C) Drugs Acting on Distal Tubule

(1) Thiazide Diuretics
Bendroflumethiazide, Benzthiazide, Chlorothiazide, Hydrochlorothiazide, Hydroflumethiazide, Methyclothiazide, Polythiazide, Trichlormethiazide.

(2) Sulfonamide Diuretics
Qualitatively similar to thiazides: eg, Chlorthalidone, Indapamide, Metolazone, Quinethazone, Xipamide, Clopamide, Mefruside.

(D) Drugs Acting on Collecting Tubule

(1) K^+- Sparing Diuretics

(a) Aldosterone Antagonists
Spironolactone, Eplerenone.

(b) Direct Acting
Triamterene, Amiloride.

(2) ADH Antagonists
Conivaptan, Lithium salts, Demeclocycline.

(E) Miscellaneous Diuretics

(1) Alkalizers
Citrates, Acetates & Bicarbonates of Sodium & Potassium.

(2) Plasma Expanders
Dextran, Albumin.

OSMOTIC DIURETICS

MANNITOL

Mechanism of Action

(1) Mannitol & other osmotic diuretics are filtered at glomerulus 2 Reabsorbed poorly, due to their large molecular size 2 Dec. reabsorption of water in proximal tubule & descending limb of loop of Henle (due to their osmotical presence) 2 Large volume of urine.

(2) Mannitol also cause an inc. in renal medullary blood flow via a prostaglandin-mediated mechanism.

Clinical Uses

(1) To inc. water excretion in preference to Na^+ excretion, eg when renal hemodynamics are compromized.

(2) To maintain urine volume & to prevent anuria, that may result from large pigment loads to kidneys (eg, hemolysis or rhabdomyolysis).

(3) To dec. intracranial pressure in neurologic conditions.

(4) To dec. intraocular pressure before ophthalmologic procedures.

Adverse Effects

(1) CNS: Headache.

(2) CVS: Complicate congestive cardiac failure.

(3) Resp. tract: Florid pulmonary edema.

(4) GIT: Nausea , vomiting.

(5) Water & electrolytes: ECF expansion & hyponatremia, severe dehydration, hypernatremia.

Dosage

50 - 200 g / day, IV.

CARBONIC ANHYDRASE INHIBITORS

MECHANISM OF ACTION

They inhibit carbonic anhydrase, predominantly at proximal convoluted tubule 2 Dec. bicarbonate (HCO_3^-) reabsorption in proximal tubule 2 Inc. loss in urine (bicarbonate diuresis).

Note: HCO_3^- depletion leads to inc. NaCl reabsorption by remaining tubule segments 2 Hyperchloremic metabolic acidosis.

CLINICAL USES

(1) Glaucoma (b/c aqueous humor formation is dec).
(2) For urinary alkalinization, eg to inc. excretion of uric acid , cystine, barbiturates or aspirin.
(3) Metabolic alkalosis;
  (a) Due to excessive use of diuretics in pts with severe cardiac failure.
  (b) In pts with respiratory acidosis.
(4) Acute mountain sickness.
(5) Petit mal epilepsy.
(6) Hypokalemic periodic paralysis.
(7) Severe hyperphosphatemia.

ADVERSE EFFECTS

(1) CNS: Drowsiness, paresthesias.
(2) Renal: Calculus (due to phosphaturia & hypercalciuria).
(3) Hypersensitivity reactions: Fever, rashes, bone marrow suppression, interstitial nephritis.
(4) Electrolytes & acid-base balance: Renal potassium wasting, hyperchloremic metabolic acidosis.

Precautions

(1) Gout.
(2) Diabetes.
(3) Pregnancy.

CONTRAINDICATIONS

(1) Hepatic cirrhosis.
(2) Chronic closed-angle glaucoma.
(3) Renal hyperchloremic acidosis.
(4) Adrenal insufficiency.
(5) Na^+ or K^+ depletion.

DOSAGE

Acetazolamide
250 mg , 1-4 times daily, orally.

LOOP (HIGH - CEILING) DIURETICS

MECHANISM OF ACTION

(1) They inhibit Na^+/ K^+/ $2Cl^-$ co-transport system in luminal memb. of thick ascending limb of Henle's loop 2
  (a) Dec. reabsorption of NaCl.
  (b) Dec. the normal lumen-positive potential that derives from K^+ recycling 2 Inc. excretion of Mg^{+2} & Ca^{+2} .
(2) Furosemide inc. renal blood flow & causes redistribution of blood flow within renal cortex.
(3) Furosemide & bumetanide weakly inhibit carbonic anhydrase.

CLINICAL USES

(1) Acute pulmonary edema.
(2) Edema associated with congestive cardiac failure, renal failure, & hepatic cirrhosis.
(3) Diabetic nephropathy.
(4) Hypercalcemia.
(5) Hyperkalemia.
(6) Acute renal failure.
(7) Anion (eg, bromide, fluoride, iodide) overdosage.
(8) Inc. intracranial pressure.

ADVERSE EFFECTS

(1) ENT: Ototoxicity.
(2) Hypersensitivity reactions: Skin rash, eosinophilia, interstitial nephritis.
(3) Water, electrolytes, & acid-base balance: Hypokalemic metabolic alkalosis, hypomagnesemia, severe dehydration, hyponatremia, hypercalcemia (due to vol. depletion).
(4) Joints: Precipitate attacks of gout (due to hyperuricemia).
(5) Muscles: Severe pain & tenderness in pts with renal failure.
(6) Blood: Transient granulocytopenia & thrombocytopenia.

CONTRAINDICATIONS

(1) Renal failure with anuria.
(2) Hepatic coma.
(3) Hypokalemia.
(4) Hypotension.
(5) Hypersensitivity to sulfonamides.

DOSAGE

Furosemide
20-80 mg/day orally, or 20-50 mg 1M or IV.

THIAZIDE DIURETICS

MECHANISM OF ACTION

(1) They inhibit NaCl reabsorption from luminal side of epithelial cells in distal convoluted tubule &, also to a small extent in late proximal tubule 2 Inc. conc. of NaCl in tubular fluid 2 Inc. urine volume.
(2) They also inc. Ca^{+2} reabsorption in distal convoluted tubule, probably resulting from a lowering of cell Na^+.
(3) They also cause direct relaxation of arteriolar smooth muscle, accounting for continued hypotensive effect.
Note: Initial hypotensive effect is due to dec. blood vol.

CLINICAL USES

(1) Hypertension.

(2) Congestive cardiac failure.
(3) Nephrolithiasis due to idiopathic hypercalciuria.
(4) Nephrogenic diabetes insipidus.
(5) Diabetic nephropathy.
(6) Nephrosis.

ADVERSE EFFECTS

(1) CNS
Weakness, fatigability, paresthesias.

(2) Hypersensitivity Reactions
Photosensitivity, generalized dermatitis, hemolytic anemia, thrombocytopenia, acute necrotizing pancreatitis, interstitial nephritis.

(3) Electrolytes & Acid - Base Balance
Hypokalemia, metabolic alkalosis, hyponatremia, hypercalcemia.

(4) Metabolism
Hyperglycemia, hyperuricemia, hyperlipidemia.

CONTRAINDICATIONS

(1) Hepatic cirrhosis.
(2) Borderline renal failure.
(3) Hypersensitivity to thiazide or sulfonamides.

DOSAGE

(1) Bendroflumethiazide 2 2.5-10 mg OD, orally.
(2) Hydrochlorthiazide 2 25-100 mg OD, orally.

POTASSIUM - SPARING DIURETICS

SPIRONOLACTONE

Mechanism of Action

(1) It binds to cytoplasmic aldosterone receptors & prevents translocation of receptor complex to nucleus in target cell 2 This results in failure to produce mediator proteins that normally stimulate Na^+ - K^+ exchange sites of collecting tubule 2 Dec. Na^+ reabsorption, & dec. K^+ & H^+ secretion, in collecting tubules & duct 2 Inc. urinary Na^+ & volume.
(2) It also dec. intracellular formation of active metabolites of aldosterone by inhibition of 5 α - reductase activity.

Clinical Uses

(1) Primary hyperaldosteronism, eg, Conn's synd, ectopic ACTH production.
(2) Secondary aldosteronism, resulting from;
  (a) Congestive cardiac failure.
  (b) Hepatic cirrhosis.
  (c) Nephrotic syndrome.
(3) As an adjuvant to other diuretics to dec. K^+ loss.

Adverse Effects

(1) CNS
Lethargy, mental confusion, headache.

(2) GIT
Nausea, diarrhea.

(3) Endo & Repro
(a) In male: Gynecomastia, impotence, benign prostatic hypertrophy.
(b) In female: Menstrual irregularities.

(4) Electrolytes & Acid - Base Balance
Hyperkalemia, hyperchloremic metabolic acidosis.

Contraindications

(1) Chronic renal insufficiency.
(2) Liver disease.
(3) Hyperkalemia.

Dosage

25 mg 1 - 4 time daily, orally.

TRIAMTERENE & AMILORIDE

Mechanism of Action

They directly interfere with Na^+ entry thru sodium-selective ion channels, that is coupled with K^+ secretion, in apical memb. of collecting tubules 2 Inc. urinary Na^+ & volume.

Clinical Uses

(1) As an adjuvant to other diuretics to dec K^+ loss.
(2) Hypertension.
(3) Edema due to secondary aldosteronism, eg from;
  (a) Congestive cardiac failure.
  (b) Hepatic cirrhosis.
  (c) Nephrotic syndrome.

Adverse Effects

(1) CNS
Dizziness.

(2) GIT
Nausea, vomiting.

(3) Electrolyte, & Acid - Base Balance
Hyperkalemia, hyperchloremic metabolic acidosis.

(4) Metabolism
Triamterene 2 Azotemia, hyperuricemia.

(5) Muscles
Leg cramps.

(6) Renal
Triamterene 2 Acute renal failure, calculus.

Contraindications

(1) Liver disease.
(2) Gout.
(3) Hyperkalemia

Dosage

(1) Triamterene
100 mg 1-3 times daily, orally.
(2) Amiloride
5 mg OD, orally.

ADH ANTAGONISTS

Mechanism of Action

They inhibit effects of ADH at collecting tubule 2 Dec. water reabsorption 2 Inc. urine volume.

Clinical Uses

(1) Syndrome of inappropriate ADH secretion (SIADH).
(2) Other conditions causing inc. ADH, eg dec. effective circulatory blood volume.

Adverse Effects

(1) CNS
Tremulousness, mental obtundation.

(2) CVS
Cardiotoxicity.

(3) Renal
Nephrogenic diabetes insipidus, renal failure.

(4) Endo
Thyroid dysfunction.

(5) Blood
Leukocytosis.

GENERIC & TRADE NAMES

(A) Osmotic Diuretics
Mannitol: Mannitol, Osmotol.

(B) Carbonic Anhydrase Inhibitors
Acetazolamide: Acemox, Diamox.
Brinzolamide: Azopt.
Dorzolamide: Trusopt, Co-dorzal*.

(C) Loop Diuretics
Furosemide: Frusinox, Lasix, Losamide, Lasoride*.

(D) Thiazide & Similar Diuretics
Hydrochlorothiazide: Diuza, Urozide.
Indapamide: Natrilix.

(E) K^+ - Sparing Diuretics
Spironolactone: Aldactazide*, Aldactone, Spiromide*.
Triamterene: Dyazide*.
Amiloride: Conserve*, Moduretic*.

Unit II

Other Renal Drugs

ANTI-DIURETICS

These are drugs that inhibit water loss from body.

Drug Classification
(1) Antidiuretic hormone (ADH).
(2) Drugs that release ADH, eg
Morphine, Nicotine, Yohimbine, Ether, Cyclopropane.
(3) Drugs that produce constriction of afferent renal arterioles, eg
Epinephrine.
(4) Thiazides (act as antidiuretic in nephrogenic diabetes insipidus).

DRUGS FOR NEPHROLITHIASIS

Drug Classification
(1) Thiazides (dec. excretion of Ca^{+2} & oxalate in urine).
(2) Sodium cellulose phosphate (binds Ca^{+2} in gut, & dec. urinary Ca^{+2} excretion).
(3) Allopurinol (reversed hyperuricemia).
(4) Potassium citrate (alkalinizes urine).

DRUGS USED TO ALLEVIATE ABNORMAL MICTURITION

Drug Classification
(A) Incontinence Preventors
(1) Antimuscarinics, eg
Oxybutynin, Propantheline.
(2) Tricyclic antidepressants, eg
Imipramine, Amitriptyline, Nortriptyline.
(3) Smooth muscle relaxants, eg
Flavoxate.
(4) Estrogens

(B) Micturition Promoters
(1) Alpha-adrenoceptor antagonists, eg
Prazosin, Doxazosin, Indoramin.
(2) Parasympathomimetics, eg
Bethanechol, Carbachol, Distigmine.

Unit III

Drug Induced Renal Diseases

DRUG CAUSING TUBULAR DISEASES

(A) Toxic Tubular Necrosis
Caused By
(1) Aminoglycosides esp. if combine with cephalosporins or furosemide.
(2) Cephalosporins.
(3) Paracetamol overdosage.
(4) Amphotericin
(5) Cisplatin
(6) Iodine contrast media

(B) Acute Ischemic Tubular Necrosis
Caused By
(1) Antihypertensives
(2) Opiates
(3) Drugs inducing volume depletion, eg
Diuretics, & Drugs causing severe diarrhea or vomiting.
(4) NSAIDs

DRUGS CAUSING TUBULO-INTERSTITIAL DISEASES

(A) Acute Tubulo-Interstitial Nephritis

Caused By

(1) Antibiotics, eg
Penicillins, Sulfonamides, Cephalothin, Rifampin.

(2) Analgesics, eg
NSAIDs, Phenylbutazone.

(3) Others, eg
Allopurinol, Azathioprine, Cimetidine, Furosemide.

(B) Chronic Interstitial Nephritis

Caused By

Analgesics, eg
Aspirin, Phenacetin, Indomethacin, Naproxen, & other NSAIDs.

DRUGS CAUSING GLOMERULAR DISEASES

Glomerulonephritis

Caused By

(1) Penicillamine
(2) Gold
(3) Captopril
(4) Troxidone

Unit IV

Drug Selection in Renal Disease

GENERAL RULES

(1) No drug should be given unless specifically indicated.
(2) Least toxic alternative must be chosen.
(3) Dosage
(a) Drugs that are wholly or largely excreted by kidneys or, drugs that produce active renally-eliminated metabolites 2 Give a normal or slightly reduced initial dose, & lower the maintenance dose or lengthen the dose interval.
(b) Drugs that are wholly or largely metabolized to inactive products 2 Give normal doses.
(c) Drugs that are partly eliminated by kidneys & partly metabolized 2 Give a normal initial dose, & modify maintenance dose or dose interval in the light of pts' renal function.
(4) Pts must be observed regularly for signs of adverse effects, & the drug stopped or dose reduced if these develop.

DRUG SELECTION

OPIOID ANALGESICS

(1) Drugs to be Avoided

Codeine, Dihydrocodeine, Morphine, Dextropropoxyphene, Pethidine.

(2) Safe Alternatives

Methadone, Naloxone.

NON-OPIOID ANALGESICS

(1) Drugs to be Avoided

NSAIDs.

(2) Safe Alternative

Acetaminophen (Paracetamol).

CNS DRUGS

(A) Sedative-Hypnotics

Start with small doses.

(B) Anticonvulsants

(1) Used with Caution

Phenobarbital, Benzodiazepines.

(2) Safe Alternatives

Phenytoin, Na valproate, Carbamazepine, Ethosuximide.

(C) Antipsychotics

Start with small doses.

(D) Anti-Parkinsonism Drugs

(1) Drugs to be Avoided

Amantadine.

(2) Safe Alternatives

Bromocriptine, Benzhexol, Levodopa.

(E) Antimanic Drugs

(1) Drugs to be Avoided

Lithium.

(2) Other Alternatives

Antipsychotics, starting with small doses.

CARDIOVASCULAR DRUGS

(1) Drugs to be Avoided

Bethanidine, Guanethidine, Procainamide.

(2) Drugs Used with Reduced Dosage

Atenolol, Propranolol & other β-blockers, Captopril, Enalapril, Lisinopril, Nifedipine, Nicardipine, Prazosin, Methyldopa, Hydralazine.

(3) Drugs Used with Inc. Dosage-Interval

Disopyramide, Na nitroprusside.

(4) Safe Alternatives

Diazoxide, Digoxin, Digitoxin, Lidocaine, Quinidine.

DIURETICS

(1) Drugs to be Avoided

Spironolactone, Amiloride, Triamterene, Ethacrynic acid, Acetazolamide, Thiazides.

(2) Safe Alternatives

Furosemide, Bumetanide, Metolazone.

GIT DRUGS

(1) Drugs to be Avoided

Sodium bicarbonate, Mg salts, Metoclopramide, Carbenoxolone.

(2) Drugs Used with Reduced Dosage
Cimetidine, Famotidine, Nizatidine, Ranitidine.

(3) Safe Alternatives
Omeprazole, Cyclizine.

ANTI-DIABETICS

(1) Drugs to be Avoided
Acetohexamide, Chlorpropamide, Glibenclamide.

(2) Drugs Used with Reduced Dosage
Gliclazide, Glipizide, Insulin.

(3) Safe Alternatives
Tolbutamide, Gliquidone.

ANTI-MICROBIALS

(1) Drugs to be Avoided
Chloramphenicol, Cinoxacin, Ethambutol, Neomycin, Tetracyclines, (except doxycycline & minocycline), Nitrofurantoin, Nalidixic acid.

(2) Drugs Used with Reduced Dosage
Aminoglycosides, Cephalosporins, Penicillins, Co-trimoxazole, Trimethoprim, Enoxacin, Norfloxacin, Isoniazid.

(3) Safe Alternative
Erythromycin.

Unit V

Self Assessment (T/F)

(See answers on page no. 241)

(105) ***Following diuretics can produce hypokalemia by continued use***
(A) Spironolactone.
(B) Acetazolamide.
(C) Amiloride.
(D) Hydrochlorothiazide.
(E) Furosemide.

(106) ***Following diuretics markedly increases the excretion of Ca^{++} from body***
(A) Acetazolamide.
(B) Chlorothiazide.
(C) Furosemide.
(D) Spironolactone.
(E) Ethacrynic acid.

(107) ***Hydrochlorothiazide can produce***
(A) Hyperkalemia.
(B) Hyperuricemia.
(C) Hypertension.
(D) Metabolic acidosis.
(E) Hyperglycemia.

(108) ***All of the following correctly pairs the diuretic drug with one of its adverse effects***
(A) Furosemide 2 Ototoxicity.
(B) Chlorthalidone 2 Hyperuricemia.
(C) Spironolactone 2 Gynecomastia.
(D) Acetazolamide 2 Metabolic acidosis.
(E) Triamterene 2 Azotemia.

(109) ***Loop diuretics are useful in the treatment of***
(A) Congestive cardiac failure.
(B) Acute pulmonary edema.
(C) Ascites from cirrhosis.
(D) Hypocalcemia.
(E) *Acute renal failure.*

13 DRUGS AFFECTING RESPIRATORY SYSTEM

Unit I

Anti - Asthmatics

INTRODUCTION

ASTHMA

It is a disease characterized by;

(1) Inc. responsiveness of trachea & bronchi to various stimuli.

(2) Widespread narrowing of airways that changes in severity either spontaneously or as a result of therapy.

Types

(1) Early onset (atopic or allergic) asthma.

(2) Late onset (non-atopic) asthma.

Clinical Features

Recurrent episodic bouts of ;

(1) Coughing.

(2) Breathlessness.

(3) Chest tightness.

(4) Wheezing.

Pathological Features

Narrowing of airways due to ;

(1) Contraction of airway smooth muscle.

(2) Mucosal thickening from edema & cellular infiltration.

(3) Inspissation in airway lumen of abnormally thick, viscid plugs of mucus.

Trigger Factors

(1) Allergens (antigens) eg, pollen, mites in house dust, animate dander etc. They causes allergic asthma.

(2) Non-antigenic stimuli eg, exercise, cold air, distilled water, tobacco smoke, emotional stress, rapid respiratory maneuvers.

Pathogenesis

Classic allergic asthma is mediated by reexposure of sensitized IgE antibodies, bound to mast cells in airway mucosa, to an antigen 2 Antigen-antibody reaction takes place on mast cells' surface 2 This triggers both the release of mediators stored in mast cells' granules &, synthesis & release of other mediators 2 These mediators diffuse thru-out the airway wall &, causes narrowing thru muscle contraction, edema, cellular infiltration & a change in mucus secretion.

Mediators of Mast Cells' Granules

(a) Histamine.

(b) Tryptase & other neutral proteases.

(c) Leukotrienes C_4 & D_4.

(d) Prostaglandin D_2.

(e) Eosinophilic chemotactic factor.

(f) Neutrophil chemotactic factor.

DRUG CLASSIFICATION

BRONCHODILATORS

(1) Sympathomimetics

(a) ~ & Non - Selective

Epinephrine, Ephedrine.

(b) $_1$ & $_2$ Non - Selective

Isoproterenol.

(c) $_2$ Selective

Albuterol (Salbutamol), Levalbuterol, Bitolterol, Metaproterenol, Terbutaline, Ritodrine, Procaterol, Isoetharine, Formoterol, Pirbuterol, Salmeterol.

(2) Antimuscarinics

Ipratropium Br, Tiotropium.

(3) Methylxanthine Drugs

Theophylline, Aminophylline (theophylline + ethylenediamine), Theobromine, Caffeine, Oxtriphylline Dyphylline, Pentoxiphylline, Acephylline.

MAST CELL STABILIZERS

Cromolyn sodium (Disodium cromoglycate), Nedocromil Na, Ketotifen.

CORTICOSTEROIDS

Beclomethasone, Budesonide, Dexamethasone, Flunisolide, Fluticasone, Hydrocortisone, Methylprednisolone, Mometasone, Prednisone, Triamcinolone.

LEUKOTRIENE PATHWAY INHIBITORS

(1) 5-Lipooxygenase Inhibitor

Zileuton,

(2) LTD_4-Receptor Antagonists

Zafirlukast, Montelukast.

MISCELLANEOUS DRUGS

(1) Anti-IgE Monoclonal Antibodies

Omalizumab.

(2) K^+ Channel Openers
Cromakalim.

(3) Ca^{++} Channel Blockers
Nifedipine, Verapamil.

BRONCHODILATORS

METHYLXANTHINE DRUGS

Mechanism of Action
(1) Inhibit enzyme phosphodiesterase (that hydrolyzes cyclic nucleotides) 2 Inc. level of intracellular cAMP 2 Smooth muscle relaxation, & cardiac stimulation.
(2) Inhibit cell surface receptors for adenosine (that causes contraction of airway smooth muscle & inc. histamine release from cells present in lung).

Pharmacological Effects
(A) Central Nervous System
(1) At Low & Moderate Doses
(a) Mild cortical arousal , with inc. alertness.
(b) Deferral of fatigue.

(2) At High Doses
(a) Medullary stimulation.
(b) Convulsions.
(c) Nervousness.
(d) Tremor.

(B) Cardiovascular System
(1) Heart
(a) Positive chronotropic effect (inc. heart rate).
(b) Positive inotropic effect (inc. contractility).

Note: At low conc., these effects results from inc. catecholamine release that is caused by inhibition of presynaptic adenosine receptors; while, at higher conc. results from Ca^{+2} influx due to inc. in cAMP level.

(2) Blood Vessels, BP, & Blood Flow
(a) Dec. blood viscosity.
(b) Inc. blood flow.
(c) At higher doses, relax vascular smooth muscle except in cerebral blood vessels, where they cause contraction.

(C) Bronchial Smooth Muscle
Bronchodilation, due to;
(1) Direct relaxation effect.
(2) Inhibition of antigen- induced release of histamine from lung tissue.

(D) Gastrointestinal Tract
(1) Inc. gastric acid secretion.
(2) Inc. digestive enzyme secretion.

(E) Kidney
Weak diuretic effect, due to;
(1) Inc. glomerular filtration.
(2) Dec. tubular Na^+ reabsorption.

(F) Skeletal Muscle
Improve contractility & reverse fatigue of diaphragm in chronic obstructive pulmonary disease (COPD).

Clinical Uses
(1) Acute asthma.
(2) Chronic asthma.
(3) Pulmonary edema associated with cardiac failure.
(4) Bronchospasm associated with bronchitis & emphysema.

Adverse Effects
(1) CNS
Headache, anxiety, seizures, insomnia.

(2) CVS
Cardiac arrhythmias, tachycardia.

(3) GIT
Anorexia, nausea, vomiting, abdominal discomfort.

Dosage
(1) 5 mg theophylline (or 6 mg aminophylline) per kg of body weight, IV, over 30 minutes.
(2) 3-4 mg /kg of theophylline, every 6 hours, orally.
(3) 0.5 gm rectal suppositories.

OTHER BRONCHODILATORS

(A) Sympathomimetics
See chapter 2, unit II.

(B) Antimuscarinics
See chapter 3, unit III.

MAST CELL STABILIZERS

CROMOLYN NA, & NEDOCROMIL

Mechanism of Action
(1) Prevent transmembrane Ca^{+2} influx provoked by IgE antibody-antigen interaction on mast cell surface 2 This stabilizes mast cell memb. 2 This prevents release of histamine & leukotrienes from sensitized mast cells.
(2) May inhibit phosphodiesterase 2 Inc. intracellular cAMP.
(3) May alter neural pathways that influence airway smooth muscle tone.

Clinical Uses
(1) Prophylaxis of ;
(a) Exercise - induced bronchoconstriction.
(b) Aspirin - induced bronchoconstriction.
(c) Bronchospasm provoked by industrial agents eg, wood dusts, toluene diisocyanate.
(2) Perennial asthma.
(3) Extrinsic (allergic) asthma in young pts.
(4) Intrinsic asthma in old pts.
(5) To prevent seasonal inc. in bronchial reactivity in pts with allergic asthma.
(6) Allergic rhinitis.

Adverse Effects
(1) Resp. tract: Throat irritation, cough, chest tightness, wheezing, pulmonary eosinophilic infiltration.
(2) GIT: Dry mouth, gastroenteritis.
(3) Skin: Dermatitis.
(4) Muscle: Myositis.
(5) Hypersensitivity reactions: Anaphylaxis.

Dosage

Cromolyn
2 - 4 mg inhaled (thru metered - dose inhaler), QID.

CORTICOSTEROIDS

Mechanism of Action in Asthma
(1) Inhibit or modify inflammatory response in airways, eg inhibit release of arachidonic acid from cell memb. & thereby inhibit first step in production of eicosanoid products from arachidonic acid (that are responsible for airway function abnormalities in asthmatic pts).
(2) Potentiate the effects of β - adrenoceptor agonists.

Clinical Uses in Asthma
(1) Mild to moderate asthma.
(2) Asthma that do not improve adequately with broncho-dilators or that worsens despite maintenance broncho-dilator therapy.
(3) Severe acute asthma (with β_2 agonists & aminophylline).

Adverse Effects
See Chapter 17, Unit IV.

Dosage in Asthma
(1) Prednisone
30 - 60 mg/day, orally.
(2) Methylprednisolone
1 mg/kg every 6 hours, IV.
(3) Beclomethasone, Triamcinolone, Budesonide, & Flunisolide
2 puffs QID, or 4 puff BD.
Note: For more detail, see Chapter 17, Unit IV.

LEUKOTRIENE PATHWAY INHIBITORS

Mechanism of Action
(1) Montelukast & zafirlukast are leukotriene receptor antagonists, that blocks the action of leukotriene D4 on the cysteinyl leukotriene receptor CysLT1 in the lungs & bronchial tubes by binding to it. This reduces the bronchoconstriction otherwise caused by the leukotriene, & results in less inflammation.
(2) Zileuton blocks leukotriene synthesis by inhibiting 5-lipoxygenase, an enzyme of the eicosanoid synthesis pathway.

Clinical Uses
(1) Maintenance treatment of asthma.
(2) To relieve symptoms of seasonal allergies.

Adverse Effects
(1) CNS: Sleep disorders.
(2) GIT: Gastrointestinal disturbances.
(3) Blood: Increased bleeding tendency.
(4) Hypersensitivity reactions.

MISCELLANEOUS DRUGS

CA^{+2} CHANNEL BLOCKERS

Mechanism of Action in Asthma
Inhibit Ca^{+2} influx in bronchial smooth muscle cells & other cells involved in asthma 2 Prevent contraction of airway smooth muscle, & secretion of mucus & other mediators.

Clinical Uses in Asthma
Bronchoconstriction induced by;
(1) Exercise.
(2) Hyperventilation.
(3) Inhalation of aerosolized histamine, methacholine, or antigen.
Note: For detail description see Chapter 11, Unit II.

GENERIC & TRADE NAMES

(A) Bronchodilators
(1) Sympathomimetics
See Chapter 2, Unit II
(2) Antimuscarinics
See Chapter 3, Unit III.
(3) Methylxanthine Drugs
Acephylline: Acefyl, Broncophylline, Etaphylline.
Aminophylline: Amphyll, Asmol*, Asmoline, Phylocontin.
Caffeine: Asmol*, Panadol extra, Trigesic....
Pentoxifylline: Agapurin.
Theophylline: Asthalin, Asmasal, Quibron-T/SR, Theo-Dur, Theograd, Theophylline.

(B) Other Antiasthmatics
(1) Mast Cell Stabilizers
Ketotifen: Asfen, Asthanil, Asthotifen, Ketofen, Mactifen, Totifen, Zatofen.
(2) Corticosteroids
See Chapter 17, Unit IV.
(3) Ca Channel Blockers
See Chapter 11, Unit II.
(4) LTD4 Antagonists
Zafirlukast: Freair, Zafir, Zukast.
Montelukast: Aerotel, Bronast, Lucast, Montiget.

Unit II

Respiratory Stimulants

(Analeptics)

DRUGS CLASSIFICATION

ANALEPTICS
It refers to drugs that stimulate respiratory centre in medulla, & are used for emergency treatment of respiratory failure.

CLASSIFICATION

(A) Direct Stimulants of Respiratory Center

(1) Brainstem Stimulants
Nikethamide, Doxapram, Ethamivan, Leptazol.

(2) Cerebral Stimulants
Caffeine, Ephedrine, Amphetamine, Atropine, Scopolamine.

(3) Competitive Opioid Antagonists
Nalorphine, Levallorphan, Naloxone.

(4) Gases
Carbon dioxide (CO_2).

(B) Reflex Stimulants of Respiratory Centre

(1) Stimulants of Chemoreceptors
CO_2, Nikethamide, Lobeline.

(2) Respiratory Mucosal Irritants
Aromatic spirit of Ammonia or Alcohol.

NIKETHAMIDE

Mechanism of Action
(1) Directly stimulate medullary respiratory centre by increasing its sensitivity to CO_2.
(2) Reflexly stimulate medullary respiratory centre thru stimulation of chemoreceptors of carotid & aortic bodies.

Clinical Uses
(1) Acute respiratory failure, eg from acute exacerbations of chronic lung diseases.
(2) Overdosage of central depressants.

Adverse Effects
(1) CNS: Restlessness, twitching (at first around mouth).
(2) CVS: Cardiac arrhythmias.
(3) GIT: Vomiting.
(4) Skin: Itching, flushing.

Contraindications
(1) Ischemic heart disease.
(2) Status asthmaticus.
(3) Severe hypertension.
(4) Thyrotoxicosis.

Dosage
1 - 5 ml of 25% sol. , IM or IV.

GENERIC & TRADE NAMES

Nikethamide: Nikethamid.
Naloxone: Naloxone.

Unit III

Anti - Tussives

INTRODUCTION

COUGH
It is a protective reflex with sudden noisy expulsion of air from airways, that serves the purpose of expelling sputum & other irritant materials from upper part of airways.

Types
(1) Productive (Useful) Cough
It effectively expels secretions, exudates, transudates, or extraneous material from respiratory tract.

(2) Unproductive (Useless) Cough
It is due to local irritation, eg smokers cough.

DRUG CLASSIFICATION

DRUGS FOR PRODUCTIVE COUGH

(1) Expectorants

(a) Sedative Expectorants
(i) Alkaline Expectorants
Potassium citrate & acetate.

(ii) Nauseant Expectorants
Tincture ipecacuanha, Ammonium chloride & carbonate.

(iii) Saline Expectorants
Sodium & Potassium iodide.

(b) Stimulant (Aromatic) Expectorants
Creosote, Guaiacol, Terpene hydrate, Guaiphenesin.

(2) Mucolytics
Acetylcysteine, Bromohexine, Carbocysteine, Methylcysteine, Proteolytic enzymes (eg, Pancreatic dornase & trypsin), Ambroxol.

DRUGS FOR UNPRODUCTIVE COUGH

(1) Peripheral Antitussives

(a) Demulcents
Liquorice lozenges.

(b) Steam Inhalation
With tincture benzoin co. or menthol.

(c) Drugs with Local Anesthetic Activity
Benzonatate.

(2) Central Antitussives

(a) Opioid Antitussives
(i) Nonaddicting Drugs
Codeine phosphate, Dihydrocodeinone, Pholcodine.

(ii) Addicting Drugs
Morphine, Methadone, Heroin, Dihydromorphinone.

(b) Nonopioid Antitussives
Dextromethorphan, Narcotine, Chlorphedianol, Carbetapentane, Oxeladin, Benzonatate.

DRUGS FOR PRODUCTIVE COUGH

EXPECTORANTS

It refers to drugs that facilitate removal of respiratory secretions by coughing.

Mechanism of Action

(A) Sedative Expectorants

They soothe inflamed respiratory mucosa by stimulating protective mucus secretions from secretory cells of respiratory airways 2 Inc. fluidity of sputum, that helps in its expectoration by cough.

(1) *Alkaline Expectorants*

Inc. alkaline reserve of blood, excess base being excreted thru bronchial glands;

(a) Mildly stimulate bronchial glands to secrete protective mucus.

(b) Dissolve mucus or sputum, by rendering it thinner or less sticky.

(2) *Nauseant Expectorants*

Stimulate sensory nerve ending in stomach & duodenum 2 Reflex stimulation of copious bronchial secretions.

(3) *Saline Expectorants*

Directly stimulate bronchial secretory cells & liquefy tenacious sputum.

(B) Stimulant Expectorant

(1) Stimulate healing & repair of chronically inflamed respiratory mucosa.

(2) Dec. amount of sputum, & remove its objectionable odor & taste.

MUCOLYTICS

It refers to drugs that liquefy viscid bronchial secretions, & so enhances therapeutic efficacy of expectorants.

Mechanism of Action

Acetyl - , Carbo - , & Methylcysteine

Split sulfhydryl groups that opens disulfide bonds in mucus, & reduces its viscosity.

Bromohexine

Reduces viscosity of bronchial secretions by depolymerization of mucopolysaccharides in ground substance of bronchial secretions.

Clinical Uses

(1) Acute & chronic bronchitis.

(2) Respiratory conditions associated with viscid mucus.

Adverse Effects

(1) CNS: Headache, tinnitus.

(2) GIT: GI disturbances.

(3) Skin: Urticaria.

Dosage

(1) Bromohexine: 8-16 mg , orally, TDS.

(2) Ambroxol: 30 mg , orally, TDS.

(3) Acetylcysteine: 1 sachet (200 mg), orally, TDS.

DRUGS FOR UNPRODUCTIVE COUGH

PERIPHERAL ANTI-TUSSIVES

Mechanism of Action

They suppress cough reflex by decreasing the input of stimuli from cough receptors in respiratory passages.

(1) Demulcents

They glutinously & soothingly coat pharynx.

(2) Steam Inhalation

Steam inhalation with tincture benzoin co. or menthol promotes secretion of protective mucus.

(3) Drugs with Local Anesthetic Activity

Benzonatate reduce cough by depressing pulmonary stretch receptors. It also has a central cough suppressant effect.

Clinical Uses

(1) Demulcents

Cough due to sore - throat & pharyngitis.

(2) Steam Inhalation

Cough due to tracheo - bronchitis.

CENTRAL ANTI-TUSSIVES

Mechanism of Action

They suppresses cough by a direct depressant effect on medullary cough centre.

Clinical Uses

Un-productive cough.

Adverse Effects

See chapter 8.

Dosage

(1) Pholcodine: 10-20 mg , orally, TDS or QID.

(2) Codeine: 15-30 mg , orally, at bed time.

(3) Dextromethorphan: 15-30 mg , orally, TDS.

GENERIC & TRADE NAMES

(A) Expectorants

Ammonium Chloride: Amchol*, Amcodrin*, Amcoride*, Ammodryl*, Ammonium Cl, Bronex*, Bronochol*, Hydryllin*, Pulmonol*.....

Ammonium Carbonate: Pacific's Mixture*.

Guaiphenesin: Azmolin*, Bilfensein*, Triaminic chest*, Triaminic E*, Ventolin*.

(B) Mucolytics

Acetylcysteine: Mucolator, Rinofluimucil.

Ambroxol: Fluibron, Mucosolvon.

(C) Central Antitussives

Pholcodine: Avanol*, Brovenol*, Davenol*, Liskoz*, Phensedyl-P*, Pholcodine, Sancos*, Tixylix*, Tricof*.

Dextromethorphan: Actified DM*, Babynol*, Benatus*, Combinol - D*, Dexodine*, Dextromethorphan, Hydrillin DM, Rondec, Triaminic cough, Tussivil.

Noscapine: Noscabine*, Triplon - N*, Tripofed*.

Unit IV

Self - Assessment (T/F)

(See answers on page no. 241)

(110) ***Regarding theophylline, following are correct***

(A) It stimulates cell surface receptors for adenosine.
(B) It causes inc. intracellular level of cAMP.
(C) It inhibits gastric acid & digestive enzyme secretions.
(D) It is useful in acute & chronic asthma.
(E) It may cause headache & tremors.

(111) ***Major action of cromolyn sodium is***

(A) Smooth muscle relaxation in bronchi.
(B) Stimulation of cortisol release by adrenals.
(C) Blockade of Ca^{++} channels in lymphocytes.
(D) Blockade of mediator release from mast cells.
(E) Blockade of cAMP synthesis in basophils.

(112) ***Regarding analeptics, following are correct***

(A) Nikethamide causes reflex, as well as direct stimulation of respiratory centre.
(B) Amphetamine is a brainstem stimulant.
(C) Nikethamide is useful for treating respiratory failure in acute asthma.
(D) Nikethamide may cause cardiac dysrhythmias.
(E) Doxapram stimulates respiratory centre in medulla.

(113) ***Central anti-tussives includes***

(A) Pholcodine.
(B) Benzonatate.
(C) Dextromethorphan.
(D) Ammonium chloride.
(E) Bromohexine.

14 GASTROINTESTINAL DRUGS

Unit I

Anti - Peptic Ulcer Drugs

INTRODUCTION

PEPTIC ULCER

It refers to an excoriation of GIT mucosa in or adjacent to an acid-bearing area.

Sites

(1) Stomach & proximal duodenum.
(2) Esophagus (with reflux esophagitis).
(3) Jejunum (in Zollinger- Ellison syndrome or after gastrectomy).
(4) Meckel's diverticulum (that contains ectopic gastric mucosa).

Etiology

(1) Imbalance b/w acid-pepsin secretion & normal defences of gastroduodenal mucosa;
  (a) Inc. gastric acid & pepsin secretion.
  (b) Dec. mucosal resistance to acid, due to ;
    (i) Dec. production of gastroduodenal mucus.
    (ii) Dec. secretion of bicarbonate by epithelial cells.
(2) Bacterium Helicobacter pylori
(3) Hereditary

Precipitating Factors

(1) Aspirin
(2) NSAIDs
(3) Mental stress
(4) Smoking
(5) Alcohol

DRUG CLASSIFICATION

ANTACIDS

(1) Dietary Antacids
Milk, Fats, Oils.

(2) Chemical Antacids

(a) Systemic Antacid
Sodium bicarbonate ($NaHCO_3$).

(b) Non-Systemic Antacids

(i) Magnesium Salts
Mg-oxide, Mg-hydroxide, Mg-carbonate, Mg-trisilicate.

(ii) Calcium Salts
Ca - carbonate.

(iii) Aluminium Salts
Al - hydroxide, Al - phosphate, Dihydroxy-aluminium aminoacetate, Basic Al-carbonate.

(c) Physical Antacids

(i) Drugs Forming Colloidal Sol.
Gastric mucin, Al - hydroxide gel, Mg-trisilicate.

(ii) Anion Exchange Resins

GASTRIC ANTI - SECRETORY DRUGS

(1) Proton Pump Inhibitors
Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole, Rapeprazole.

(2) H_2 - Receptor Antagonists
Cimetidine, Famotidine, Nizatidine, Ranitidine.

(3) Anti - Muscarinics
Pirenzepine, Propantheline, Methscopolamine.

MUCOSAL PROTECTIVE AGENTS

(1) Sucralfate (Al - sucrose sulfate).
(2) Colloidal Bismuth compounds, eg;
Bismuth subsalicylate, Bismuth dinitrate, Bismuth subcitrate.
(3) Carbenoxolone.
(4) Prostaglandins analogues, eg;
Misoprostol.

ANTACIDS

MECHANISM OF ACTION

Antacids are weak bases that neutralizes gastric acidity by reacting with gastric HCl to form a salt & water.

(A) Sodium Bicarbonate
$NaHCO_3 + HCl$ 2 $NaCl + CO_2 + H_2O$.

(B) Magnesium Oxide
$MgO + 2HCl$ 2 $MgCl_2 + H_2O$. (**Note:** $MgCl_2$ reacts with $NaHCO_3$ of intestinal secretions to form carbonate, & chloride is released & reabsorbed).

Box 14.1 PROPERTIES OF AN IDEAL ANTACID

1) Immediate & prolonged neutralization of acid without increasing pH above 4.
2) Action should be confined to GIT.
3) No constipating or laxative effects.
4) No effects on acid - base balance.
5) Free from adverse effects.
6) Palatable to pts.

(C) Magnesium Trisilicate

(1) Mg - Trisilicate + 2HCl 2 $MgCl_2$ + Silicon dioxide.

(2) Silicon dioxide has also a demulcent action, & also adsorbs gastric HCl.

(D) Calcium Carbonate

$CaCO_3$ + 2HCl 2 $CaCl_2$ + CO_2 + H_2O.

Note: In small intestine $CaCl_2$ is precipitated as carbonate, phosphate & insoluble soap.

(E) Aluminium Hydroxide

(1) $Al(OH)_3$ + 3HCl 2 $AlCl_3$ + $3H_2O$.

Note: $AlCl_3$ reacts with intestinal secretions to produce insoluble salts esp. phosphate, & chloride is released & reabsorbed.

(2) Al - compounds also acts via a direct cytoprotective action, or by binding HCl & pepsin.

CLINICAL USES

(A) Sodium Bicarbonate

(1) As antacid for;
  (a) Gastric hyperacidity.
  (b) Peptic ulcer.

(2) As base for systemic acidosis.

(3) As urine alkalinizer.

(B) Magnesium Compounds & Aluminium Hydroxide

Usually available in combinations (to balance their purgative & constipative effects);

(1) Gastric hyperacidity.
(2) Peptic ulcer.
(3) Dyspepsia.
(4) Hiatus hernia.
(5) Acute & chronic recurrent gastritis.

(C) Calcium Compounds

(1) Gastric hyperacidity.
(2) Peptic ulcer

ADVERSE EFFECTS

(A) Sodium Bicarbonate

(1) GIT

Gastric distension & discomfort, peptic ulcer perforation or hemorrhage, acid rebound.

Note: These effects are due to CO_2.

(2) Water & Acid - Base Balance

Metabolic alkalosis, fluid retention.

(B) Magnesium Compounds

(1) GIT

Diarrhea.

(2) Electrolyte Balance

Hypermagnesemia (in pts with renal insufficiency).

(C) Calcium Carbonate

(1) GIT

Constipation, acid rebound.

(2) Kidney

Nephrolithiasis.

(3) Electrolyte Balance

Hypercalcemia.

(4) Milk - Alkali Syndrome

Occur with concomitant heavy milk drinking (often advised in peptic ulcer), & is characterized by;

(a) Headache, weakness.
(b) Anorexia, nausea, vomiting, abdominal pain, constipation.
(c) Thirst, polyuria, temporary or permanent renal damage.

(D) Aluminium Hydroxide

(1) GIT

Constipation.

(2) Electrolyte Balance

Hypophosphatemia.

(3) Drugs Adsorption

Reduces bioavailability of some drugs, eg tetracyclines, atropine.

CONTRAINDICATIONS

(A) Sodium Bicarbonate

(1) Renal insufficiency.
(2) Cardiac failure.
(3) Hypertension.
(4) Peripheral & pulmonary edema.
(5) Toxemia of pregnancy.

(B) Magnesium & Calcium Compounds

Renal insufficiency.

GASTRIC ANTI - SECRETORY DRUGS

H_2 - RECEPTOR ANTAGONISTS

Mechanism of Action

(1) Competitively block histamine at H_2-receptors on gastric parietal cells 2 Dec. HCl secretion.

(2) Competitively block histamine at H_2-receptors on vascular smooth muscle cells 2 Block histamine induced vasodilation.

Pharmacological Effects

(1) Gastrointestinal Tract

(a) Inhibits gastric acid secretion stimulated by histamine, gastrin, insulin, caffeine, muscarinic drugs, & vagal stimulation.
(b) Dec. basal, food-stimulated, & nocturnal secretion of gastric acid.
(c) Dec. volume & H^+ conc. of gastric juice.

(2) Liver

Cimetidine & ranitidine (to a lesser extent) inhibit cytochromic P-450 mixed function oxidase system 2 Slows hepatic microsomal metabolism of some drug, eg warfarin, theophylline, diazepam, phenytoin, lignocaine, propranolol.

Note: Famotidine & nizatidine have no effect on hepatic drug metabolism.

(3) Endocrine

Cimetidine (& only rarely ranitidine & famotidine) inc. serum prolactin level, & alter estrogen metabolism in males 2 Reversible gynecomastia & sexual dysfunction.

Clinical Uses

(1) Duodenal ulcer.
(2) Benign gastric ulcer.
(3) Stomal ulcer.
(4) Reflux esophagitis.
(5) Prophylaxis of GI bleeding due to gastric erosions, eg from burns, fulminant hepatic failure, renal failure, trauma.
(6) Before anesthesia for emergency surgery & before labor to lessen the risk of aspirating gastric acid.
(7) Zollinger - Ellison syndrome.
(8) Systemic mastocytosis, & multiple endocrine adenomas.

Adverse Effects

(1) CNS

Confusional states, headache, somnolence, hallucinations, delirium, brainstem dysfunction, peripheral neuropathy.

(2) CVS

Bradycardia, cardiac conduction defects.

(3) GIT

Diarrhea, constipation.

(4) Liver

Transient & reversible change in liver function tests (LFTs).

(5) Endo

(a) In male: Gynecomastia, impotence.
(b) In female: Galactorrhea.
(See also pharmacological effects above).

(6) Blood

Reversible blood dyscrasias.

Precautions

(1) Malignancy.
(2) Renal insufficiency.
(3) Pregnancy & lactation.

Dosage

(1) Cimetidine

(a) Oral: 400 - 600 mg BD, or 800 mg at bed - time.
(b) IM: 200 mg; may be repeated at 4 - 8 hourly intervals.
(c) IV: 400 mg diluted in 100 ml 5% Dextrose, given over 30 minutes; upto a max of 2400 mg daily.

(2) Ranitidine & Nizatidine

150 mg BD orally, or 300 mg at bed - time.

(3) Famotidine

20 mg BD orally, or 40 mg at bed - time.

PIRENZEPINE

Mechanism of Action

Blocks selectively gastric M_1-muscarinic cholinoceptors 2 Inhibits gastric secretions.

Clinical Uses

(1) Gastric ulcer.
(2) Duodenal ulcer.

Adverse Effects

(1) CNS: Headache.
(2) Eye: Difficulty in visual accommodation.
(3) GIT: Dry mouth, constipation, diarrhea.

Dosage

25 - 50 mg BD orally before meals, for 4 - 6 weeks.

PROTON PUMP INHIBITORS (PPI)

Mechanism of Action

Irreversibly inhibit gastric parietal cell proton pump (H^+/K^+ ATPase) 2 Inhibit exchange of proton (H^+) in cell cytoplasm & K^+ in canalicular lumen 2 No H^+ is secreted in canaliculi to combine with Cl^- &, so, no HCl forms.

Clinical Uses

(1) Erosive reflux esophagitis.
(2) Benign peptic ulcers unresponsive to conventional treatment.
(3) Zollinger - Ellison syndrome.
(4) Systemic mastocytosis & multiple endocrine neoplasias.

Box 14.2 ERADICATION THERAPY

1) It is used for H pylori associated peptic ulcer.
2) The goal is to heal the ulcer & eradicate the organism.
3) First 2 antibiotics & a proton pump inhibitor are given for 10-14 days;
   a) PPI twice daily + clarithromycin 500 mg BD + amoxicillin 1 g BD
   b) PPI twice daily + clarithromycin 500 mg BD + metronidazole 500 mg BD (in patients allergic to penicillin)
4) Then PPI alone for further 4-6 weeks.

Adverse Effects

(1) CNS: Headache.
(2) GIT: Nausea, diarrhea, constipation.
(3) Skin: Rashes.

Contraindications

(1) Pregnancy & lactation.
(2) Malignancy.
(3) Renal insufficiency (Lansoprazole).

Dosage

(1) Omeprazole

20 - 40 mg OD, orally or IV, for 4 - 8 weeks.

(2) Lansoprazole

30 mg OD, orally, for 4 - 8 weeks.

(3) Rabeprazole

20 mg OD, orally, for 4 - 8 weeks.

MUCOSAL PROTECTIVE AGENTS

SUCRALFATE

Mechanism of Action

(1) In acid environment of stomach, Al^{+3} moiety dissociates & negatively charged sucrose-sulfate binds electro-statically to positively charged protein molecules that transude from necrotic ulcer base 2 Result is a viscuous paste that adheres selectively to ulcer base, where it act as a barrier to acid, pepsin, & bile.
(2) Binds to & inactivates pepsin & bile salts.
(3) Stimulate endogenous prostaglandin synthesis.
(4) Prevent damaging back-diffusion of H^+ from lumen to mucosa.

Clinical Uses

(1) Benign gastric ulcer.
(2) Duodenal ulcer.
(3) Chronic gastritis.

Adverse Effects

(1) GIT: Benign gastric ulcer
(2) Drug absorption: Al content interfere with absorption of other drugs, eg tetracyclines, phenytoin, cimetidine, digoxin.

COLLOIDAL BISMUTH COMPOUNDS

Mechanism of Action

(1) Selectively bind to an ulcer & coat it, to protect from acid & pepsin.
(2) Inhibit pepsin activity .
(3) Stimulate mucus production.
(4) Stimulate endogenous prostaglandin synthesis.
(5) Have some antimicrobial activity against Helicobacter pylori.

Clinical Uses

(1) Duodenal ulcer.
(2) Gastric ulcer.

Adverse Effects

GIT: Darkens tongue, teeth, & stool.

CARBENOXOLONE

Mechanism of Action

(1) Inc. production & viscosity of gastric & intestinal mucus.
(2) Dec. H^+ diffusion from lumen into mucosa.
(3) Dec. rate of shedding of gastric mucosal cells.

Clinical Uses

(1) Gastric ulcer.
(2) Duodenal ulcer.

Adverse Effects

Results from its aldosterone - like activity.
(1) CVS: Hypertension, heart failure.
(2) Water & electrolyte balance: Fluid retention. edema, hypokalemia.

MISOPROSTOL

Mechanism of Action

(1) Inhibit gastric secretion thru inhibition of histamine - stimulated cAMP production.
(2) Stimulate mucus & bicarbonate secretion.
(3) Prevent luminal H^+ from diffusing into mucosa, eg in response to aspirin, ethanol & bile salts.
(4) Inc. rate of mucosal cell replication.
(5) Maintain adequate mucosal blood flow 2 Remove H^+ & ensures a supply of O_2 & nutrients.

Clinical Uses

(1) Duodenal ulcer.
(2) Gastric ulcer.
(3) Treatment & prophylaxis of NSAID - induced peptic ulceration.

Adverse Effects

(1) GIT: Diarrhea, abdominal pain.
(2) Endo & Repro: Dysmenorrhea, spotting.
(3) Pregnancy: Abortion.

Box 14.3

DRUGS CONTRAINDICATED IN PEPTIC ULCER

1) Salicylates
2) NSAIDs
3) Adrenal steroids & ACTH
4) Phenylbutazone
5) Reserpine
6) Tolazoline
7) Alcohol
8) Xanthine beverages (coffee, tea)
9) Tobacco

GENERIC & TRADE NAMES

(A) Antacids

Sodium Bicarbonate: Citro-soda*, Eno*, Gaviscon*, Gripe water.
Magnesium Hydroxide: Phillips milk of Magnesia.
Magnesium Trisilicate: Amtri.
Aluminium Hydroxide: Actal.
Al - Hydroxide & Mg - Hydroxide: Geogil, Magalcid, Magnacid.
Al – Hydroxide, Mg – Hydroxide & Simethicone: Alucid, Gelusil, Mylanta 2, Simeco.
Al – Hydroxide, Mg – Hydroxide & Oxethazaine: Dicaine, Mucaine.
Al – Hydroxide, Mg – Hydroxide, Simethicone & Dicyclomine: Colenticon.
Al - Hydroxide & Mg - Carbonate: Algicon.
Al – Phosphate & Simethicone: Aluphagel.

(B) Gastric Antisecretory Drugs

Omeprazole: Encid, Losec, Omezol, Ramezol, Risek, Teph 20.
Esomeprazole: Esodin, Esopra, Nexum.
Lansoprazole: Agopton, Gerd, Lanzac, Lazol, Zoton.
Pantoprazole: Gastrocid, Pantozol, Pezole.
Rabeprazole: Rabz, Repar.

Cimetidine: Cimet, Cimetamat, Citamet, Normacid, Semidine, Tagamet, Ulceloc, Ulcemet, Ulcerex.
Famotidine: Fadiphene, Famdine, Famopsin, Famot, H2F, Pepcidine, Peptiban, Zepcin.
Nizatidine: Axid, Ulcid.
Ranitidine: Apsar, Hitac, H2 Rec, Ranax, Ranidine, Ranitid, Ranitin, Zantac.
Pirenzepine: Gastrozepin.

(C) Mucosal Protective Agents

Sucralfate: Alusulin, Macralfate, Sucfate, Sulcrate, Ulcerat, Ulsanic.
Bismuth Subsalicylate: Bismol.
Misoprostol: Cytotec.

Unit II

Anti - Emetics

INTRODUCTION

VOMITING (EMESIS)

It is a protective reflex mechanism for eliminating irritant or harmful substances from upper GIT.

Control of Vomiting

Vomiting is controlled by 'vomiting centre' located in reticular formation of medulla, that co-ordinates act of emesis on receiving stimuli from;

(1) Chemoreceptor trigger zone (CTZ).
(2) Vestibular system.
(3) Periphery, eg in distension or irritation of gut, myocardial infarction, biliary or renal calculus.
(4) Cortical centres.

Causes of Vomiting

(1) Pregnancy.
(2) Motion sickness.
(3) GI obstruction.
(4) Peptic ulcer.
(5) Drug toxicity.
(6) Myocardial infarction.
(7) Renal failure.
(8) Hepatitis.

DRUG CLASSIFICATION

CENTRAL ANTIEMETICS

(1) Dopamine D_2 - Receptor Antagonist
Droperidol, Haloperidol.
(2) Sedative - Hypnotics
Barbiturates, Benzodiazepines.
(3) Neurokinin Receptor Antagonists
Aprepitant.
(4) Cannabinoids
Dronabinol, Nabilone.

CENTRAL & PERIPHERAL ANTIEMETICS

(1) D_2 - Receptor Antagonists

(a) Substituted Benzamides
Metoclopramide, Trimethobenzamide.

(b) Phenothiazines
Chlorpromazine, Prochlorperazine, Promethazine Thiethylperazine.

(2) Serotonin $5HT_3$ - Receptor Antagonists
Ondansetron, Granisetron, Dolasetron, Palonosetron.
(3) Antimuscarinics
Scopolamine, Atropine.
(4) H_1 - Receptor Antagonists
Cyclizine, Cinnarizine Meclizine, Dimenhydrinate, Diphenhydramine.

PERIPHERAL ANTIEMETICS

(1) Demulcents
Gum acacia, Gum tragacanth.
(2) Adsorbents
Aluminium hydroxide, Kaolin.
(3) Gastric Mucosal Anesthetics
Chloretone (Chlorbutanol), Dilute hydrocyanic acid.

METOCLOPRAMIDE

MECHANISM OF ACTION

(1) Central
Block dopamine D_2 - receptors in CTZ.
(2) Peripheral
Enhances action of acetylcholine at muscarinic nerve endings in gut 2 This causes;
(a) Inc. tone of lower esophageal sphincter.
(b) Relaxation of pyloric antrum & duodenal cap.
(c) Inc. peristalsis & emptying of upper gut.

CLINICAL USES

(1) Nausea & vomiting associated with;
(a) GI disorders.
(b) Postsurgical conditions.
(c) Cytotoxic drugs.
(d) Radiotherapy.
(2) To empty stomach (ie, prokinetic use);
(a) Before emergency anesthesia.
(b) In labor.
(c) In diabetic gastroparesis (delayed gastric emptying).
(d) After vagotomy.
(e) In gastroesophageal reflux.

ADVERSE EFFECTS

(1) CNS: Restlessness, torticollis, facial spasms, trismus, oculogyric crisis, tardive dyskinesia.
(2) GIT: Diarrhea.

(3) Endocrine: Gynecomastia, lactation (due to inc. prolactin secretion).

Precautions

(1) Pregnancy & lactation.
(2) Renal or hepatic impairment.

CONTRAINDICATIONS

(1) Recent gastrointestinal surgery.
(2) Prolactin - dependent breast carcinoma.
(3) Pheochromocytoma.

DOSAGE

10 mg TDS orally, IM or IV.

DRUG TREATMENT OF SPECIFIC VOMITING

(A) Motion Sickness

(1) Cinnarizine.
(2) Cyclizine.
(3) Dimenhydrinate.
(4) Scopolamine.
(5) Promethazine.

(B) Vomiting due to Cytotoxic Drugs

(1) Dexamethasone.
(2) Lorazepam.
(3) Metoclopramide.
(4) Ondansetron.

(C) Vomiting in Pregnancy

(1) Promethazine.
(2) Thiethylperazine.
(3) Vit B_6 (Pyridoxine).
(4) Vit B_6 plus Meclizine.

(D) Vertigo

(1) Scopolamine.
(2) Phenothiazines, eg Prochlorperazine or Thiethylperazine.
(3) Cyclizine.
(4) Betahistine (a histamine analogue).
(5) Cinnarizine.

GENERIC & TRADE NAMES

(A) D_2 - Receptor Antagonists

Haloperidol: Haldol, Serenace.
Metoclopramide: Digestine, Fimet, Gastrolon, Maxolon, Metoclon, Metomide, Plasil, Regelan.
Domperidone: Costi, Motilium, Pelton, Peridone.
Chlorpromazine: Largactil, Sedectil.
Prochlorperazine: Dometil, Stabil, Stemetil.
Promethazine: Avomine, Phenergan, Phenerzine,
Thiethylperazine: Torecan.
Acepromazine: Acozine.

(B) 5 - HT_3 - Receptor Antagonists

Ondansetron: Ondison, Setron, Zofran.
Granisetron: Gytril.
Tropisetron: Navoban.

(C) Antimuscarinics

See chapter 3.

(D) H_1 - Receptor Antagonists

Cyclizine: Marzine, Migril*.
Cinnarizine: Cerebrin, Stugeron.
Dimenhydrinate: Devinate, Dimenic, Gravinate.
Meclizine: Navidoxine, Sevidoxine.
Promethazine: Miprozine, O - Zine, Phenergan, Promazine, Semozin.

Unit III

Anti-Diarrheals

[Constipatives]

INTRODUCTION

DIARRHEA

It refers to inc. frequency & liquidity of feces.

Causes (Types) of Diarrhea

(1) Travellers' diarrhea
(2) Infective Diarrheas
(a) Amebic dysentery.
(b) Giardiasis.
(c) Typhoid fever.
(d) Cholera.
(e) Bacillary dysentery.
(f) Food poisoning.
(3) Malabsorption Diarrheas
(a) Celiac disease.
(b) Tropical sprue.
(c) Whipple's disease.
(d) Lactose intolerance.
(e) Stagnant loop syndrome.
(4) Bowel Inflammations
(a) Ulcerative colitis.
(b) Crohn's disease.
(5) Drug - Induced Diarrheas
(a) Antimicrobials, eg penicillins, cephalosporins, clindamycin, lincomycin.
(b) Mg - containing antacids.
(c) Iron salts.
(d) NSAIDs, eg indomethacin, mefenamic acid, flurbiprofen.

DRUG TREATMENT OF DIARRHEA

FLUID & ELECTROLYTE TREATMENT

Oral rehydration therapy (ORT) with glucose-electrolyte solution (eg ORS).

SPECIFIC TREATMENT OF CAUSE

(1) Anti - bacterials, eg
Trimethoprim or ciprofloxacin for typhoid fever, food poisoning & bacillary dysentery.
(2) Amebicides, eg
Metronidazole for amebic dysentery.
(3) Bile salt-binding resins, eg
Cholestyramine or colestipol for diarrhea cause by excess fecal bile acids.
(4) Octreotide (a somatostatin analog) for diarrhea caused by carcinoid tumor, VIPoma, vagotomy, dumping syndrome, short bowel syndrome or AIDS.
(5) Withdrawal of food causing malabsorption.
(6) Withdrawal of drugs causing diarrhea.

ANTI - DIARRHEALS

(1) Gastrointestinal Protectives & Adsorbents
Bismuth subsalicylate, Attapulgite, Kaolin, Pectin.

(2) Astringents
Vegetable drugs that release tannic acid, eg;
Kino, Krameria, Cathechu.

(3) Anti - Motility Drugs
(a) Antimuscarinics
Atropine, Mepenzolate, Propantheline, Dicyclomine.

(b) Opioid Derivatives
Codeine, Diphenoxylate, Loperamide.

GENERIC & TRADE NAMES

(A) Oral Rehydration Salt (ORS)
Arosal F, Neolyte, Babylyte ORS, Orasal-F, Peditral, Pedialyte.

(B) Adsorbents
Bismuth subsalicylate: Bismol.
Attapulgite: Detox, Entox - P, Jetox, Kaltin AP*, Kaopectal, Neo-Intestopan, Novotox, Semotox.
Kaolin & Pectin: Diarhol, Kaltin, Kaolin pectin, Kaomagma, Kaostop, Kaptin, Streptomagma.

(C) Antimuscarinics
See chapter 3.

(D) Opioid Derivatives
Diphenoxylate: Lomotil*, Motilex*, Reostop*, Rexotil*.
Loperamide: Diastop, Imodium, Loperamide 2, Lopra, Tabromide.

Unit IV

Laxatives

[Anti-Constipatives, Purgatives, Cathartics, Evacuants, Aperient]

INTRODUCTION

CONSTIPATION

It refers to infrequent or difficult evacuation of hard feces.

Causes of Constipation
(1) Inadequate diet & lifestyle, eg
Lack of fibre & exercise.
(2) Drugs, eg;
(a) Opioid analgesics.
(b) Anti-inflammatory agents.
(c) Ca - & Al - containing antacids.
(d) Anti - depressants.
(e) Diuretics.
(f) Antimuscarinics, eg atropine.
(3) Psychiatric & neurological disorders, eg;
(a) Ignoring call to stool.
(b) Physical disability.
(4) Organic diseases of anus, rectum, & colon.
(5) Secondary intestinal motility disorders, eg;
(a) Hypothyroidism.
(b) Disease of colonic muscle or nervous plexuses, eg scleroderma.

DRUG CLASSIFICATION

BULK LAXATIVES

(1) Hydrophilic Colloids
Agar, Psyllium seeds & husks (Ispaghula husk), Methylcellulose, Polycarbophil, Bran, Sterculia.

(2) Osmotic Laxatives
(a) Saline Cathartics
Magnesium citrate, Mg hydroxide, Mg oxide (milk of magnesia), Sodium citrate, Na sulfate, K - Na - tartarate.

(b) Non-absorbable Sugar
Sorbitol, Lactulose.

(c) Balanced polyethylene glycol

STIMULANT (IRRITANT) LAXATIVES

(1) Mild Stimulants
Figs & prunes, Castor oil.

(2) Moderate Stimulants
(a) Anthraquinone group, eg
Senna, Danthrone, Cascara, Rhubarb, Aloes.
(b) Phenolphthalein.
(c) Bisacodyl.
(d) Serotonin $5HT_4$ receptor agonists, eg

Tegaserod.

(3) Severe Stimulants

(a) Resinous laxatives, eg
Resins of jalap, colocynth, podophyllum.
(b) Croton oil.

STOOL SOFTENERS (EMOLLIENTS)

(1) Surface Active Agents

(a) Docusate sodium (Dioctyl Na sulfosuccinate).
(b) Poloxamers eg, Poloxalkol.

(2) Mineral Oils

Liquid Paraffin.

MISCELLANEOUS

(1) Suppositories

Bisacodyl, Glycerin.

(2) Enemas

Sodium phosphate.

MECHANISM OF ACTION OF LAXATIVES

HYDROPHILIC COLLOIDS

They form gel by imbibing water within large intestine 2 Inc. volume & dec. viscosity intestinal contents 2 Intestinal distension that stimulates peristaltic activity 2 Large, soft, solid stool.

OSMOTIC LAXATIVES

These are poorly absorbed from GIT 2 Hold water in intestinal lumen by osmotic force & cause distension 2 Evacuation.

STIMULANT LAXATIVES

Castor Oil

It is hydrolyzed in small intestine to glycerol & ricinoleic acid 2 Ricinoleic acid stimulates peristalsis & reduces fluid absorption.

Anthraquinone Laxatives

They contain amodin alkaloids that are liberated & absorbed from small intestine 2 Excreted in colon, where it stimulates peristalsis (probably thru Auerbach's plexus).

Bisacodyl & Phenolphthalein

They promote evacuation by stimulating sensory endings in colon via direct action from lumen.

Serotonin $5HT_4$ Receptor Agonists

They stimulate $5HT_4$ receptors on presynaptic terminal of submucosal intrinsic primary afferent nerves, enhancing the release of their neurotransmitters that stimulate second-order enteric neurons to promote peristaltic reflex.

STOOL SOFTENERS

Surface Active Agents

(1) Softens feces by lowering the surface tension of fluids in bowel which allows more water to remain in feces.
(2) Also stimulates bowel.

Liquid Paraffin

It is indigestible, & acts by softening & lubrication of feces.

ENEMAS

Produce defecation by softening feces & distending bowel.

CLINICAL USES OF LAXATIVES

(1) Constipation.
(2) To remove ingested poison (saline laxatives are preferred).
(3) To evacuate GIT,
(a) Before surgery.
(b) Before radiological examination of GIT.
(c) Before abdominal ultrasound.
(4) Before & after anti - helmintics (saline laxatives are preferred).
(5) To prevent straining in pts with,
(a) Hernia.
(b) Cardiovascular disease.
(6) Hepatic encephalopathy (lactulose).
(7) To soften stool in fistula - in - ano.

ADVERSE EFFECTS OF LAXATIVES

Liquid Paraffin

(1) Resp. Tract
Lipid pneumonia (if gain access to lungs).

(2) GIT
Pruritus ani, anal polyp, typical foreign body reaction in intestinal mucosa (& also in mesenteric lymph nodes, liver, & spleen).

(3) Wound Healing
Delayed wound healing after anorectal surgery.

(4) Drug Absorption
Interferes with absorption of fat - soluble vitamins, calcium, & phosphate.

Anthraquinone Laxatives

(1) GIT
Colicky pain, melanotic pigmentation of colonic mucosa.

(2) Urinary Tract
Discolored urine to yellowish-brown (if acidic), or reddish-violet (if alkaline).

(3) Lactation
Affect infant suckling

Phenolphthalein

(1) Urinary Tract
Discolored urine to red (if alkaline).

(2) Skin
Rashes.

CONTRAINDICATIONS OF LAXATIVES

(1) Intestinal obstruction.
(2) Abdominal pain of unknown etiology.
(3) Acute surgical abdomen.
(4) Pregnancy.

GENERIC & TRADE NAMES

Ispaghula husk: Fiberad, Fybogel, Ispalax.
Lactulose: Constilac, Duphalac, Laevolac.
Castor oil: Castor oil.
Bisacodyl: Bicolax, Bisacon, Dulcolax.
Liquid Paraffin: Cremaffin*, Paraffin liquid.
Phenolphthalein: Irzafin, Phenothin.
Tegaserod: Tegmac, Uniserod.
Glycerine: Glycerine suppositories, Microenema*.
Sodium phosphate: Instant enema*, Kleen enema*, Radi enema*.

Unit V

Miscellaneous GIT Drugs

PROKINETICS

These are drugs that selectively stimulate gut motor function.
(1) Drugs that increase lower esophageal sphincter pressure 2 Useful for GERD.
(2) Drugs that improve gastric emptying 2 Useful for gastroparesis & postsurgical gastric emptying delay.
(3) Drugs that stimulate small intestine 2 Useful for postoperative ileus or chronic intestinal pseudo-obstruction.
(4) Drugs that increase colonic transit 2 Useful for constipation.

Drug Classification

(1) Cholinomimetic Drugs
(a) Bethanechol for GERD & gastroparesis.
(b) Neostigmine for chronic intestinal pseudo-obstruction (Ogilvie's syndrome).

(2) D2 Receptor Antagonists
Metoclopramide & Domperidone for GERD, gastroparesis, postsurgical delayed gastric emptying, nonulcer dyspepsia.

(3) Macrolides
Erythromycin in gastroparesis.

(4) Chloride Channel Activator
Lubiprostone for chronic constipation.

DRUG TREATMENT OF IRRITABLE BOWEL SYNDROME (IBS)

IBS is an idiopathic chronic, relapsing disorder characterized by abdominal discomfort (pain, bloating, distension or cramps) in association with alterations in bowel habits (diarrhea, constipation or both).

Drug Classification

(1) Anti-diarrheals
In patients with predominant diarrhea.

(2) Osmotic laxatives & fiber supplements
In patients with predominant constipation.

(3) Anti-spasmodics
Dicyclomine & Hyoscyamine.

(4) Serotonin $5HT_3$ Receptor Antagonists
Alosetron.

(5) Serotonin $5HT_4$ receptor Agonists
Tegaserod.

DRUG TREATMENT OF INFLAMMATORY BOWEL DISEASE (IBD)

It denotes 2 distinct disorders: ulcerative colitis & Crohn's disease.

Drug Classification

(1) Aminosalicylates
(a) Azo compounds eg, Sulfasalazine, Balsalazine, Olsalazine.
(b) Mesalamine compounds eg, Pentasa, Asacol.

(2) Glucocorticoids
(a) Oral prednisone, prednisolone or budesonide.
(b) Hydrocortisone enemas or suppositories.

(3) Purine Analogs
Azathioprine, 6-Mercaptopurine.

(4) Methotrexate

(5) Anti-tumor Necrosis Factor
Infliximab.

EMETICS

Drug Classification

(A) Central Emetics
Apomorphine.

(B) Peripheral Emetics
(1) Rapidly Acting
(a) Salts of heavy metals, eg Copper sulfate, Zinc sulfate.
(b) Hypertonic salt solutions.
(c) Mustard in warm water.

(2) Slowly Acting
(a) Vegetable irritants, eg Tincture lpecacuanha, Tincture senega.
(c) Ammonium carbonate.

Clinical Uses
In cases of poisoning, to prevent further absorption of poison.

Contraindications
(1) Unconscious pts.
(2) Corrosive poisoning.
(3) Petroleum poisoning.
(4) Pregnancy.

SIALOGOGUES

It refers to drugs that increase salivary gland secretions.

Drug Classification
(1) Parasympathomimetics
Nicotine, Lobeline, Pilocarpine.

(2) Direct Salivary Stimulants
Potassium, Iodine, & Mercury salts.

(3) Reflex Sialogogues
(a) Stomachics (see below).
(b) Emetics, eg Ammonium carbonate, Tincture ipecacuanha.

ANTI - SIALOGOGUES

It refers to drugs that inhibit salivary gland secretions.

Drug Classification
(1) Parasympatholytics, eg Atropine, Scopolamine, Methscopolamine.
(2) Ganglion blockers.
(3) Demulcents.
(4) Astringents.

STOMACHICS

It refers to drugs that improve appetite, & reflexly inc. salivary & gastric secretions.

Drug Classification
(1) Locally Acting
(a) Bitters
(i) Simple Bitters: Quassia, Calumba, Gentians.
(ii) Aromatic Bitters: Bitter orange peel.
(iii) Astringent Bitters: Cosparia, Cascarilla.
(iv) Alkaloidal Bitters: Quinine, Strychnine.
(b) Spices
Pepper.

(2) Centrally Acting
Pizotifen, Cyproheptadine, Buclizine, Metopine.

(3) Others
(a) Flavors, eg volatile oils.
(b) Ethyl alcohol beverages (upto 7 %).

CARMINATIVES

It refers to drugs that causes expulsion of gases from stomach by eructation.

Drug Classification
(1) Chloroform
(2) Ether.
(3) Volatile oils, eg
Oils of peppermint, Camphor, Anise, Caraway, Cinnamon.
(4) Carbonated waters, eg
Cola beverages.

SPASMOLYTICS (ANTI- SPASMODICS)

It refers to drugs that relieve smooth muscle spasm (eg, of GIT, genito urinary tract, biliary tract), & are used in the treatment of colics.

Drug Classification
(1) Antimuscarinics
Atropine, Scopolamine, Methscopolamine, Ciclonium, Dicyclomine, Pipenzolate, Propantheline, Anisotropine.

(2) Direct Spasmolytics
Volatile oils, Khellin, Papaverine, Aminophylline, Nitrites, Mebeverine, Tiropramide, Drotaverine, Pramiverine, Fenoverine.

Unit VI

Self-Assessment (T/F)

[See answers on page no. 241]

(114) ***All of the following drugs are correctly matched to their actions***
(A) Cimetidine 2 Blocks H_2 histamine receptors.
(B) Misoprostol 2 Inhibits adenyl cyclase.
(C) Omeprazole 2 Activates adenyl cyclase.
(D) Sucralfate 2 Protects ulcerated mucosa.
(E) Pirenzepine 2 Selectively blocks muscarinic receptors in stomach.

(115) ***Bulk-forming laxative includes***
(A) Castor oil.
(B) Psyllium.
(C) Colloidal bismuth.
(D) Sucralfate.
(E) Phenolphthalein.

(116) ***Use of a Al- containing antacid is most likely to cause***
(A) Constipation.
(B) Diarrhea.
(C) Hypertension.
(D) Headache.

(E) Nausea.

(117) ***Regarding anti-peptic ulcer drugs, all of the following statements are correct***

(A) Omeprazole blocks muscarinic receptors of parietal cell.
(B) Pirenzepine is similar to atropine in its action.
(C) Famotidine blocks the action of gastrin on parietal cells.
(D) Carbenoxolone increases the amount & quality of mucus.
(E) Chronic use of omeprazole may results in gastric tumor.

(118) ***Anti- emetics include***

(A) Apomorphine.
(B) Ammonium carbonate.
(C) Cyclizine.
(D) Chlorpromazine.
(E) *Aluminium hydroxide.*

15 HEPATO-PANCREATICO-BILIARY DRUGS

Unit I

Liver & Drugs

HEPATIC DRUGS

CHOLERETICS

It refers to drugs that stimulate hepatic cells to secrete bile, resulting in inc. volume & solid constituents of bile.

Drug Classification

(1) Primary Bile Acids
Cholic acid, Chenodeoxycholic acid.

(2) Secondary Bile Acids
Deoxycholic acid, Lithocolic acid.

(3) Bile Acid Conjugates
Sodium glycocholate, Sodium taurocholate, Sodium choleate.

Clinical Uses

(1) To help digestion.
(2) To promote vit K absorption in obstructive jaundice.
(3) To relieve flatulence, dyspepsia, & constipation.

HYDROCHOLERETICS

It refers to drugs that act on hepatocytes, & increases bile volume (but not its solid constituents).

Drugs Classification

(1) Oxidized bile acids, eg dehydrocholic acid.
(2) Salicylates.
(3) Benzoates.

Clinical Uses

To flush diseased biliary passage.

Contraindications

Acute hepatitis

DRUG TREATMENT OF VIRAL HEPATITIS

(A) Treatment of Acute Hepatitis

(1) A light diet supplemented by fruit drinks & glucose (about 2000 -3000 Kcal daily).
(2) Drugs should be avoided.

(B) Treatment of Fulminant Hepatic Failure

(1) For Encephalopathy
Neomycin, Lactulose, Enemas.

(2) For Cerebral Edema
Mannitol 20%.

(3) Nutrition
Glucose, Fluid & Electrolyte therapy.

(4) For Infection
Broad-spectrum antibiotics, eg Cefotaxime.

(5) To Prevent GI Bleeding
Cimetidine, Ranitidine.

(C) Prophylaxis of Viral Hepatitis

(1) For Hepatitis A
Immune globulin (IG).

(2) For Hepatitis B
Hepatitis B immune globulin (HBIG), Hepatitis B vaccine (inactivated surface antigen).

DRUG INDUCED HEPATIC DAMAGE

TYPE A (AUGMENTED)

Hepatic injury occurs as the dose of some drugs is raised.

(1) Centrizonal Necrosis
Caused by Paracetamol & Carbon tetrachloride.

(2) Hepatocellular Necrosis
Caused by Salicylates.

(3) Fatty Liver
Caused by Tetracyclines.

(4) Hepatitis
Caused by Alcohol & Amiodarone.

(5) Interference with Bilirubin Metabolism & Excretion
Caused by;
Androgens, Anabolic steroids, Estrogens, Progestins, Rifampin, Fusidic acid, Cholecystographic media.

TYPE B (BIZARRE)

Hepatic injury is due to unusual properties of pt interacting with drug, & is unrelated to dose.

(1) Acute Hepatocellular Necrosis
Caused by;
(a) General anesthetics, eg Halothane, Methoxyflurane.
(b) Anticonvulsants, eg Carbamazepine, Phenytoin, Na valproate, Phenobarbital.
(c) Antidepressants, eg MAO inhibitors.
(d) NSAIDs, eg Indomethacin, Ibuprofen.
(e) Antimicrobials, eg Sulfonamides, Nitrofurantoin.
(f) Anti - hypertensives, eg Methyldopa, Hydralazine.

(2) Cholestatic Hepatitis

Caused by;
(a) Phenothiazines, esp. Chlorpromazine.
(b) Antidiabetics, eg Chlorpropamide, Tolbutamide, Glibenclamide.
(c) Carbimazole, Erythromycin, & Gold.

TYPE C (CONTINUED USE)

Hepatic injury is due to prolonged use of drugs.

(1) Chronic Active Hepatitis
Caused by;
Methyldopa, Isoniazid, Dantrolene, Nitrofurantoin.

(2) Hepatic Cirrhosis
Caused by Alcohol & Methotrexate.

TYPE D (DELAYED EFFECTS)

Benign Hepatic Tumors
Caused by anabolic steroids & oral contraceptives, when used for more than 5 years.

DRUGS SELECTION IN PATIENTS WITH HEPATIC DISEASE

GENERAL PRINCIPLES

(1) Drugs should only be used, when clearly indicated.
(2) Smaller than usual doses should be given initially.
(3) Frequency of administration should be determined from effects.
(4) Monitor liver function tests regularly.

DRUG SELECTION

(A) CNS Drugs

(1) Sedative - Hypnotics
Lorazepam, Oxazepam, & Temazepam are preferred.

(2) Antiepileptics
Should be used in lowest effective doses.

(3) Antidepressants
Tricyclics may be used, but avoid MAO inhibitors.

(B) Analgesics

(1) Opioid Analgesics
Should be avoided.

(2) Non - Opioid Analgesics
Paracetamol is used in lowest dose.

(C) CVS Drugs

(1) Beta - Blockers
Propranolol & Labetalol should be used in reduced initial doses.

(2) Ca^{+2} Channel Blockers
Nicardipine, Nifedipine & Verapamil should be used in reduced initial doses.

(3) Diuretics
Potassium - sparing diuretics are preferred.

(D) GIT Drugs
Antacids should be avoided.

(E) Antimicrobials
Isoniazid, Erythromycin, Rifampin, Tetracyclines & Ketoconazole should be avoided or used in reduced doses.

(F) Endocrine Drugs
Androgens, Anabolic steroids, Oral contraceptives, Metformin, Chlorpropamide & Tolbutamide should be avoided.

(G) Respiratory System Drugs
Theophylline should be used in reduced doses.

GENERIC & TRADE NAMES

(A) Choleretics
Sodium Choleate: Panchol*.

(B) Hydrocholeretics
Dehydrocholic acid: Bilsan*.

(C) Hepatitis Vaccines
Hepatitis A vaccine: Avaxim, Havrix.
Hepatitis B vaccine: Engerix -B, Heprovac B.

Unit II

Biliary & Pancreatic Drugs

CHOLAGOGUES

It refers to drugs that stimulate flow of bile from gall-bladder to duodenum.

Drug Classification

(A) Drugs that Relax Sphincter of Oddi
Mg- sulfate.

(B) Drugs that Causes Gallbladder Contraction
Cholecystokinin, Parasympathomimetics, Pituitrin.

GALLSTONE DISSOLUTANTS

It refers to drugs that dissolves small gall-stones.

Drug Classification

(1) Primary Bile Acid
Chenodiol (Chenodeoxycholic acid), Ursodiol (Ursodeoxycholic acid).

(2) Others
(a) Methyl tert-butyl ether.
(b) Monoctanoin.

PANCREATIC ENZYMES

Drug Classification
(1) Pancreatin .
(2) Pancrelipase.

Clinical Uses

Pancreatic exocrine insufficiency.

DRUG TREATMENT OF VARICEAL HEMORRHAGE

Drug Classification

(1) Somatostatin & octreotide.
(2) Vasopressin & terlipressin.
(3) Beta-receptor blockers.

GENERIC & TRADE NAMES

Ursodiol: Urosofalk.
Pancreatin: Pepzym, Plasil with enzyme, Wobenzym N.
Somatostatin: Somatosan.
Octreotide: Sandostatin.

Unit III

Self - Assessment (T/F)

[See answers on page no. 241]

(119) ***Choleretics include***
(A) Chenodeoxycholic acid.
(B) Deoxycholic acid.
(C) Sodium taurocholate.
(D) Dehydrocholic acid.
(E) Salicylates.

(120) ***Drugs that cause hepatic damage includes***
(A) Halothane.
(B) Carbamazepine.
(C) Paracetamol.
(D) Isoniazid.
(E) *Quinidine.*

16 AUTACOIDS & ITS ANTAGONISTS

Unit I

Histamine & its Antagonists

INTRODUCTION

SYNTHESIS

Histamine is formed by decarboxylation of L-histidine, catalyzed by histidine decarboxylase.

STORAGE SITES

Histamine is stored in bound form in granules of ;

(1) Mast cells & basophils, in lungs & skin.
(2) Atypical mast cells in gastrointestinal mucosa.
(3) Neurons in tuberomamillary nucleus of posterior hypothalamus.

RELEASING FACTORS

(1) Allergy & anaphylaxis.
(2) Destruction of storage cells as a result of cold, bacterial toxins, bee sting venoms, trauma, etc.
(3) Dissolution of cytoplasmic granules as a result of actions of radiation or surfactants.
(4) Drugs, eg tubocurarine, morphine, dextran, or radiographic contrast media.

INACTIVATION PATHWAYS

(1) Conversion to methylhistamine by imidazole N-methyltransferase 2 Oxidation to methylimidazole-acetic acid by diamine oxidase.
(2) Direct conversion to imidazoleacetic acid by diamine oxidase.

HISTAMINE

MECHANISM OF ACTION

Histamine binds to its specific cell surface receptors (see box 16.1), that is associated with various G proteins similar to adrenoceptors (see chapter 2).

(1) Activation of H_1 receptors causes inc. phospho-inositol hydrolysis & inc. intracellular Ca^{++}.
(2) Activation of H_2 receptors causes inc. intracellular cAMP.
(3) Activation of H_3 & H_4 receptors causes dec. histamine release from histaminergic neurons & blood cells, mediated by dec. Ca^{++} influx.

Box 16.1 HISTAMINE RECEPTORS

Receptor	Location	Agonists	Antagonists
H_1	Smooth muscle, endothelium, brain	Histaprodifen	Mepyramine, Loratadine
H_2	Gastric mucosa, cardiac muscle, mast cells, brain	Amthamine	Ranitidine, Tiotidine
H_3	*Presynaptic* Brain, Myenteric plexus, other neurons	R-α-Methyl-histamine, Imetit, Immepip	Thioperamide, Iodophenpro-pit
H_4	*Eosinophils, neutrophils, CD4 T cells*	Clobenpropit, Imetit, Clozapine	Thioperamide

PHARMACOLOGICAL EFFECTS

(A) Cardiovascular System

(1) Heart

(a) Inc. pacemaker rate (+ve chronotropism).
(b) Inc. contractility (+ve inotropism).

(2) Blood Vessels & BP

(a) Vasodilation of arterioles & precapillary sphincters ↕ Dec. BP.
(b) Vasodilation & inc. permeability of vessels of microcirculation esp. postcapillary vessels 2 Edema.

Triple Response

Results from intradermal inj. of histamine:

(i) Reddening at the site of inj., due to dilation of small vessels.
(ii) Edematous wheal at the site of inj., due to inc. microvasculature permeability.
(iii) Red irregular flare surrounding the wheal.

(B) Extravascular Smooth Muscle

(1) GIT smooth muscle 2 Contraction.
(2) Bronchiolar smooth muscle 2 Contraction.
(3) Pregnant uterus 2 Contraction 2 Abortion.

(C) Nerve Endings

Stimulation of sensory nerve endings, esp. those mediating pain & itching.

(D) Secretory Tissues

Inc. gastric acid secretion, & also pepsin & intrinsic factor (to a lesser extent). Also potentiates gastric acid secretion induced by gastrin & acetylcholine.
(2) Inc. small & large intestinal secretions.
(3) Inc. pancreatic & bronchiolar secretions.
(4) Inc. lacrimation & salivation.

CLINICAL USES

(1) As a provocative test of bronchial hyperreactivity.
(2) As a diagnostic agent in testing for gastric acid secreting ability. (Now pentagastrin is used for this purpose).
(3) For diagnosis of pheochromocytoma (now obsolete).

ADVERSE EFFECTS

(1) CNS: Headache.
(2) CVS: Flushing, tachycardia, hypotension, wheals.
(3) Resp. Tract: Bronchoconstriction, dyspnea.
(4) GIT: Diarrhea.

CONTRAINDICATIONS

(1) Asthma.
(2) Peptic ulcer.
(3) GIT bleeding.

HISTAMINE ANTAGONISTS (ANTI-HISTAMINICS)

DRUG CLASSIFICATION

(A) H_1-Receptor Antagonists

(1) Ethanolamines
Carbinoxamine, Dimenhydrinate, Doxylamine, Diphenhydramine.

(2) Ethylenediamines
Antazoline, Pyrilamine (Mepyramine), Tripelennamine.

(3) Piperazine Derivatives
Buclizine, Cyclizine, Hydroxyzine, Meclizine.

(4) Alkylamines
Bromopheniramine, Chlorpheniramine.

(5) Phenothiazine Derivatives
Promethazine.

(6) Piperidines
Astemizole, Terfenadine, Fexofenadine.

(7) Miscellaneous
Cyproheptadine, Loratadine, Desloratadine, Cetirizine, Azelastine, Clemastine, Emedastine, Epinastine, Ketotifen, Levocabastine, Olopatadine, Phenindamine.

(B) H_2 - Receptor Antagonists

Cimetidine, Ranitidine, Famotidine, Nizatidine.
(For detail, See Chapter 14 Unit I).

(C) H_3 - Receptor Antagonists

Thioperamide, Iodophenpropit.

(D) H_4 - Receptor Antagonists

Thioperamide.

H_1- RECEPTOR ANTAGONISTS

Mechanism of Action

Block action of histamine by reversible competitive antagonism at H_1- receptors.

Pharmacological Effects

(A) Effects Caused by H_1- Receptor Blockade

Smooth Muscles

(1) Microvascular smooth muscle 2 Dec. histamine-induced permeability 2 Dec. edema.
(2) GIT smooth muscle 2 Reverses histamine-induced contraction.
(3) Bronchiolar smooth muscle 2 Reverses histamine-induced bronchoconstriction.

(B) Effects Not Caused by H_1- Receptor Blockade

These probably results from similarity of drug's general structure to drugs that have effects at muscarinic cholinoceptors, α- adrenoceptors, serotonin & local anesthetic receptor sites.

(1) Central Nervous System
(a) **Sedation**
(i) Marked sedation 2 Dimenhydrinate, Diphenhydramine, Doxylamine, Promethazine.
(ii) Moderate sedation 2 Carbinoxamine, Ethylenediamines, Cyproheptadine.
(iii) Slight sedation 2 Piperazine derivatives, Alkylamines.
(iv) Little or no sedation 2 Piperidines, Loratadine.
(b) Antinausea & antiemetic effects.
(c) Anti- Parkinsonism effects.
(d) Serotonin blocking effects (Cyproheptadine).

(2) Autonomic Nervous System
(a) Atropine-like effects (Ethanolamines, Ethylenediamines).
(b) α-adrenoceptor blocking effects (phenothiazines).

(3) Local Anesthesia
Diphenhydramine & Phenothiazine produces local anesthetic effect by blocking Na- channels in excitable membranes.

Clinical Uses

(1) Allergic reactions, eg
(a) Allergic rhinitis (Hay fever).
(b) Urticaria.
(c) Allergic conjunctivitis.
(d) Allergic drug reactions.
(e) Anaphylaxis.
(2) Prophylaxis of motion sickness & vestibular disturbances.
(3) Nausea & vomiting of pregnancy.

Adverse Effects

(1) CNS
Sedation, nervousness, lassitude.

(2) Eye
Blurred vision.

(3) ENT
Tinnitus.
(4) CVS
Orthostatic hypotension, arrhythmias (Astemizole).
(5) GIT
GI distress.
(6) Urinary Tract
Urinary retention.
(7) Allergic Reactions
(8) Acute Poisoning
Results from overdosage esp. in children, manifested by; Hallucinations, excitement, ataxia, convulsions.

GENERIC & TRADE NAMES

(A) H_1- Receptor Antagonists

Carbinoxamine: Davenol*, Rondec*.
Dimenhydrinate: Devinate, Dimenic, Gravinate.
Diphenhydramine: Acefyl*, Benatus*, Benadryl*, Brondyl*, Chlorohist*.
Antazoline: Cural -A, Spersallerg.
Pyrilamine: Decon -A*, Tussivil*.
Buclizine: Longifene.
Cyclizine: Marzine, Migril*.
Hydroxyzine: Roxyzine.
Meclizine: Navidoxine, Sevidoxine.
Chlorpheniramine: Allergon, Allerphene, Coldrex*, Histamol, Piriton, Tempramine*.
Promethazine: Diprozine, Phenergan, Tixylix.
Astemizole: Mayasen.
Fexofenadine: Fenadex, Fexet, Fexet D*.
Cyproheptadine: Periactin, Tres -orix forte*.
Loratadine: Alor, Claridine, Histadine, Softin.
Desloratadine: Aloret, Destina.
Cetrizine: Cipzin, Rigix.
Azelastin: Azosin, Rhinolast.
Clemastine: Tandegyl.
Emedastine: Emadine.
Ketotifen: Asfen, Asthanil, Ketofen.

(B) H_2 - Receptor Antagonists

See chapter 14, Unit I.

Unit II

Serotonin & its Antagonists

SEROTONIN (5 - HYDROXY - TRYPTAMINE)

Synthesis

Serotonin (5 - HT) is an indole - ethylamine formed from amino acid tryptophan by hydroxylation of indole ring followed by decarboxylation of amino acid.

Mechanism of Action

Actions of 5 - HT is mediated thru a variety of cell memb.

Box 16.2 SEROTONIN RECEPTOR SUBTYPES

Receptors	Location	2nd Messenger Effects	Agonists	Antagonists
5- HT1A	Raphe nuclei, hippocampus	3 cAMP, 1 K^+ conductance	Buspirone	
5- HT1B	Substantia nigra, globus pallidus, basal ganglia	3 cAMP,	5- Hydroxy-3 tetrahydro-pyridyl-4-azaindole, Eletriptan	
5- HT1Da,b	Brain	3 cAMP,	Sumatriptan, Eletriptan	
5- HT1E	Cortex, putamen	3 cAMP,		
5- HT1F	Cortex, hippocampus	3 cAMP,	Eletriptan	
5- HT1P	Enteric nervous system	Slow EPSP	5-Hydroxyindalpine	Renzapride
5- HT2A	Platelets, smooth muscle, cerebral cortex	1 IP3	α- methyl-5-HT	Ketanserin, Ritanserin
5- HT2B	Stomach fundus	1 IP3	α- methyl-5-HT	
5- HT2C	Choroid, hippocampus, substantia nigra	1 IP3	α- methyl-5-HT	Mesulergine
5- HT3	Area postrema, sensory & enteric nerve	Receptor is a Na^+/K^+ ion channel	2-methyl-5-HT	Tropisetron, Ondansetron, Granisetron
5- HT4	CNS & myenteric neurons, smooth muscle	1 cAMP	5-methoxytryptamine, Metoclopramide, Renzapride, Cisapride, Tegaserod	
5- $HT5_{A,B}$	Brain	3 cAMP		
5- HT6,7	Brain	1 cAMP		Clozapine (7)

receptors, that include both G protein - coupled receptors (similar to adrenoceptors) & a ligand - gated ion channels. (See box 16.2).

Pharmacological Effects

(A) Central Nervous System

Act as a neurotransmitter in pathways originating from neurons in raphe or midline regions of pons & upper brainstem.

(1) In most areas, causes strong inhibitory effect.
(2) In some cells, causes slow excitement.
(3) Concerned with regulation of sleep, temperature, appetite, & neuroendocrine control.

(B) Peripheral Nervous System

(1) Stimulation of pain & itch sensory nerve endings.
(2) Activation of chemosensitive endings located in coronary vascular bed 2 Chemoreceptor reflex 2 Bradycardia & hypotension.

(C) Cardiovascular System

(1) Heart

(a) Direct positive chronotropic & inotropic effects.
(b) Reflex bradycardia (described above).

(2) Blood Vessels

(a) Vasoconstriction, more marked in pulmonary & renal vessels.
(b) Vasodilation in skeletal muscle & cardiac vessels.
(c) Venoconstriction & inc. capillary filling 2 Flush.

(3) Blood Pressure

Triphasic blood pressure response;
(a) Initially, dec. in heart rate, cardiac output, & BP (due to chemoreceptor reflex).
(b) Followed by, inc. BP (due to vasoconstriction).
(c) Finally, again, dec BP (due to vasodilation in skeletal muscles).

(D) Blood

Aggregation of platelets.

(E) Gastrointestinal Tract

(1) Contraction of GIT smooth muscle 2 Inc. tone & peristalsis.
(2) Little effect on secretions, generally inhibitory.

(F) Respiration

(1) Bronchoconstriction.
(2) Hyperventilation (due to chemoreceptor reflex).

Clinical Uses

Serotonin has no clinical application as a drug.

Serotonin Agonists

(1) Buspirone
As non-benzodiazepine anxiolytic.

(2) Triptans, eg Almotriptan, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan & Zolmitriptan
(a) Acute migraine
(b) Cluster headache

(3) Tegaserod
Irritable bowel syndrome with constipation.

SEROTONIN RECEPTOR ANTAGONISTS

Examples

Cyproheptadine, Ketanserin, Ritanserin, Ondansetron, Granisetron, Tropisetron, Clozapine.

Clinical Uses

(A) Cyproheptadine

(1) Treatment of smooth muscle manifestations of carcinoid tumor.
(2) Postgastrectomy dumping syndrome.
(3) Cold - induced urticaria.
(4) As appetite stimulant.

(B) Ketanserin

(1) Hypertension.
(2) Vasospastic conditions.

(C) Ondansetron & Tropisetron

Prophylaxis of nausea & vomiting associated with cancer chemotherapy.

GENERIC & TRADE NAMES

(A) Serotonin Analogues

Buspirone: Buspar, Novatil.
Eletriptan: Alle.
Sumatriptan: Sumapan.
Zolmitriptan: Zomig, Zominat.
Tegaserod: Uniserod.

(B) Serotonin Antagonists

Cyproheptadine: Periactin, Tres-orix forte*.
Ondansetron: Setron, Zofran.
Granisetron: Kytril.
Tropisetron: Navoban.
Clozapine: Clozaril.

Unit III

Eicosanoids

PROSTAGLANDINS & THROMBOXANE

SYNTHESIS

(1) Synthesis begin with PGG_2 formation from arachidonic acid, catalyzed by cyclooxygenase 2 Peroxidase converts PGG_2 into PGH_2.
(2) Depending on the tissues, PGH_2 is converted into;
(a) PGD_2 (by PGD synthetase).
(b) PGE_2 (by PGE synthetase) 2 $PGF_{2\alpha}$ (by PGE 9 - ketoreductase).
(c) PGI_2 (by PGI synthetase).
(d) TXA_2 (by TX synthetase).

METABOLISM

Prostaglandins are rapidly catabolized in the body by;
(1) 15 - Hydroxydehydrogenase pathway.
(2) Cytochrome P450 system.

MECHANISM OF ACTION

Prostaglandins bind to specific cell surface receptor that are G protein - linked 2 Activation of adenyl cyclase or phosphatidylinositol metabolism 2 1 cAMP or 1 IP_3.

PHARMACOLOGICAL EFFECTS

(A) Smooth Muscle

(1) Vascular

(a) PGE_2 & PGI_2 causes relaxation of arteriolar smooth muscle (vasodilation).
(b) TXA_2 & $PGF_{2\alpha}$ causes smooth muscle contraction esp. of veins (vasoconstriction).

(2) Gastrointestinal Tract

(a) PGE_2 & $PGF_{2\alpha}$ causes contraction of longitudinal muscle.
(b) PGE_2 also causes relaxation of circular muscle.
(c) PGI_2 & $PGF_{2\alpha}$ causes contraction of circular muscle.

(3) Respiratory Tract

(a) PGE_1, PGE_2, & PGI_2 causes bronchodilation.
(b) TXA_2 & $PGF_{2\alpha}$ causes bronchoconstriction.

(B) Platelets

(1) PGE_1 & PGI_2 inhibit aggregation.
(2) TXA_2 facilitates aggregation.

(C) Central Nervous System

PGE_1 & PGE_2 increases body temperature.

(D) Peripheral Nervous System

PGE inhibit norepinephrine release from sympathetic presynaptic nerve endings.

(E) Neuroendocrine

PGE promote release of growth hormone, prolactin, thyroid - stimulating hormone, adrenocorticotropic hormone, follicle - stimulating hormone, & luteinizing hormone.

(F) Reproductive System

(1) Female

PGE_2 & $PGF_{2\alpha}$ promote uterine contractions 2
(a) Abortion.
(b) Facilitation of labor.
(c) Dysmenorrhea during menstruation.

(2) Male

Men with a low seminal prostaglandin conc. are relatively infertile.

CLINICAL USES

(A) PGE_1

(1) To maintain patency of ductus arteriosus in neonates with congenital cardiac diseases, until surgery can be performed.
(2) Hypertension.
(3) Raynaud's phenomenon.
(4) Peripheral atherosclerosis.
(5) Impotence or erectile dysfunction (Intra-cavernosal inj. therapy).
(6) Prophylaxis of NSAID - induced gastric ulcer.

(B) PGE_2

(1) For 1st - & 2nd - trimester abortion (given as vaginal suppositories).
(2) To initiate & stimulate labor.
(3) Hypertension.
(4) Raynaud's phenomenon.
(5) Peripheral atherosclerosis.
(6) As bronchodilator (given in aerosol form).

(C) $PGF_{2\sim}$

(1) For 1st - & 2nd - trimester abortion (given intra - amniotically or intra - muscularly).
(2) To initiate & stimulate labor.

(D) PGI_2

(1) Primary & secondary pulmonary hypertension.
(2) Raynaud's phenomenon.
(3) Peripheral atherosclerosis.
(4) As anti - thrombosis.
(5) To prevent cell - mediated organ transplant rejection.

GENERIC & TRADE NAMES

(A) PGE_1 Analogues

Alprostadil: Caverject, Prostavasin.

(B) PGE_2 Analogues

Dinoprostone: Prostin E2, Prepidil.

(C) $PGF_{2\sim}$ Analogues

Dinoprost: Prostin F2 alpha, Preglan.

Unit IV

Self - Assessment (T/F)

(See answers on page no. 241)

(121) ***Regarding histamine, following are correct***
(A) It has positive inotropic & positive chronotropic effects.
(B) It causes triple response, when injected in skin.
(C) Thru H_1 receptor stimulation, it causes smooth muscle relaxation.
(D) Combination of histamine with H_2 receptors causes stimulation of gastric acid secretion.
(E) Used for diagnosis of pheochromocytoma.

(122) ***Histamine H_1 receptor blockers are useful in the treatment of***
(A) Urticaria.
(B) Seasonal rhinitis.

(C) Drug reactions.
(D) Bronchial asthma.
(E) Peptic ulcer.

(123) ***Cyproheptadine is useful in the treatment of***
(A) Carcinoid tumors.
(B) Postgastrectomy dumping syndrome.
(C) Hepatitis.
(D) Migraine.
(E) *Pruritic dermatosis.*

17 ENDOCRINE DRUGS

Unit I

Hypothalamic & Pituitary Hormones

HYPOTHALAMIC HORMONES & ANTAGONISTS

HORMONES AFFECTING GROWTH HORMONE RELEASE

(A) Growth Hormone-Releasing Hormone (GHRH)

Pharmacological Effects

Stimulates pituitary production of growth hormone (GH).

Clinical Uses

(1) Diagnostically, to evaluate the cause of GH deficiency.
(2) Therapeutically, in GH deficiency where pituitary somatotrophs are responsive to GHRH.

(B) Somatostatin (GH-Inhibiting Hormone) & Octreotide

Pharmacological Effects

(1) Inhibit growth hormone release.
(2) Also inhibit release of glucagon, insulin, & gastrin.

Clinical Uses

Octreotide (a somatostatin analogue) is used in;
(1) Acromegaly.
(2) Carcinoid syndrome.
(3) Gastrinoma.
(4) Glucagonoma.
(5) Nesidioblastosis.
(6) Watery diarrhea, hypokalemia & achlorhydria (WDHA) syndrome.
(7) Diabetic diarrhea.

Note: Octreotide, an analog of somatostatin, is 45 times more potent than somatostatin in inhibiting GH release.

CORTICOTROPIN-RELEASING HORMONE (CRH)

Pharmacological Effects

Stimulates ACTH secretion from anterior pituitary.

Clinical Uses

Diagnostically, to distinguish Cushing's disease from ectopic ACTH secretion.

THYROTROPIN- RELEASING HORMONE (TRH)

Pharmacological Effects

Stimulates pituitary production of thyrotropin.

Clinical Uses

(1) To diagnose hyperthyroidism.
(2) To diagnose hypothyroidism.

GONADOTROPIN- RELEASING HORMONE (GNRH)

Pharmacological Effects

Stimulates pituitary production of FSH & LH.

Clinical Uses

(1) To diagnose & treat hypogonadotropic hypogonadism in both males & females.
(2) To induce biochemical castration;
   (a) In adults with prostatic cancer, uterine fibroids, endometriosis, & polycystic ovary syndrome.
   (b) In children with precocious puberty.

GNRH RECEPTOR ANTAGONISTS

Examples

Ganirelix, Cetrorelix.

Pharmacological Effects

Inhibits pituitary production of FSH & LH in a dose-dependent manner.

Clinical Uses

For preventing LH surge during controlled ovarian hyperstimulation.

ANTERIOR PITUITARY HORMONES & ANTAGONISTS

GROWTH HORMONE (GH, SOMATOTROPIN)

Pharmacological Effects

(1) Anabolic

GH produces growth of bone & soft tissues, mediated indirectly by somatomedins which is produced in liver).

(2) Metabolic

(a) Initially: Insulin-like effect with inc. tissue uptake of both glucose & amino acids, & dec. lipolysis.
(b) Within a few hours: Peripheral insulin-antagonistic effects with impaired glucose uptake, & inc. lipolysis.

Clinical Uses

(1) Growth failure in pediatric patients associated with;

(a) Growth hormone deficiency.
(b) Chronic renal failure.
(c) Prader-Willi syndrome.
(d) Turner's syndrome.
(e) Idiopathic short stature.
(2) Growth hormone deficiency in adults.
(3) Wasting in patients with AIDS.
(4) Short bowel syndrome.

ADRENOCORTICOTROPIN (CORTICOTROPIN, ACTH)

Pharmacological Effects

(1) Stimulates adrenal cortex to produce glucocorticoids, mineralocorticoids, & androgens.
(2) Stimulates adrenal hypertrophy, & hyperplasia.
(3) Inc. skin pigmentation.

Clinical Uses

(1) To diagnose adrenal insufficiency.
(2) To distinguish late-onset congenital adrenal hyperplasia from ovarian hyperandrogenism.
(3) In chronic conditions, as an anti-inflammatory or immunosuppressive agent.

THYROID-STIMULATING HORMONE (TSH, THYROTROPIN)

Pharmacological Effects

It stimulates production of thyroid hormones by follicles of thyroid gland.

Clinical Uses

To diagnose hypothyroidism & recurrence of thyroid carcinoma.

FOLLICLE- STIMULATING HORMONE (FSH), & LUTEINIZING HORMONE (LH)

Pharmacological Effects

(1) FSH stimulate gametogenesis & follicular development in women, & spermatogenesis in men.
(2) Both LH & FSH are needed for proper ovarian steroidogenesis.
(3) FSH stimulates sertoli cells in testes to produce androgen-binding protein.

Clinical Uses

Human menopausal gonadotropins (hMG), a mixture of partially catabolized human FSH & LH, are used in;
(1) Pituitary or hypothalamic hypogonadism with infertility.
(2) Women with anovulatory conditions eg, primary amenorrhea, secondary amenorrhea, polycystic ovary syndrome, & anovulatory cycles.
(3) Male infertility.

PROLACTIN

Pharmacological Effects

(1) Stimulates milk production.
(2) Induces mitogenesis in lymphocytes.

Clinical Uses

No preparation is available for clinical use.

DOPAMINE AGONISTS (PROLACTIN ANTAGONISTS)

Examples

Bromocriptine, Cabergoline, Pergolide, Quinagolide.

Pharmacological Effects

Suppress prolactin release in patients with hyperprolactinemia.

Clinical Uses

(1) Hyperprolactinemia.
(2) To suppress physiologic lactation.

POSTERIOR PITUITARY HORMONES & ANTAGONISTS

OXYTOCIN

Pharmacological Effects

(1) Alters transmemb. ionic currents in myometrial smooth muscle cells to produce sustained uterine contraction.
(2) Causes contraction of myoepithelial cells surrounding mammary alveoli 2 Milk ejection.
(3) Weak antidiuretic & pressor activity.

Clinical Uses

(1) To diagnose intrauterine growth retardation.
(2) To induce labor & augment dysfunctional labor in,
(a) Maternal diabetes.
(b) Preeclampsia.
(c) Rh problems.
(d) Uterine inertia.
(e) Incomplete abortion.
(3) To control postpartum hemorrhage (PPH).
(4) Impaired milk ejection.

OXYTOCIN ANTAGONISTS

Examples

Atosiban.

Pharmacological Effects

An antagonist of oxytocin receptors.

Clinical Uses

Preterm labor.

VASOPRESSIN (ANTIDIURETIC HORMONE, ADH)

Pharmacological Effects

(1) Stimulate V_1 receptors on vascular smooth muscle cells 2 Vasoconstriction.
(2) Stimulate V_2 receptors on renal tubule cells 2 Antidiuresis thru inc. water permeability & water reabsor- ption in collecting tubules.
(3) Stimulate extrarenal V_2 - like receptors 2 Release of coagulation factor VIIIc & von Willebrand factor.

Clinical Uses

(1) Pituitary diabetes insipidus.
(2) Esophageal variceal bleeding.
(3) Colonic diverticular bleeding.

VASOPRESSIN ANTAGONISTS

Examples
Conivaptan, Tolvaptan.

Pharmacological Effects
Antagonists of V_1 & V_2 vasopressin receptors.

Clinical Uses
Hyponatremia.

GENERIC & TRADE NAMES

(A) Hypothalamic Hormones & Antagonists
Octreotide: Sandostatin.
Goserelin (Gn RH analogue): Zoladex.
Ganirelix: Orgalutran.

(B) Anterior Pituitary Hormones & Antagonists
Somatropin (GH analogue): Eutropin, Genotropin, Hht, Humatrope, Norditropin.
Somatostatin: Ikestatina.
ACTH: Acthar gel.
Menotropins (hMG): Humegon, Pergonal.
Bromocriptine: Bromicon, Brotin, Parlodel.

(C) Posterior Pituitary Hormones & Antagonists
Oxytocin: Syntocinon.

Unit II

Thyroid & Antithyroid Drugs

THYROID HORMONES & ANALOGUES

CLASSIFICATION

(A) Endogenous
Thyroxine (T4), Triiodothyronine (T3).

(B) Animal Origin
Desiccated thyroid.

(C) Synthetic
Levothyroxine, Liothyronine, Liotrix.

PHARMACOLOGICAL EFFECTS
(1) Regulate growth & development in children.
(2) Exert a calorigenic effect by increasing basal metabolic rate.
(3) Accelerate carbohydrate utilization, & enhance lipolytic reactions.
(4) Inhibit pituitary secretion of thyrotropin by negative feedback.
(5) Stimulate cardiovascular system.

CLINICAL USES
(1) Hypothyroidism.
(2) Myxedema coma.
(3) To prevent cretinism in hypothyroid infants.
(4) To treat infertility in hypothyroid women.

ADVERSE EFFECTS

(A) In Children
Restlessness, insomnia, & accelerated bone maturation & growth.

(B) In Adults
Nervousness, heat intolerance, palpitation, tachycardia, unexplained weight loss.

ANTI - THYROID DRUGS

DRUG CLASSIFICATION

(A) Drugs Interfering with Synthesis of Thyroid Hormones

(1) Thioamides
Propylthiouracil, Methimazole, Carbimazole, Thiouracil, Thiourea.

(2) Anion Inhibitors
Perchlorate, Pertechnetate, Thiocyanate.

(B) Drugs Preventing Release of Thyroid Hormones

(1) Iodides
Potassium iodide, Sodium iodide.

(2) Iodinated Contrast Media
Diatrizoate, Iohexol.

(C) Drugs Producing Thyroid Gland Destruction
Radioactive iodine (I^{131}).

(D) Adjunctive Drugs
(1) β - Blockers, eg Propranolol.
(2) Adrenergic neuron blockers, eg Guanethidine, Reserpine.
(3) Diltiazem.
(4) Aspirin or NSAIDs.
(5) Corticosteroids.

THIOAMIDES

Mechanism of Action
(1) Inhibit thyroid peroxidase 2 Block iodine organification (ie, iodination of tyrosine) 2 Prevent synthesis of T_4 & T_3.
(2) Propylthiouracil & (to a much lesser extent) methimazole inhibit peripheral deiodination of T_4 & T_3.

Clinical Uses
(1) Hyperthyroidism (thyrotoxicosis).
(2) Thyroid storm (thyrotoxic crisis).
(3) Preoperative preparation in toxic multinodular goitre.
(4) Thyrotoxicosis during pregnancy (propylthiouracil).
Note: Methimazole is avoided b/c of the risk of fetal scalp defects.
(5) Neonatal Graves' disease (propylthiouracil).

Adverse Effects
(1) CVS: Vasculitis.
(2) Liver: Cholestatic jaundice, hepatitis.
(3) Blood: Hypoprothrombinemia, agranulocytosis.

(4) Lymph nodes: Lymphadenopathy.
(5) Serous memb: Polyserositis.
(6) Joints: Arthralgia.
(7) Body temp: Fever.
(8) Skin: Maculopapular pruritic rash, urticarial rash, lupus - like reaction.

ANION INHIBITORS

Mechanism of Action

Block uptake of iodide by thyroid gland thru competitive inhibition of iodide transport mechanism.

Clinical Uses

No therapeutic use b/c of their toxicity, eg aplastic anemia (perchlorate); however, can be used for diagnostic purposes.

IODIDES

Mechanism of Action

(1) Inhibit hormone release thru inhibition of thyroglobulin proteolysis.
(2) Inhibit organification.
(3) Dec. vascularity, size, & fragility of hyperplastic thyroid gland.

Clinical Uses

(1) Thyroid storm.
(2) Iodine deficiency goitre.
(3) Preoperative preparation for thyroidectomy.

Adverse Effects

Iodism

(1) Eye: Conjunctivitis.
(2) ENT: Rhinorrhea.
(3) Blood: Bleeding disorders.
(4) GIT: Swollen salivary glands, metallic taste.
(5) Mucus memb: Ulcerations.
(6) Skin: Acneiform rash.
(7) Allergic reactions: Drug fever, anaphylaxis.

IODINATED CONTRAST MEDIA

Mechanism of Action

(1) Inhibit conversion of T_4 to T_3 in liver, kidneys, pituitary gland, & brain.
(2) Inhibit thyroid hormone release due to release of iodine.

Clinical Uses

(1) As adjunct in thyroid storm.
(2) As alternatives, when thioamides or iodides are contraindicated.

RADIOACTIVE IODINE (I^{131})

Mechanism of Action

It is rapidly incorporated into colloid of thyroid follicles 2 Emit beta rays that destroy thyroid parenchyma.

Clinical Uses

(1) Hyperthyroidism esp. in pts over 30 years of age.
(2) Toxic uninodular goitre.

Adverse Effects

(1) Delayed hypothyroidism.
(2) Delayed onset in control of hyperthyroidism.

Contraindications

(1) Pregnancy.
(2) Lactation.

GENERIC & TRADE NAMES

(A) Thyroid Hormones & Analogues

Thyroxine: Thyroxine.

(B) Anti - Thyroid Drugs

Propylthiouracil: Procarbizol.
Carbimazole: Carbizole, Mercazole, Neomercazole.
Iodine: Lugol's Iodine.

Unit III

Anti - Diabetic Drugs

INTRODUCTION

DIABETES MELLITUS

It is a clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin.

Types

(1) Type I (Insulin Dependent Diabetes Mellitus)

(a) Occur commonly in juveniles, & occasionally in non-obese adults.
(b) Associated with ketoacidosis in untreated state.
(c) Circulating insulin is virtually absent & pancreatic B cells fail to respond to all insulinogenic stimuli.

(2) Type II (Non-Insulin Dependent Diabetes Mellitus)

(a) Occur predominantly in obese adults, & occasionally in adolescents.
(b) Circulating endogenous insulin is sufficient to prevent ketoacidosis.
(c) There is tissue insensitivity to insulin, & an accompanying deficiency of pancreatic B cell's response to glucose.

Clinical Features

(1) Polyuria, thirst, & polydipsia (due to osmotic diuresis).
(2) Fatigue (due to hyperglycemia).
(3) Vulvitis & balanitis (due to glycosuria).
(4) Hypotension & hypothermia (due to ketoacidosis).
(5) Wasting & weight loss (due to inc. catabolism).

Drugs Causing Diabetes Mellitus

(1) Corticosteroids.
(2) Thiazide diuretics.
(3) Phenytoin.

CLASSIFICATION OF ANTI - DIABETIC DRUGS

INSULIN PREPARATIONS

(1) Rapid Acting Insulins

(a) Standard

Insulin lispro, Human insulin inhaled.

(b) Purified

Insulin aspart, Insulin glulisine.

(2) Short Acting Insulins

(a) Standard

Regular insulin (crystalline Zn insulin), Regular iletin I insulin.

(b) Purified

Regular, Regular humulin, Regular iletin II, Velosulin, Humulin BR.

(3) Intermediate Acting Insulins

(a) Standard

Isophane NPH (neutral protamine Hagedorn), Lente, Lente iletin I, NPH iletin I.

(b) Purified

Lente humulin, Lente iletin II, NPH humulin, NPH iletin II, NPH.

(4) Long Acting Insulins

(a) Standard

Ultralente, Ultralente iletin I.

(b) Purified

Ultra lente, Ultralente humulin.

(5) Premixed Insulins

Consists of 70% NPH, & 30% Regular;

(a) Novolin 70/30.

(b) Humulin 70/30.

ORAL HYPOGLYCEMIC AGENTS

(1) Insulin Secretogogues

(a) Sulfonylureas

(i) First Generation

Tolbutamide, Chlorpropamide, Tolazamide, Acetohexamide.

(ii) Second Generation

Glyburide (Glibenclamide), Glipizide, Glimepiride, Gliclazide.

(b) Meglitinides

Repaglinide.

(c) D-Phenylalanine Derivatives

Nateglinide.

(2) Biguanides

Phenformin, Buformin, Metformin.

(3) Thiazolidinedione Derivatives

Ciglitazone, Pioglitazone, Englitazone, Rosiglitazone.

(4) Alpha-Glucosidase Inhibitors

Acarbose, Miglitol.

(5) Miscellaneous

Pramlintide, Exenatide, Sitagliptin.

INSULIN PREPARATIONS

MECHANISM OF ACTION

Insulin binds to extracellular α- subunit of insulin receptors on target cells 2 This stimulates tyrosine kinase activity in β - subunit of insulin receptors (that spans the cell memb) 2 This results in,

(1) Self - phosphorylation of β - subunit 2 Inc. aggregation of α–β heterodimers, & stabilization of activated state of receptor tyrosine kinase.

(2) Phosphorylation of other intracellular proteins 2 Translocation of glucose transporter proteins from sequestered sites within the cells to exposed locations on cell surface 2 Inc. transport of glucose into cells. (See Box 17.1).

Finally, insulin - receptor complex is internalized 2 This may contributes to further insulin action, or terminate the action of insulin by removing insulin & its receptor into scavenger lysosomes.

Box 17.1 GLUCOSE TRANSPORTERS

Transporter	Location	Function
GLUT 1	All tissues esp RBCs, brain	Basal uptake of glucose, transport across BBB
GLUT 2	B cells of pancreas, liver, kidney, gut	Regulation of insulin release
GLUT 3	Brain, kidney, placenta, other tissues	Uptake of glucose
GLUT 4	Muscle, adipose tissue	Uptake of glucose
GLUT 5	Gut, kidney	Intestinal absorption of fructose

PHARMACOLOGICAL EFFECTS

(A) Liver

(1) Reversal of Catabolic Features of Insulin Deficiency

(a) Inhibits glycogenolysis.

(b) Inhibits conversion of fatty acids & amino acids to keto acids.

(c) Inhibits gluconeogenesis.

(2) Anabolic Actions

(a) Promotes glucose storage as glycogen.

(b) Increases triglyceride & VLDL synthesis.

(B) Muscle

(1) Inc. protein synthesis.

(2) Inc. glycogen synthesis.

(C) Adipose Tissue

Inc. triglyceride storage.

CLINICAL USES

(1) Insulin - dependent diabetes mellitus (IDDM).

(2) Non - insulin - dependent diabetes mellitus (NIDDM).

ADVERSE EFFECTS

(1) Hypoglycemia.
(2) Insulin allergy.
(3) Immune insulin resistance.
(4) Lipodystrophy at injection site.

SULFONYLUREAS

Mechanism Of Action

(1) Stimulate insulin secretion from pancreatic β - cells.
(2) Dec. serum glucagon levels.
(3) Potentiates the action of insulin on its target tissues.

Clinical Uses

Non - insulin - dependent diabetes mellitus.

Adverse Effects

(1) Metabolism: Hypoglycemia.
(2) GIT: Nausea, vomiting.
(3) Endo: Inappropriate ADH secretion.
(4) Blood: Leukopenia, agranulocytosis, thrombocytopenia, pancytopenia, hemolytic anemia.
(5) Skin: Rashes, flushing, photosensitivity.

Contraindications

(1) Hepatic impairment.
(2) Renal insufficiency.

BIGUANIDES

Mechanism Of Action

(1) Direct stimulation of glycolysis in peripheral tissues, with inc. glucose removal from blood.
(2) Dec. hepatic gluconeogenesis.
(3) Slowing of glucose absorption from GIT.
(4) Dec. plasma glucagon levels.
(5) Inc. insulin binding to insulin receptors.

Clinical Uses

(1) Pts with refractory obesity whose hyperglycemia is due to ineffective insulin action.
(2) Non - insulin - dependent diabetes mellitus (in combination with sulfonylureas).

Adverse Effects

GIT: Anorexia, nausea, vomiting, abdominal discomfort, diarrhea.

Contraindications

(1) Renal disease.
(2) Alcoholism.
(3) Hepatic disease.
(4) Chronic cardiopulmonary dysfunction.

GENERIC & TRADE NAMES

(A) Insulin Preparations

Actrapid, Humalog, Humulin Ultralente, Humulin-70 30-mix, Humulin-N, Humulin-R, Insulatard, Insulin Inj, Lantus, Mixtard 30-hm, Novopen, Novormx 30, Zansulin 70/30, Zansulin N.P.H., Zansulin Regular.

(B) Oral Hypoglycemics

Chlorpropamide: Diabenese, Diabtus.
Glyburide: Benil, Daonil, Diabeta, Diamide, Euglocon, Glabinol, Glaonil, Gliben, Glicon, Semi - Glicon.
Glipizide: Glibenese, Glipase, Minidiab.
Glimepiride: Amaryl, Diatrol, Geopride, Getformin, Getryl, Glyset.
Gliclazide: Diabetron, Diaglic, Diamicron, Diclazide, Glicozid, Gluconorm, Zaclazide.
Repaglinide: Novonorm, Repaglin.
Metformin: Dianorm, Getformin, Glimet, Glucometl, Tabrophage.
Pioglitazone: Diazone, Gliden, Zolid.
Rosiglitazone: Rosita, Rozi.
Acarbose: Glucobay.

Unit IV

Adrenocorticosteroids & Analogues

DRUG CLASSIFICATION

(A) Glucocorticoids

(1) Short- to Medium- Acting

Hydrocortisone (cortisol), Cortisone, Prednisone, Prednisolone, Fluocortolone, Methylprednisolone, Meprednisone.

(2) Intermediating - Acting

Triamcinolone, Paramethasone, Fluprednisolone.

(3) Long - Acting

Betamethasone, Dexamethasone.

(B) Mineralocorticoids

Aldosterone, Fludrocortisone, Deoxycorticosterone acetate.

Note: Hydrocortisone & Cortisone have also some mineralocorticoid activity.

MECHANISM OF ACTION

Corticosteroids diffuse or transported thru cell memb., & bind to cytoplasmic steroid receptors 2 Steroid - receptor complex is then transported into nucleus, where it interacts with corticosteroid response elements (CREs) on various genes & other regulatory proteins 2 This stimulates or inhibits the expression of CREs & regulatory proteins (eg enzymes), that control rate - limiting reactions in various metabolic pathways.

PHARMACOLOGICAL EFFECTS

(A) Glucocorticoids

(1) Central Nervous System
Behavioral disturbances, euphoria.

(2) Neuroendocrine
(a) Inhibit pituitary release of ACTH, & β - lipotropin.
(b) Dec. secretion of TSH, & FSH.

(3) Cardiovascular System
Maintenance of cardiovascular function by potentiating norepinephrine.

(4) Gastrointestinal Tract
Large dose stimulate excessive acid - pepsin secretion in stomach.

(5) Blood
Inc. RBCs & platelets count.

(6) Metabolism
(a) Stimulate gluconeogenesis in fasted state, & in diabetics.
(b) Inc. glycogen deposition in liver.
(c) Inc. lipolysis.

(7) Anti - Inflammatory & Immunosuppressive Effects
(a) Dec. neutrophil migration.
(b) Dec. circulating lymphocytes, monocytes, eosinophils, & basophils (which are moved to lymphoid tissues).
(c) Inhibit functions of leukocytes, & tissue macrophages.
(d) Stabilizes lysosomal membrane.
(e) Dec. prostaglandin & leukotriene synthesis.
(f) Dec. capillary permeability.

(B) Mineralocorticoids
(1) Inc. reabsorption of Na^+ by distal renal tubules, loosely coupled with secretion of K^+ & H^+.
(2) Inc. reabsorption of Na^+ in sweat & salivary glands, & GI mucosa.

CLINICAL USES

(A) Adrenal Disorders
(1) Addison's disease (Cortisol + Fludrocortisone).
(2) During & after adrenalectomy.
(3) To diagnose Cushing's syndrome (dexamethasone suppression test).

(B) Nonadrenal Disorders
(1) Prophylaxis of respiratory distress syndrome in premature infants (betamethasone to mother).
(2) Allergic reactions, eg
Asthma, angioneurotic edema, drug reactions, rhinitis, serum sickness, urticaria.
(3) Collagen - vascular disorders, eg
Lupus erythematosus, polymyositis, rheumatoid arthritis, Giant cell arteritis.
(4) Eye diseases, eg
Acute uveitis, allergic conjunctivitis, choroiditis, optic neuritis.
(5) Gastrointestinal diseases, eg
Inflammatory bowel disease, non-tropical sprue, subacute hepatic necrosis.
(6) Hematologic disorders, eg
Acquired hemolytic anemia, autoimmune hemolytic anemia, leukemia, idiopathic thrombocytopenic purpura, multiple myeloma.
(7) Infections, eg
Acute respiratory distress syndrome, sepsis, systemic inflammatory response sydrome.
(8) Inflammatory conditions of joints & bones, eg
Arthritis, bursitis, tenosynovitis.
(9) Neurologic disorders, eg
Cerebral edema, multiple sclerosis.
(10) Pulmonary diseases, eg
Aspiration pneumonia, sarcoidosis.
(11) Renal disorders, eg
Nephrotic syndrome.
(12) Skin diseases, eg
Atopic dermatitis, dermatoses, seborrheic dermatitis.
(13) Thyroid diseases, eg
Malignant exophthalmos, sub - acute thyroiditis.
(14) In organ transplantation, for prevention & treatment of rejection.

ADVERSE EFFECTS

(A) Iatrogenic Cushing's Syndrome
Occurs when 100 mg cortisol (or equivalent synthetic steroid) is given daily for more than 2 weeks.
(1) CNS: Insomnia, inc. appetite.
(2) Face: Altered by rounding, puffiness, & plethora.
(3) Musculo - Skeletal: Muscle wasting, osteoporosis, aseptic necrosis of hip.
(4) Skin: Inc. growth of fine hair over thighs & trunk, acne, & thinning of skin with stria & bruising.
(5) Fat deposition: Redistributed from extremities to trunk & face.
(6) Metabolic: Hyperglycemia, diabetes.
(7) Body weight: Weight Gain.
(8) Wound Healing: Impaired.

(B) Other
(1) CNS: Psychosis, dizziness.
(2) Eye: Posterior subcapsular cataract, glaucoma.
(3) CVS: Hypertension, congestive cardiac failure.
(4) GIT: Peptic ulcer, nausea.
(5) Water, electrolytes, & acid - base balance: Hypernatremia, edema, hypokalemia, hypochloremic alkalosis.
(6) Endo: Adrenal suppression.
(7) Growth: Growth retardation in children.

CONTRAINDICATIONS

(1) Peptic ulcer.
(2) Heart disease or hypertension with congestive cardiac failure.

(3) Infections.
(4) Psychosis.
(5) Diabetes mellitus.
(6) Osteoporosis.
(7) Glaucoma.
(8) Herpes simplex infection.

DOSAGE

(1) Betamethasone
0.5 - 5 mg/d, orally; reduce for maintenance to min. effective dose.

(2) Dexamethasone
(a) In chronic conditions 2 20 mg IM ; repeated as necessary.
(b) 5 - 20 mg by intra - articular & soft tissue inj. ; may be repeated at intervals of 1 - 3 weeks.

(3) Hydrocortisone
100 - 500 mg by slow IV inj.

Box 17.2 CORTICOSTEROID ANTAGONISTS

1) Synthesis Inhibitors & Glucocorticoid Antagonists
   a) Metyrapone
   b) Aminoglutethimide
   c) Ketoconazole
   d) Mifepristone
   e) Mitotane
   f) Trilostane
2) Mineralocorticoid Antagonists
   a) Spironolactone
   b) Eplerenone
   c) Drospirenone

GENERIC & TRADE NAMES

Glucocorticoids

Hydrocortisone: Cortisol, Daktacort, Fusac H*, Hydrosone, Hysone, Neo-cort*, Solu-cortef, Daktacort*.
Prednisolone: Blephapred, Deltacortil, Fortipred, Mildopred, Mydosone, Pred forte, Prednicol, Biopred*.
Fluocortolone: Ultralanum.
Methylprednisolone: Depo-medrol, Solu-medrol.
Triamcinolone: Kenacomb*, Kenacort, Kenacort-A, Kenalog, Kenoidal*, Ledercort, Tricort.
Betamethasone: Anglosone, Betacin N*, Betaderm, Betanate, Betnesol, Betnesol - N*, Probeta, Probeta - N*.
Dexamethasone: Baycuten, Decadron, Decadron - N*, Dexa N, Dexone, Dosachlor*, Fortecortin, Fradex*, Phesone.

Unit V

Gonadal Hormones & Antagonists

FEMALE GONADAL HORMONES

ESTROGENS

Classification

(A) Natural Steroidal
Estradiol, Estrone, Estriol.

(B) Synthetic Steroidal
Ethinyl estradiol, Mestranol, Quinestrol.

(C) Synthetic Nonsteroidal
Diethylstilbestrol, Chlorotrianisene, Methallenestril, Dienestrol, Benzestrol, Hexestrol, Methestrol.

Mechanism of Action

Estrogen enter its target cell by diffusion 2 Transported to nucleus, where it binds to estrogen receptors 2 Estrogen - receptor complex forms a homodimer that binds to estrogen response element on gene & interacts with specific cellular proteins 2 Activate transcription & regulate the formation of specific mRNA 2 Induction of protein synthesis in cell.

Pharmacological Effects

(1) Female Sex Organs
(a) Stimulate development of vagina, uterus, & uterine tubes.
(b) Stimulate stromal development & ductal growth in breast.
(c) Stimulate development of secondary sex characteristics, eg growth of axillary & pubic hairs, broadening of pelvis, & redistribution of body fat so as to produce typical female body contours.

(2) Skeletal System
(a) Accelerate growth phase & closing of epiphyses of long bones at puberty.
(b) Decrease rate of bone resorption.

(3) Pigmentation
Inc. pigmentation in nipples, areolas, & genital regions.

(4) Blood
(a) Inc. blood levels of transcortin, thyroxine-binding globulin, sex hormone-binding globulin, transferrin.
(b) Inc. blood levels of factor II, VII, IX, & X, & dec. antithrombin III level 2 Inc. coagulability.
(c) Inc. plasminogen levels.
(d) Dec. platelet adhesiveness.
(e) Inc. HDL & triglyceride levels.
(f) Dec. LDL & cholesterol levels.

Clinical Uses

(1) As replacement therapy in,
   (a) Primary hypogonadism, eg Turner's syndrome & panhypopituitarism in girls.
   (b) Postmenopausal synd. (hot flushes, osteoporosis).
(2) Intractable dysmenorrhea.

(3) Hirsutism & amenorrhea, due to excessive secretion of androgens by ovary.
(4) To stop excessive uterine bleeding due to endometrial hyperplasia.
(5) As oral contraceptive (see below).

Adverse Effects

(1) CNS: Migraine headache.
(2) CVS: Hypertension.
(3) GIT: Nausea.
(4) Biliary Tract: Cholestasis, gallbladder disease.
(5) Repro: Postmenopausal bleeding, breast tenderness, hyperpigmentation.
(6) Cancer: Inc. risk of breast & endometrial cancer.

Contraindications

(1) Carcinoma of endometrium.
(2) Carcinoma of breast.
(3) Undiagnosed genital bleeding.
(4) Liver disease.
(5) Thromboembolic disorder.

PROGESTINS

Classification

(1) Natural

Progesterone.

(2) Synthetic

(a) 21-Carbon Compounds
Hydroxyprogesterone, Medroxyprogesterone, Megestrol.

(b) 17-Ethinyl Testosterone Derivatives
Dimethisterone.

(c) 19-Nortestosterone Derivatives
Desogestrel, Norgestimate, Norethynodrel, Lynestrenol, Norethindrone, Ethynodiol, Norgestrel.

Mechanism of Action

Progestins enter cell & bind to progestin receptors that are distributed b/w nucleus & cytoplasmic domains 2 Progestin - receptor complex binds to a response element on gene & interacts with specific cellular proteins 2 This stimulates or inhibits expression of response element & cellular proteins.

Pharmacological Effects

(1) Female Sex Organs

(a) Causes maturation & secretory changes in endometrium following ovulation.
(b) Causes alveolo-lobular development of secretory apparatus in breast.

(2) Metabolism

(a) Stimulates lipoprotein lipase activity, & favors fat deposition.
(b) Inc. basal insulin level, & insulin response to glucose.
(c) Promote glycogen storage in liver.
(d) Promote ketogenesis.

(3) Central Nervous System

(a) Alters temperature - regulation centre in hypothalamus 2 Inc. body temperature.
(b) Inc. respiratory centre response to CO_2.
(c) Depressant & hypnotic effects on brain.

(4) Renal

(a) Competes with aldosterone at renal tubule 2 Dec. Na^+ reabsorption 2 Inc. aldosterone secretion.
(b) Inc. urinary nitrogen excretion.

(5) Blood

Dec. plasma level of many amino acids.

Clinical Uses

(1) As replacement therapy in,
  (a) Primary hypogonadism.
  (b) Postmenopausal syndrome.
(2) As oral contraceptive (see below).
(3) Dysmenorrhea, endometriosis, hirsutism, & bleeding disorders when estrogens are contraindicated.
(4) Precocious puberty.
(5) As a test of estrogen secretion.

Adverse Effects

(1) CNS: Depression.
(2) CVS: Hypertension, myocardial infarction.
(3) Blood: Low HDL levels.
(4) Resp. tract: Pulmonary embolus.
(5) Body fluid: Edema.
(6) Body weight: Weight gain.
(7) Lymphatics: Thrombophlebitis.

ORAL CONTRACEPTIVES

It refers to hormonal preparations that decreases fertility & prevent the occurrence of pregnancy, when taken orally.

Drug Classification

(A) Combination Pills

(1) Monophasic Combination Pills
It involves same dose of estrogen & progestin thru - out the menstrual cycle, eg;
(a) Ethinyl estradiol + Norethindrone, Desogestrel, Norgestrel, Ethynodiol, or Norgestimate.
(b) Mestranol + Norethindrone, Norethynodrel, or Ethynodiol.

(2) Biphasic Combination Pills
It involves 2 different doses of estrogen & progestin, given in 2 divided phases of menstrual cycle, eg; Ethinyl estradiol + Norethindrone.

(3) Triphasic Combination Pills
It involves 3 different doses of estrogen & progestin, given in 3 divided phases of menstrual cycle, eg; Ethinyl estradiol + Norgestrel, Norethindrone, or Norgestimate.

(B) Single Pills

(1) Daily Progestin Pills
Norethindrone, Norgestrel.

(2) Postcoital Pills
Conjugated estrogens, Ethinyl estradiol, Diethylstilbestrol, Norgestrel.

Mechanism of Action

(A) Combination Pills

Suppress mid-cycle surge of LH & FSH 2 Suppress ovulation, & ovarian follicle growth.

(B) Progestin Pills
Thickens the consistency of cervical mucus, which is a barrier to sperm.

Pharmacological Effects
(A) Ovary
(1) Depress ovarian functions, with minimal follicular development.
(2) Dec. ovarian size.

(B) Uterus
(1) Stromal deciduation towards the end of cycle.
(2) Glandular atrophy.
(3) Hypertrophy & polyp formation in cervix.
(4) Thick, & less copious cervical mucus.

(C) Breast
(1) Slight enlargement.
(2) Suppress lactation.

(D) Other
(1) CNS
(a) Estrogen increases excitability in brain.
(b) Progestins decreases excitability in brain, & also has thermogenic effects.

(2) CVS
Inc. heart rate & BP 2 Inc. cardiac output.

(3) Endocrine
(a) Inhibit pituitary gonadotropin secretion.
(b) Inc. plasma cortisol level, due to inc. plasma conc. of corticosteroid - binding globulin.
(c) Inc. aldosterone secretion, due to inc. plasma renin activity.
(d) Inc. plasma thyroxine level, due to inc. thyroxine - binding globulin.

(4) Liver
(a) Inc. synthesis of various α_2 - globulins, & fibrinogen.
(b) Dec. haptoglobin synthesis.
(c) Inc. cholic acid, & dec. chenodeoxycholic acid in bile 2 Cholelithiasis.
(d) Dec. bile flow.

(5) Blood
(a) Inc. factor VII, VIII, IX, & X 2 Serious thromboembolic phenomena.
(b) Inc. serum iron & total iron - binding capacity.
(c) Folic acid deficiency anemias.

(6) Metabolism
(a) Slightly dec. triglycerides & HDL.
(b) Dec. rate of carbohydrate absorption from GIT, & inc. basal insulin level.

(7) Skin
(a) Inc. skin pigmentation (chloasma).
(b) Inc. or dec. in sebum secretion & acne.

Clinical Uses
(1) Oral contraception.
(2) Endometriosis.

Adverse Effects
(A) Mild Adverse Effects
(1) CNS: Headache, worsening of migraine.
(2) GIT: Nausea.
(3) Repro: Mastalgia, break - thru bleeding, failure of withdrawal bleeding.
(4) Body fluids: Edema.
(5) Blood: Changes in serum proteins (see above), inc. ESR.

(B) Moderate Adverse Effects
(1) Repro: Break-thru bleeding, vaginal infections, amenorrhea after discontinuance, galactorrhea.
(2) Urinary tract: Ureteral dilation, bacteriuria.
(3) Skin: Inc. pigmentation, acne, hirsutism.
(4) Body weight: Weight gain.

(C) Severe Adverse Effects
(1) CNS: Depression.
(2) CVS: Venous thromboembolic disease, myocardial infarction, cerebrovascular accident.
(3) GIT: Ischemic bowel disease secondary to thrombosis of celiac & mesenteric vessels.
(4) Hepato-biliary tree: Cholestatic jaundice, cholecystitis, cholangitis, hepatic adenoma.

Contraindications
(1) Thrombophlebitis.
(2) Thromboembolic phenomena.
(3) Cerebrovascular accidents.
(4) Vaginal bleeding of unknown cause.
(5) Breast tumor or other estrogen-dependent neoplasms.
(6) Adolescents in whom epiphyseal closure has not yet been completed.

Precautions
(1) Liver disease.
(2) Asthma.
(3) Eczema.
(4) Migraine.
(5) Diabetes.
(6) Hypertension.
(7) Optic neuritis.
(8) Retrobulbar neuritis.
(9) Convulsive disorders.
(10) Congestive cardiac failure.

ESTROGEN & PROGESTERONE INHIBITORS & ANTAGONISTS

Drug Classification
(1) Antiestrogens
(a) Receptor antagonists
(i) Full antagonists, eg Fulvestrant.
(ii) Selective estrogen receptor modulator (SERMs), eg Tamoxifen,Toremifene, Raloxifene, Clomiphene.

(b) Aromatase inhibitors
Anastrozole, Letrozole, Exemestane, Fadrozole.

(c) GnRH agonists
Nafarelin, Buserelin.

(d) Danazol

(2) Antiprogestins
Mifepristone.

TAMOXIFEN

Mechanism of Action

(1) Tamoxifen competitively binds to estrogen receptors on tumors & other tissue targets, producing a nuclear complex that decreases DNA synthesis & inhibits estrogen effects.
(2) It is a nonsteroidal agent with potent antiestrogenic properties which compete with estrogen for binding sites in breast & other tissues.
(3) It causes cells to remain in the G0 & G1 phases of the cell cycle.

Clinical Uses

(1) Breast cancer treatment, both early & advanced ER+ (estrogen receptor positive) breast cancer in pre- & post-menopausal women.
(2) Prevention of breast cancer in women at high risk of developing the disease.
(3) Infertility in women with anovulatory disorders.
(4) Gynecomastia.
(5) Bipolar disorder (by blocking protein kinase C, an enzyme that regulates neuron activity in the brain).
(6) Control of gene expression (as a research tool).

Adverse Effects

(1) Blood: Triglyceridemia, increased risk of thromboembolism
(2) Liver: Fatty liver, otherwise known as steatorrheic hepatosis or steatosis hepatis.
(3) Repro: Reduction of libido.
(4) Cancer: Inc. risk of endometrial & uterine cancer.

Dosage

10-20 mg BD.

MALE GONADAL HORMONES & ANTAGONISTS

ANDROGENS

Classification

(A) Natural

Testosterone, Dihydrotestosterone, Androstenedione, Dehydroepiandrosterone.

(B) Synthetic

(1) With Equal Androgenic & Anabolic Activity
Testosterone cypionate, Testosterone enanthate, Testosterone propionate, Methyltestosterone.

(2) With More Anabolic Activity
Fluoxymesterone, Methandrostenolone, Oxy-metholone, Ethylestrenol, Oxandrolone, Nandrolone phenpropionate, Nandrolone decanoate, Stanozolol, Dromostanolone propionate.

Mechanism of Action

Similar to progestins & corticosteroids.
(1) In muscle & liver, testosterone itself is the active compound.
(2) In reproductive tissues & skin, testosterone is first converted to 5α - dihydrotestosterone (DHT). Synthetic androgens that cannot be converted to DHT have less effect on reproductive system.

Pharmacological Effects

(A) Male Sex Organs

Development of secondary sex characteristics;
(1) Penis.
(2) Scrotum.
(3) Prostate.
(4) Seminal vesicles.

(B) Skin

(1) Appearance of pubic, axillary & beard hair, & frontal baldness.
(2) More active sebaceous glands, with thicker & oilier skin 2 Acne.
(3) Darkening of skin.
(4) Inc. skin circulation.

(C) Larynx

Enlargment, with thickening of vocal cords 2Low-pitched voice.

(D) Musculo - Seketal System

(1) Stimulate skeletal growth, with epiphyseal closure acceleration.
(2) Inc. musculature.

(E) Blood

Stimulate erythrocyte production.

(F) Protein Metabolism

Inc. protein synthesis & dec. protein breakdown 2 Dec. nitrogen excretion in urine.

Clinical Uses

(1) Androgen replacement therapy in hypogonadal men.
(2) Gynecologic disorders in women;
  (a) To reduce breast engorgement during postpartum period (usually with estrogens).
  (b) To eliminate endometrial bleeding in postmeno-pausal period (with estrogens).
  (c) Breast tumors in premenopausal women.
(3) As protein anabolic agent, eg
After trauma, surgery, or prolonged immobilizations, & in pts with debilitating diseases.
(4) Refractory anemias.
(5) Osteoporosis.
(6) To stimulate growth in prepubertal boys.
(7) As anabolic steroid (androgen abuse).
(8) Aging.

Adverse Effects

(A) In Women & Prepubertal Children

(1) Repro: Depression of menses, clitoral enlargement, endometrial bleeding.
(2) Skin: Hirsutism, acne.
(3) Larynx: Deepening of voice.
(4) Blood: Alter serum lipids 2 Inc. susceptibility to atherosclerotic disease.

(B) In Infants

(1) Profound effects on maturation of CNS centres governing sexual development.
(2) Masculinization of external genitalia of female infant, if given to mother during pregnancy.

(C) Other Adverse Effects

(1) Hepato-biliary tree: Hepatic dysfunction, cholestatic jaundice, hepatocellular carcinoma.
(2) Fluid & electrolyte balance: Sodium retention, edema.
(3) Males: Prostatic hyperplasia.

Contraindications

(1) Pregnancy.
(2) Carcinoma of prostate.
(3) Carcinoma of breast in males.
(4) Infants & young children.

ANTIANDROGENS

Drug Classification

(1) Receptor antagonists, eg Flutamide.
(2) 5-α-reductase inhibitors, eg Cyproterone, Finasteride, Bicalutamide, Nilutamide, Spironolactone.
(3) Synthesis inhibitor, eg Ketoconazole.
(4) Others, eg GnRH agonists, combined oral contraceptives.

GENERIC & TRADE NAMES

(A) Estrogens

Estradiol: Femoston, Kliogest, Progyluton, Progynon depot, Progynova.
Estriol: Ovestin.

(B) Progestins

Progesterone: Cyclogest, Progesterone.
Hydroxyprogesterone: Gravibinan, Hydroxy-progesterone, Proluton Depot.
Medroxyprogesterone: Ciclotal, Depo-provera, Medrosterona, Roxyprog Depo.
Lynestrenol: Orgametril.
Norgestrel: Emkit, Mirena, Ovral, Postinor.

(C) Oral Contraceptives

Ethinyl estradiol + Norgestrel: Ovral.
Ethinyl estradiol + Levonorgestrel: Famila 28, Nordette, Nova, Novodol, Ovlodiol, Redate.
Ethinyl estradiol + Norethisterone: Geogynon, Gyneric, Gynorit.
Ethinyl estradiol + Desogestrel: Marvelon, Meliane.

(D) Antiestrogens

Tamoxifen: Nolvadex, Tamofen, Tamooex, Tamoplex, Tamox, Tamoxifen, Lachema, Tamoxin, Temocab, Tumen, Zitazonium.
Raloxifene: Denser, Evista, Raloxi, Relofin, Revera.
Clomiphene: Bemot, Clocit, Clofer, Clomid, Clomitab, Clomocite, Hope, Lexofene, Umeed.
Anastrozole: Arimidex.
Letrozole: Femara.
Danazol: Danocrine, Danzol.

(E) Androgens

Testosterone: Androxon, Sustanon 250, Testosterone, Testoviron, Vigrol forte*.
Ethylestrenol: Orabolin.
Nandrolone: Abolon, Durabolin.
Stanozolol: Anasynth.

(F) Antiandrogens

Flutamide: Eulexin, Flutacan, Fluten.
Cyproterone: Androcur, Climen, Diane 35.
Finasteride: Genesis, Proscar.
Bicalutamide: Casodex.

Unit VI

Self - Assessment (T/F)

(See answers on page no. 241)

(124) ***Effects of glucocorticoids include all of the following***
(A) Inc. RBC count.
(B) Suppresses leukocyte migration.
(C) Stabilizes lysosomal membrane.
(D) Inc. gluconeogenesis.
(E) Dec. lipolysis.

(125) ***Adverse effects of corticosteroids include all of the following***
(A) Hypoglycemia.
(B) Osteoporosis.
(C) Psychosis.
(D) Peptic ulcer.
(E) Salt retention.

(126) ***All of the following agents are useful as oral or implantable contraceptives except***
(A) Ethinyl estradiol.
(B) Mestranol.
(C) Clomiphene.
(D) Norethindrone.
(E) Norgestrel.

(127) ***All of the following are recognized effects of oral contraceptives***
(A) Inc. risk of myocardial infarction.
(B) Nausea.
(C) Edema.
(D) Inc. risk of endometrial cancer.
(E) Dec. risk of ovarian cancer.

(128) ***All of the following are recognized effects of natural androgens or androgenic steroids***
(A) Growth of facial hair.
(B) Inc. muscle bulk.
(C) Inc. milk production in nursing women.
(D) Induction of growth spurt in prepubertal boys.
(E) Inc. alkaline phosphatase & SGOT level in blood.

(129) ***In order to achieve rapid control of severe ketoacidosis in a hospitalized 13 year old boy, the appropriate antidiabetic agent to use is***
(A) Crystalline zinc insulin.
(B) Isophane (NPH) insulin.

(C) Protamine zinc or ultralente insulin.
(D) Tolbutamide.
(E) Glyburide.

(130) ***All of the following act by stimulating insulin release from pancreatic beta - cells***
(A) Tolbutamide.
(B) Tolazamide.
(C) Chlorpropamide.
(D) Glipizide.
(E) Phenformin.

(131) ***Effects of insulin include all of the following***
(A) Inc. glucose transport into cells.
(B) Induction of lipoprotein lipase.
(C) Dec. gluconeogenesis.
(D) Stimulation of glycogenolysis.
(E) Inc. protein synthesis.

(132) ***Possible complications of insulin therapy include***
(A) Dilutional hyponatremia.
(B) Hypoglycemia.
(C) Pancreatitis.
(D) Inc. bleeding tendency.
(E) Lipodystrophy at injections site.

(133) ***Important drugs used in the treatment of thyrotoxicosis include***
(A) Propylthiouracil.
(B) Potassium iodide.
(C) Thyroglobulin.
(D) Radioactive iodine.
(E) Methimazole.

(134) ***Following are recognized adverse effects of propylthiouracil***
(A) Agranulocytosis.
(B) Lymphadenopathy.
(C) Hyperglycemia.
(D) Hypokalemia.
(E) *Cholestatic jaundice.*

18 CHEMOTHERAPY OF BACTERIAL INFECTIONS

Unit I

Introduction

CHEMOTHERAPY

It refers to drug treatment of parasitic infections in which the parasites (bacteria, viruses, protozoa, fungi, worms) are destroyed or removed without injuring the host.

ANTIMICROBIAL AGENTS

These are agents that kills microorganisms or suppresses their multiplication or growth.

Classification of Antimicrobials

(1) Antibacterial agents.
(2) Antiviral agents.
(3) Antiprotozoal agents.
(4) Antifungal agents.
(5) Antihelmintic agents.

Antibiotics

These are soluble compounds that are derived from certain microorganisms & that inhibit the growth of other microorganisms.

Bacteriostatic Drugs

These are drugs that temporarily inhibits the growth of a microorganism. When the drug is removed, organism will resume growth & infection or disease may recur.

Typical bacteriostatics: Tetracyclines, sulfonamides.

Bactericidal Drugs

These are drugs that attaches to its receptor on micro-organisms, & causes their death.

Typical bactericidals: Penicillins, cephalosporins, aminoglycosides.

MECHANISM OF ACTION OF ANTIMICROBIALS

(1) Thru inhibition of cell wall synthesis
eg Penicillins , Cephalosporins, Cycloserine, Vancomycin, Bacitracin, Ristocetin.
(2) Thru inhibition of cell memb. function
eg Amphotericin B, Nystatin, Imidazoles, Colistin, Polymyxins.
(3) Thru inhibition of protein synthesis
eg Chloramphenicol, Tetracyclines, Aminoglycosides, Erythromycin, Lincomycin.
(4) Thru inhibition of nucleic acid synthesis
eg Sulfonamides , Trimethoprim, Pyrimethamine, Rifampin, Quinolines, Novobiocin.

USE OF ANTIMICROBIALS

(1) Choice of Antimicrobials

(a) It follows automatically from the clinical diagnosis.
(b) It should be based, wherever possible, on bacteriological identification & sensitivity test.

(2) Administration of Antimicrobials

(a) Oral: It is convenient & less unpleasant but the food retards absorption & peak plasma conc. are therefore lower. So, in general, antimicrobials should be taken, b/w meals or at least one hour before a meal.
(b) Parenteral: It is used for serious infection. IV route is generally preferred.

(3) Combinations of Antimicrobials

2 or more antimicrobials can be used concomitantly:
(a) To obtain potentiation.
(b) To delay development of drug resistance.
(c) To broaden the spectrum of antibacterial activity.

Disadvantages of Combined Therapy

(a) A false sense of security, discouraging efforts towards accurate diagnosis.
(b) Broader suppression of normal flora with inc. risk of opportunistic infection with resistant organisms.
(c) Inc. incidence & variety of adverse effects.

PROBLEMS WITH ANTIMICROBIALS

(1) Microbial Resistance to Drugs

Mechanism of Resistance

(a) Via producing enzymes that destroy active drug, eg staphylococcal resistance to penicillin G.
(b) Via altering memb. permeability to drug, eg streptococcal resistance to aminoglycosides.
(c) Via developing an altered structural target for drug, eg resistance to aminoglycosides.
(d) Via developing an altered metabolic pathway that bypasses the reaction inhibited by drug, eg resistance to sulfonamide.
(e) Via developing an altered enzyme that can still perform its metabolic function but is much less affected by the drug, eg resistance to sulfonamide.

Origin of Drug Resistance

(a) Nongenetic Origin

(i) Microorganisms that are metabolically inactive (nonmultiplying) may be resistant to drugs; however, their offspring are fully susceptible.

(ii) Microorganism may lose the specific target structure for a drug for several generations & thus be resistant.

(b) Genetic Origin

(i) Chromosomal resistance: This develops as a result of spontaneous mutation in a locus on bacterial chromosome that controls susceptibility to a given antimicrobial. A change in the structural receptors for the drug occur which causes resistance.

(ii) Extrachromosomal resistance: Plasmids are extrachromosomal circular DNA molecules. Plasmid genes for antimicrobial resistance control the formation of enzymes capable of destroying antimicrobial drugs.

Cross Resistance

Microorganism resistant to a certain drug may also be resistant to other drugs that share a mechanism of action or attachment, this is called cross-resistance.

(2) Opportunistic Infection

When any antimicrobial drug is used, there is suppression of part of the normal flora of pt, which varies according to drug. Often, this causes no ill effects, but sometimes a drug-resistant organism, freed from competition, proliferates to an extent that can be fatal. This is opportunistic infection.

eg, antibiotic-associated colitis with drugs esp. lincomycin, clindamycin, amoxycillin, ampicillin & cephalosporins.

(3) Adverse Effects of Antimicrobials

(a) Allergic-type effects occur commonly.

(b) Direct organ toxicity also occur.

(4) Drug Interactions with Antimicrobials

(a) On absorption: Tetracycline chelates iron & Ca, & absorption of all from the gut is dec.

(b) On metabolism: Rifampin induces hepatic drug metabolizing enzymes & may cause an oral contraceptive to fail; metronidazole, cefamandole & latamoxef inhibit alcohol metabolism to cause a disulfiram-like reaction.

(c) On elimination: Probenecid competes with penicillin for renal tubular anion transport mechanism, causing penicillin to be retained.

(d) On organs: Gentamicin & furosemide in high dose create inc. risk of ototoxicity.

(5) Treatment Failure

(a) It may be due to drug resistance.

(b) Where the organism is sensitive to the drug used, failure is due to the way the drug is used or due to some factor peculiar to the pts.

Unit II

Penicillins

DRUG CLASSIFICATION

(A) According to Nature

(1) Natural Penicillins

Penicillin G or Benzyl penicillin.

(2) Semisynthetic Penicillins

(a) Long Acting Penicillins

Procaine penicillin, benzathine penicillin G.

(b) Orally Effective Penicillins

Phenoxymethyl penicillin (Penicillin V), Phenbenicillin, Propicillin.

(c) Penicillinase - Resistant (Antistaphylococcal) Penicillins

(i) Methicillin.

(ii) Nafcillin.

(iii) **Isoxazolyl penicillins:** Oxacillin, Cloxacillin, Dicloxacillin, Flucloxacillin.

(d) Broadspectrum Penicillins (Aminopenicillins)

Ampicillin, Amoxycillin, Bacampicillin, Pivampicillin, Cyclacillin, Hetacillin, Amoxycillin plus Clavulanic acid, Ampicillin plus Cloxacillin, Amdinocillin/Mecillinam.

(e) Anti - Pseudomonal Penicillins

(i) **Carboxypenicillins**: Carbenicillin, Carbenicillin indanyl Na, Ticarcillin.

(ii) **Ureidopenicillins**: Azlocillin, Mezlocillin, Piperacillin.

(B) On the Basis of Penicillinase Sensitivity

(1) Penicillinase Sensitive

(a) Acid Labile

Penicillin G, Procaine Penicillin, Benzathine Penicillin G, Carbenicillin, Ticarcillin, Azlocillin, Mezlocillin, Piperacillin, Amdinocillin/Mecillinam.

(b) Acid Stable

Penicillin V, Phenbenicillin, Propicillin, Ampicillin, Amoxycillin, Bacampicillin, Pivampicillin, Amoxycillin plus Clavulanic acid, Ampicillin plus Cloxacillin, Carbenicillin indanyl.

(2) Penicillinase Resistant

(a) Acid Labile

Methicillin, Nafcillin.

(b) Acid Stable

Oxacillin, Cloxacillin, Dicloxacillin, Flucloxacillin.

MECHANISM OF ACTION

Penicillins inhibit bacterial cell wall synthesis by binding to specific PBP (penicillin binding protein) receptors on bacteria 2 This results in;

(1) Inhibition of cell wall synthesis by blocking trans-peptidation of peptidoglycan by interfering with the enzymes transpeptidase & endopeptidase.
(2) Activation of autolytic enzymes in cell wall resulting in lesions that causes bacterial death.

RESISTANCE

(1) Certain bacteria (eg many staphylococcus aureus, some H. influenzae, gonococci) produce beta-lactamases (penicillinases) which opens up beta-lactam ring & hydrolyzes it to penicilloic acid, a harmless form.
(2) Certain bacteria lack specific receptors.
(3) In some bacteria autolytic enzyme in cell wall is not activated, eg streptococci.
(4) Certain organisms lack cell wall, eg mycoplasma.

CLINICAL USES

(A) Penicillin G

(1) Pneumococcal infections, eg pneumonia, meningitis, suppurative arthritis, mastoiditis, endocarditis, pericarditis, osteomyelitis.
(2) Group 'A' streptococcal infections, eg pharyngitis, scarlet fever, impetigo, puerperal sepsis, rheumatic fever.
(3) Meningococcal infections, eg nasopharyngitis, meningococcemia, Waterhouse-Friderichsen synd., arthritis, endocarditis, meningitis.
(4) Non-beta lactamase producing staphylococcal & gonococcal infections.
(5) Treponema pallidum inf., eg syphilis.
(6) Bacillus anthracis inf., eg anthrax.
(7) Clostridial inf., eg tetanus, gas gangrene.
(8) Actinomycosis.
(9) Listeria infections.
(10) Diphtheria.
(11) Rat bite fever.
(12) Bacteroides inf. (except of B. fragilis).

(B) Penicillin V

(1) Pneumococcal infections.
(2) Group 'A' streptococcal inf.
(3) Staphylococcal inf.
(4) Meningococcal inf.
(5) Gonococcal inf.

(C) Procaine Penicillin

Gonococcal inf., eg gonorrhea, prostatitis, arthritis, salpingitis, urethritis, meningitis.

(D) Broadspectrum Penicillins

(1) Uncomplicated gonorrhea.
(2) H. influenza inf., eg meningitis, osteomyelitis, epiglottitis, pneumonia, septic arthritis.
(3) Acute urinary tract inf. (caused by gram negative bacteria).
(4) Salmonella inf., eg typhoid & paratyphoid fever.
(5) Mixed bacterial inf. of respiratory tract, eg sinusitis, otitis, bronchitis.
(6) In inf. where penicillin G is the drug of choice but oral therapy is preferred.

(E) Antipseudomonal Penicillins

Infection caused by gram-negative bacteria esp. pseudomonas aeruginosa, indole-positive proteus & enterobacter (eg bacteremia, pneumonia, burn inf., urinary tract inf.)

(F) Penicillinase-Resistant Penicillins

Beta-lactamase producing staphylococcal inf., eg bacteremia, cellulitis, osteomyelitis, pneumonia, carbuncles, enteritis, wound inf.

ADVERSE EFFECTS

(1) GIT

Nausea, vomiting, diarrhea, & enteritis occur with oral therapy (due to luxuriant overgrowth of staphylococci, pseudomonas, proteus or yeasts).

(2) Liver

Hepatitis.

(3) Bone Marrow

Bone marrow depression, agranulocytosis.

(4) Blood

Impairment of platelet aggregation, hypokalemia & elevated serum transaminase with carbenicillin.

(5) Allergic Reactions

(a) Anaphylaxis: Severe hypotension & shock, or laryngeal edema, or diffuse pruritus, urticaria & flushing.
(b) Serum sickness reactions: Urticaria, fever, joint swelling, angioneurotic edema, intense pruritus, & respiratory embarrassment.
(c) Skin lesions: Skin rashes, stevens-johnson synd., morbilliform eruptions, erythematous eruptions, urticaria, dermatitis.
(d) Oral lesions: Glossitis, stomatitis, furred tongue, chellosis.
(e) Blood dyscrasias: Eosinophilia, hemolytic anemia, thrombocytopenia.
(f) Drug fever
(g) Interstitial nephritis
(h) Vasculitis

(6) IV Administration

Causes phlebitis, thrombophlebitis, local pain, induration or degeneration of accidentally injected nerve.

CONTRAINDICATIONS

(1) History of previous hypersensitivity reaction to penicillins &/or cephalosporins.

(2) Parenteral inj. into or near an artery or nerve.

DOSAGE

Penicillin Units

Activity of penicillin G was originally defined in units. Crystalline Na penicillin G contains approx 1600 unit/mg (1unit = 0.6 μg; 1million units = 0.6g). Most semisynthetic penicillins are prescribed by weights rather units.

(1) Penicillin G 2 0.6 - 5 million units (0.36-3 g) per day; IM, QID.
(2) Procaine penicillin 2 4.8 to 10 million units (2.8-6 g), OD, IM.
(3) Ampicillin 2 300-500 mg QID; orally, IM or IV.
(4) Cloxacillin 2 0.25 - 0.5 g orally every 4 - 6 hrs.
(5) Carbenicillin 2 300 - 500 mg/kg/d; IV.

BETA-LACTAMASE INHIBITORS

Examples

Clavulanic acid, Sulbactam, Tazobactam.

Mechanism of Action

They are β-lactamase inhibitors that extends antibacterial spectrum of the companion β-lactam antibiotics by irreversibly binding to & inhibiting the enzyme.

Clinical Uses

(1) Combination of clavulanic acid & amoxycillin is used to treat infections caused by beta-lactamase producing strains of H. influenza, B. catarrhalis, S. aureus, E. coli, Klebsiella & enterobacter.
(2) Combination of sulbactam & ampicillin or cefoperazone is used to treat infections caused by beta-lactamase producing strains of H. influenza, N gonorrheae, S. aureus, E. coli, salmonella, shigella, & K pneumoniae.
(3) Combination of tazobactam & piperacillin is also used to treat infections caused by beta-lactamase producing strains of H. influenza, N gonorrheae, S. aureus, E. coli, salmonella, shigella, & K pneumoniae

Adverse Effects

There are no serious adverse effects associated with β-lactamase inhibitors .

MONOBACTAMS

Examples

Aztreonam.

Mechanism of Action

Aztreonam is similar in action to penicillin. It inhibits mucopeptide synthesis in the bacterial cell wall.

Clinical Uses

Effective against a wide range of gram-negative bacteria including Citrobacter, Enterobacter, E coli, Hemophilus, Klebsiella, Proteus, & Serratia species.

Adverse Effects

(1) **Skin**: Injection site reactions, rash, toxic epidermal necrolysis.
(2) **GIT**: Nausea, vomiting, diarrhea.
(3) **Blood:** Drug-induced eosinophilia.

CARBAPENEMS

Examples

Ertapenem, Imipenem, Meropenem.

Mechanism of Action

(1) Imipenem acts as an antimicrobial thru inhibiting cell wall synthesis of various aerobic & anaerobic Gram positive as well as Gram negative bacteria, including P aeruginosa & the Enterococcus species.
(2) It remains very stable in the presence of beta-lactamase (both penicillinase & cephalosporinase)

Adverse Effects

(1) **CNS:** Seizures (imipenem).
(2) **Skin**: Injection site reactions, rash.
(3) **GIT**: Nausea, vomiting, diarrhea.

Dosage

Imipenem: 0.25-0.5 gm, TDS or QID, intravenously.

VANCOMYCIN

Mechanism of Action

Similar to penicillins.

Clinical Uses

(1) Serious staphylococcal inf.
(2) Endocarditis not responding to other treatment.
(3) Pseudomembranous colitis (caused by clostridium difficile).

Adverse Effects

(1) Allergic reactions: Skin rashes, anaphylaxis
(2) ENT: Deafness.
(3) Nephrotoxicity
(4) IV inj: Thrombophlebitis

Dosage

0.5 gm, QID.

GENERIC & TRADE NAMES

(1) Natural Penicillins

Penicillin G: Polybiotic*, Benzyl penicillin inj.

(2) Semi - Synthetic Penicillins

Procaine Penicillin: Polybiotic*.
Penicillin V: Penicillin V.
Cloxacillin: Auropen, Cloxacillin, Cloxazan, Orbenin, Venal.

Ampicillin: Amicil, Ampicil, Ampcigen, Ampicap, Ampiceena, Ampicillin, Amplipen, Anglocillin, Epocillin, Fedrapen, Omnipen, Penbritin, Pencin.
Amoxycillin: Adamox, Amocillin, Amoxil, Amoxycillin, Amoxygen, Cipamox, Geomoxin, Maxil, Ocemox, Ospamox, Princimox, Wilmox, Zeemox.
Bacampicillin: Penglobe.
Carbenicillin: Pyopen.
Piperacillin: Pipril.
Ticarcillin: Timentin.
Ampicillin Plus Cloxacillin: Amcopen, Ampiclox, Anclox, Anglocin, Apoclox, Bioclox, Cloxapen, Dicillin, Dosaclox, Elkobiotic, Jaclox, Linclox, Maxiclox, Novoclox, Penciclox, Pencit.
Amoxycillin Plus Flucloxacillin: Aflox, Bactoxyl, Deflox, Fclox, Flomoxin, Flucomox, Twin, Varaflox, Biflocin.
Amoxycillin plus Clavulanic acid: Augmentin, Clamentin, Fortecin, Loment, Potentin.
Amoxycillin Plus Sulbactum: Moxsul, Sulbamox, Sulbarex, Sulzone.
Piperacillin Plus Tazobactam: Tanzo, Tazocin.

(3) Other Drugs

Aztreonam: Azactam.
Imipenem: Tienam.
Meropenem: Meronem.
Vancomycin: Vanacin.

Unit III

Cephalosporins

DRUG CLASSIFICATION

(A) First Generation Cephalosporins

Narrow-spectrum, beta-lactamase sensitive antibiotics, having poor CSF penetrability.
(1) Oral drugs: Cefadroxil, Cephalexin, Cephradine.
(2) Parenteral drugs: Cefazolin, Cephalothin, Cephapirin, Cephaloridine.

(B) Second Generation Cephalosporins

Intermediate-spectrum antibiotics, variably stable to beta-lactamase, having unreliable CSF penetrability.
(1) Oral drug: Cefaclor.
(2) Parenteral drugs: Cefamandole, Cefonicid, Ceforanide, Cefoxitin, Cefuroxime, Cefmetazole, Cefotetan, Cefprozil, Cefpodoxime, Loracarbef.

(C) Third Generation Cephalosporins

Broad-spectrum, beta-lactamase resistant antibiotics, having good CSF penetrability.
(1) Oral drug: Cefixime, Cefdinir, Cefditoren pivoxil, Ceftibuten.
(2) Parenteral drugs: Cefoperazone, Cefotaxime, Cefixime, Ceftazidime, Ceftizoxime, Ceftriaxone, Moxalactam.

(D) Fourth Generation Cephalosporins

More broad-spectrum & more beta-lactamase resistant than third generation cephalosporins, & also have good CSF penetrability.
Parenteral drugs: Cefepime.

MECHANISM OF ACTION

Similar to penicillins.

RESISTANCE

(1) Poor penetration of bacteria by the drugs.
(2) Lack of PBP for a specific drug.
(3) Degradation of drug by beta-lactamases (cephalosporinases).
(4) Failure of activation of autolytic enzymes in cell wall.

CLINICAL USES

(A) First Generation Cephalosporins

(1) Oral Drugs
(a) Urinary tract infections.
(b) Staphylococcal inf., eg skin inf., osteomyelitis, endocarditis.
(c) Minor polymicrobial inf., eg cellulitis, soft tissue abscess.

(2) Parenteral Drugs
(a) Surgical prophylaxis during the insertion of prosthetic devices.
(b) K. pneumonia inf.
(c) As an alternative in penicillin allergic pts.

(B) Second Generation Cephalosporins

(1) Branhamella catarrhalis inf., eg sinusitis, otitis media.
(2) H. influenzae inf., eg sinusitis, otitis media.
(3) H. influenza meningitis (only cefuroxime is used).
(4) Mixed anaerobic inf., eg peritonitis, diverticulitis.
(5) Sepsis.

(C) Third Generation Cephalosporins

(1) Meningitis, caused by pneumococci, meningococci, H. influenza & enteric gram negative rods (except cefoperazone).
(2) Sepsis.

(D) Fourth Generation Cephalosporins

Infections caused by P aeruginosa, S aureus, multiple drug resistant S pneumonia & Enterobacteriaceae.

ADVERSE EFFECTS

(1) GIT

Anorexia, nausea, vomiting, diarrhea.

(2) Blood Dyscrasias
Hemolytic anemia, neutropenia, leukopenia, thrombocytopenia, hypoprothrombinemia.

(3) Renal
Nephritis & tubular necrosis with cephaloridine.

(4) Allergic Reactions
Anaphylaxis, drug fever, skin rashes, nephritis, granulocytopenia, hemolytic anemia.

Note: Cross-allergenicity to cephalosporins in penicillin allergic pts occurs in about 10% cases.

(5) IM Inj
Local irritation causing severe pain.

(6) IV Inj
Thrombophlebitis.

(7) Superinfection
Resistant gram positive organisms esp. staphylococci & enterococci, as well as fungi often proliferate & induce superinfection.

CONTRAINDICATIONS

(1) Hypersensitivity to cephalosporins or penicillins.
(2) Combination with aminoglycosides & loop diuretics, b/c of their potential of causing nephrotoxicity.

DOSAGE

(1) Cefadroxil 2 0.5-1g BD, orally.
(2) Cephalexin 2 0.25-0.5 g QID, orally.
(3) Cephradine 2 Same as cephalexin.
(4) Cefazolin 2 1-2 g TDS, IV.
(5) Cefaclor 2 10-15 mg/kg/d in 3-4 divided doses, orally.
(6) Cefuroxime 2 0.75-1.5 g, IV every 8-12 hrs.
(7) Cefoperazone 2 25-100 mg/kg/d, IV every 8-12 hrs.
(8) Ceftriaxone 2 15-30 mg/kg/d, IV every 12-24 hrs.

GENERIC & TRADE NAMES

(1) First Generation Cephalosporins
Cefadroxil: Camex, Cedrox, Duricef, Evacef, Neucef.
Cephalexin: Anglolexin, Cefalex, Ceporex, Kavelex, Keflex, Keforal, Oceflox, Oracef, Ospexin, Safexin, Solvocef, Zafalexin.
Cephradine: Amspor, Biocef, Cefatil, Cefrinex, Ceprol, Dynacef, Kaysef, Kefril, Monocef, Polycef, Sefrin, Valodin, Vefradin, Velosef.
Cephazolin: Cefazolin.

(2) Second Generation Cephalosporins
Cefaclor: Ceclor, Cedrate, Ceclor, Cetaclor, Proclor.
Cefamandole: Kafadol.
Ceforanide: Precef, Rancef.
Cefuroxime: Apotex, Cefroxil, Cefuzin, Maxima, Roxime, Zecef, Zinacef.
Cefprozil: Cefzil, Zilpro.
Cefpodoxime: Cefpomed, Cefprox, Evodoxim, Nefdoxim, Neudoxin, Posoxime, Prelox, Trusef.

(3) Third Generation Cephalosporins
Cefoperazone: Cefobid, Cefapezone, Hanpezon, Prontokef.
Cefotaxime: Baxim, Cefax, Cefotam, Cefotax, Cefoxim, Taxime, Wintax.
Ceftazidime: Cefazid, Cefcom, Fortazim, Fortum, Zatron.
Ceftizoxime: Cefizox, Sydocef, Tezox, Zoxcef.
Ceftriaxone: Ceftison, Ceftrex, Cefxone, Maxef, Rocephin, Tazecef, Titan, Vexa.
Cefixime: Bestar, Caricef, Cebosh, Cefacef, Cefamax, Cefspan, Maxpan, Refixime, Refspan, Tycef.
Cefdinir: Cefnir, Dinor.

(4) Fourth Generation Cephalosporins
Cefepime: Cef-4, Cefstar, Endopime, Maxipime, Neupime, Perin, Pime, Swisspime.

Unit IV

Chloramphenicol, Macrolides, & Clindamycin

CHLORAMPHENICOL

MECHANISM OF ACTION
It binds reversibly to a receptor site on 50 S ribosomal subunit 2 This interferes with incorporation of amino acids into newly formed peptides by blocking the action of peptidyl transferase 2 Microbial protein synthesis is inhibited.

RESISTANCE
It results from the production of 'chloramphenicol acetyl-transferase' that inactivates the drug.

CLINICAL USES
(A) Systemic Uses
(1) Salmonella inf, eg typhoid & paratyphoid fever.
(2) H. influenzae inf, eg meningitis, laryngotracheitis or pneumonia.
(3) Meningococcal inf.
(4) Anaerobic or mixed inf. in CNS, eg brain abscess, cerebritis, meningitis.
(5) Rickettsial inf.
(6) Brucellosis.
(7) Melioidosis.
(8) Sepsis.

(B) Topical Uses
(1) Superficial conjunctival &/or corneal inf.

(2) Superficial gram-positive or gram-negative inf of external auditory canal

ADVERSE EFFECTS

(1) CNS
Headache, mild depression, mental confusion, delirium.

(2) GIT
Nausea, vomiting, diarrhea.

(3) Blood Dyscrasias
Bone marrow depression leading to aplastic anemia, hypoplastic anemia, reticulocytopenia, thrombocytopenia, granulocytopenia.

(4) Allergic Reactions
eg Drug fever, macular rashes, vesicular rashes, angioedema, urticaria, anaphylaxis.

(5) Gray Baby Syndrome
It occurs in newborn infants due to chloramphenicol accumulation b/c of the absence glucuronic acid conjugation mechanism, & is characterized by;
Vomiting, flaccidity, hypothermia, gray color, shock, cyanosis, irregular respiration, & cardiovascular collapse.

(6) Superinfection
Oropharyngeal candidiasis, vaginal candidiasis & acute staphylococcal enterocolitis can occur.

CONTRAINDICATIONS
History of previous hypersensitivity to &/or toxicity from chloramphenicol.

DRUG INTERACTIONS
(1) It inhibits metabolism of dicumarol, phenytoin, tolbutamide, chlorpropamide & warfarin.
(2) Antagonize bactericidal action of penicillins & aminoglycosides.
(3) Concomitant use of paracetamol inc. its serum level.

DOSAGE
(1) Adults: 50 mg/kg/d in divided doses 6 hrly.
(2) Children: Under 2 weeks, half adult dose; over 2 weeks, same as adult.

MACROLIDES

Examples
Erythromycin, Clarithromycin, Azithromycin, Oleandomycin, Spiramycin, Telithromycin.

Mechanism of Action
Similar to chloramphenicol.

Clinical Uses
(1) Corynebacterial inf, eg diphtheria, sepsis, erythrasma.
(2) Chlamydial inf of respiratory tract, eye, genital tract, & neonates.
(3) Mycoplasmal pneumonia.
(4) Campylobacter jejuni inf.
(5) As penicillin alternatives in penicillin allergic pts with streptococcal or pneumococcal inf.
(6) Legionnaires' disease.
(7) Acne.

Adverse Effects
(1) GIT: Anorexia, nausea, vomiting, diarrhea.
(2) Allergic reactions: Cholestatic hepatitis, fever, eosinophilia, rashes.
(3) IV inj: Thrombophlebitis.
(4) Superinfection: Candidiasis

Dosage
0.25-0.5 gm, QID.

Drug Interactions
It inc. the effects & toxicity of oral anticoagulants, carbamazepine, digoxin & theophylline compounds, by interfering with hepatic metabolism.

CLINDAMYCIN (& LINCOMYCIN)

Mechanism of Action
Similar to chloramphenicol.
Note: Clindamycin is a chlorine - substituted derivative of lincomycin.

Clinical Uses
(1) Bacteroides inf, esp. B. fragilis which causes anaerobic abdominal inf.
(2) Acne.
(3) Anaerobic intrauterine inf.
(4) Female genital tract inf, eg septic abortion, pelvic abscess.

Adverse Effects
(1) GIT: Pseudomembranous colitis resulting in diarrhea, abdominal pain, fever &, mucus & blood in stools.
(2) Liver: Impaired liver function with or without jaundice.
(3) Blood: Neutropenia.

Dosage
0.15-0.3 gm, QID.

GENERIC & TRADE NAMES

(1) Chloramphenicol
Biostat*, Chloramphenicol, Chlorofen, Chloromycetin, Chloromycetin -H*, Dexachlor*, Decachlor, Methachlor, Neo-Phenicol, Vasochlor, Vitachlor.

(2) Macrolides
Erythromycin: Ecin, Emycin, Erithrine, Erythromycin, Erybron*, Eryderm, Erythrocin, Trocin.
Clarithromycin: Amiclar, Bv-clar, Clarabac, Clarithro, Klaricid, Megaklar, Neo-klar, Tarithrocid.
Azithromycin: Azibect, Azicin, Azimycin, Azithrocin, Azoxin, Azrocin, Rezoxin, Zithrosan, Zomysin.
Spiramycin: Rovamycine.
Telithromycin: Engtel.

(3) Clinda- & Lincomycin

Clindamycin: Clindacin, Dalacin C, Dalacin T.
Lincomycin: Amlin, Limera, Lincin, Linco, Lincocin, Lincomycin, Olinc.

Unit V

Tetracyclines

DRUG CLASSIFICATION

(A) Short Acting Tetracyclines
Half lives 2 6-9 hrs, eg;
Tetracycline, Oxytetracycline, Chlortetracycline.

(B) Intermediate Acting Tetracyclines
Half lives 2 14 - 16 hrs, eg;
Demeclocycline, Methacycline.

(C) Long Acting Tetracyclines
Half lives 2 17 - 20 hrs, eg;
Doxycycline, Minocycline, Tigecycline.

MECHANISM OF ACTION

Tetracyclines bind reversibly to receptors on 30 S ribosomal subunit, in a position that blocks binding of aminoacyl-tRNA to acceptor site on mRNA ribosome complex 2 This prevents addition of new amino acids to growing peptide chain 2 This inhibits bacterial protein synthesis.

RESISTANCE

(1) Organisms lack an active transport mechanism across cell memb., & thus do not concentrate tetracyclines in their cells.
(2) Organisms may lack passive permeability to tetracyclines.

CLINICAL USES

(1) Rickettsial inf, eg Rocky Mountain spotted fever, Q fever, Brill's disease, Murine & scrub typhus, Rickettsial pox.
(2) Chlamydial inf, eg lymphogranuloma venereum, inclusion conjunctivitis, trachoma, psittacosis.
(3) Mycoplasmal inf.
(4) Intestinal amebiasis.
(5) Bacillary inf, eg brucellosis, tularemia, cholera, some shigella & salmonella inf.
(6) Venereal inf, eg gonorrhea, syphilis, chancroid, granuloma inguinale, chlamydial urethritis or cervicitis.
(7) Mixed bacterial inf of respiratory tract esp. sinusitis & bronchitis.
(8) Skin inf esp. inflammatory acne.
(9) Leptospirosis.
(10) Urinary tract inf.
(11) Syndrome of inappropriate ADH secretion (Demeclocycline).

ADVERSE EFFECTS

(1) ENT
Vestibular disturbances, eg dizziness, vertigo, nausea, vomiting, occur with minocycline.

(2) Teeth & Bones
Tetracyclines given to children, b/c of their chelating properties, bound to Ca deposits on growing bones & teeth with the formation of a tetracycline-Ca orthophosphate complex. This causes;
(a) Yellow & then brown discoloration of teeth.
(b) Enamel dysplasia.
(c) Inc. sensitivity to carries.
(d) Growth inhibition of bones.

(3) GIT
Epigastric pain, nausea, vomiting, diarrhea.

(4) Liver
Impair hepatic function, hepatic necrosis.

(5) Renal Toxicity

(6) Allergic Reactions
eg, skin rashes, drug fever.

(7) Skin
Photosensitization esp. with demeclocycline.

(8) Local Tissue Toxicity
(a) IV inj. causes thrombophlebitis.
(b) IM inj. causes painful local irritation.

(9) Fanconi Syndrome
It results from ingestion of outdated & degraded tetracyclines, & characterized by renal tubular dysfunction which can lead to renal failure

(10) Superinfection
Vaginal or oral candidiasis, staphylococcal enterocolitis, pseudomembranous colitis & anal pruritus.

CONTRAINDICATIONS

(1) Hypersensitivity to tetracyclines.
(2) Pregnancy.
(3) Children below 12 years of age.
(4) Renal insufficiency (except doxycycline).

DOSAGE

(1) Short acting tetracyclines 2 250 mg QID, orally.
(2) Methacycline 2 300 mg BD, orally.
(3) Doxycycline 2 100-200 mg OD, orally or IV.
(4) Minocycline 2 100 mg BD, orally.

GENERIC & TRADE NAMES

(1) Short Acting Tetracyclines

Tetracycline: Achromycin, Chemicycline, Dosamycin, Furosal*, Pexocycline, Tetrawil, Vagmycin*.

Oxytetracycline: Egocin, Epoxylin, Marvicycline, Oxyn, Oxywil.

(2) Long Acting Tetracyclines

Doxycycline: Apdoxy, Capsidon, Dekomycin, Doxymycin, Etidoxine, Megadox, Novodox, Vibramycin, Vibradoxine, Wellcodox.

Minocycline: Minocin, Minowil.

Unit VI

Aminoglycosides (AG)

DRUG CLASSIFICATION

(A) AG Causing Cochlear Nerve Damage
Amikacin, Netilmycin, Kanamycin

(B) AG Causing Vestibular Nerve Damage
Streptomycin, Tobramycin, Gentamycin

(C) AG Not For Parenteral Use
Neomycin, Paromomycin, Framycetin.

(D) Others
Spectinomycin.

MECHANISM OF ACTION

AGs bind specifically to bacterial 30 S ribosomal subunit 2 This inhibits ribosomal protein synthesis, via;

(1) Interfering with the initiation complex of peptide formation.
(2) Inducing misreading of code on mRNA template which causes incorporation of incorrect amino acids into peptides.
(3) Causing a breakup of polysomes into nonfunctional monosomes.

RESISTANCE

(1) Alteration in cell surface occur which interfere with the permeation of aminoglycosides into cell.
(2) Receptors on 30S ribosomal subunit may be altered.
(3) Microorganisms acquire the ability to produce enzyme that inactivate the drug by adenylation, acetylation or phosphorylation.

CLINICAL USES

(A) Streptomycin
(1) Pulmonary tuberculosis.
(2) Miliary dissemination.
(3) Bacterial meningitis.
(4) Plague.
(5) Tularemia.
(6) Subacute bacterial endocarditis (caused by enterococci or streptococcus viridians).
(7) Brucellosis.
(8) Peritonitis.
(9) Urinary tract inf.
(10) Respiratory tract inf.

(B) Neomycin, Paromomycin, Framycetin, & Kanamycin

(1) Topical
(a) Injected into abscess cavity, or in a infected body cavity eg joints, pleural cavity or, other tissue spaces.
(b) Applied on infected skin lesions.
(c) Applied in the nares for suppression of staphylococci.

(2) Oral
(a) For preoperative reduction of gut flora before surgery.
(b) In hepatic coma, to dec. the number of bacteria in intestine esp. coliforms.
(c) Intestinal amebiasis (paromomycin).

(C) Gentamycin, Tobramycin, Netilmycin, & Amikacin

(1) Parenteral
(a) Sepsis & pneumonia, caused by gram-negative bacteria esp. pseudomonas, enterobacter, serratia, proteus, acinetobacter, & klebsiella.
(b) Endocarditis or sepsis, by enterococci (with Penicillin G).

(2) Topical
(a) Infected burns, wounds or skin lesions.
(b) Prophylaxis of intravenous catheter inf.

(3) Intrathecal
Meningitis, by gram negative bacteria.

(D) Spectinomycin
Gonorrhea (in pts with allergy or resistance to penicillin).

ADVERSE EFFECTS

(1) Eye
Scotomas, due to optic nerve dysfunction (with streptomycin).

(2) ENT
(a) Vestibular nerve damage manifested by dizziness, vertigo, ataxia, & loss of balance.
(b) Cochlear nerve damage manifested by hearing loss, & tinnitus.

(3) GIT
Anorexia, nausea, vomiting, inc. salivation, stomatitis.

(4) Neuromuscular Junction

Neuromuscular blockade causing progressive flaccid paralysis & potentially fatal respiratory arrest; occur esp. when the drug (esp. kanamycin) is given in high dose, or in combination with cruriform drugs.

(5) Urinary Tract

Acute renal insufficiency, tubular necrosis, proteinuria, azotemia, oliguria.

Note: Gentamycin is most nephrotoxic.

(6) Blood

Eosinophilia, hemolytic anemia, bleeding due to antagonism of factor V.

(7) Bone Marrow

Bone marrow depression.

(8) Allergic Reactions

eg skin rashes, pruritus, urticaria, fever.

CONTRAINDICATIONS

(1) Known hypersensitivity.
(2) Myasthenia gravis.

DOSAGE

(1) Amikacin 2 15 mg/kg/d, IM or IV.
(2) Kanamycin 2 1gm/d in 2 - 4 divided doses for max. of 6 days , IM.
(3) Tobramycin 2 3-5 mg/kg/d in 3-4 divided doses, IM or IV.
(4) Gentamycin 2 Upto 5 mg/kg/d in 3 divided doses for 7-10 days; orally, IM or IV.

GENERIC & TRADE NAMES

Amikacin: Amika, Amikin, Amkay, Grasil.
Kanamycin: Kanabid, Kanacyn, Kanacillin*, Kumycin.
Tobramycin: Abbocin, Bromycin, Nebcin, Nebra, Tobracin , Tobradex*, Tobrex.
Gentamycin: Gentacil, Gentalek, Genicol, Genticyn-B*, Genticyn, Genticyn HC*.
Streptomycin: Polybiotic*, Streptomycin.
Neomycin: Flogocid, Newcin, Probeta N*, Xyloaid.
Framycetin: Fradex*, Framycin, Sofra-tulle.
Spectinomycin: Trobicin.

Unit VII

Sulfonamides

DRUG CLASSIFICATION

(A) Oral Absorbable Agents

(1) Short Acting Sulfonamides

Sulfisoxazole, Sulfadiazine, Sulfamethoxazole, Sulfacytine, Sulfadimidine, Sulfamethizole.

(2) Long Acting Sulfonamides

Sulfamethoxypyridazine, Sulfametopyrazine, Sulfaphenazole, Sulfadoxine.

(B) Oral Nonabsorbable Agents

Phthalyl sulfathiazole (Sulfathalidine), Sulfasalazine.

(C) Topical Agents

Sulfacetamide, Maphenide, Sulfapyridine, Silver Sulfadiazine.

MECHANISM OF ACTION

Sulfonamides inhibit DNA synthesis by preventing incorporation of para-aminobenzoic acid into folic acid (by dihydropteroate synthetase thru competitive inhibition) which, in the reduced form, is necessary in purine biosynthesis for the transfer of one carbon units.

RESISTANCE

(1) Some microorganism produce a large excess of PABA.
(2) Others may be relatively impermeable to sulfonamides.
(3) A structural change may occur in folic acid synthesizing enzyme with a lowered affinity for sulfonamides

CLINICAL USES

(A) Oral

(1) Acute uncomplicated urinary tract inf.
(2) Chlamydia trachomatis inf. of eye, genital tract, & respiratory tract.
(3) Bacterial inf., eg nocardiosis, sinusitis, bronchitis, pneumonitis, otitis media, bacillary dysentery.
(4) Dermatitis herpetiformis.
(5) Toxoplasmosis.

(B) Topical

(1) For temporary inhibition of intestinal aerobic flora in preparing the bowel for surgery (Phthalylsulfathiazole).
(2) Applied to burn skin esp burn sepsis & wounds (Mafenide, Silver sulfadiazine).
(3) Inclusion conjunctivitis (Sulfacetamide).
(4) Ulcerative colitis, enteritis & other inflammatory bowel disease (Sulfasalazine).

(C) Intravenous

Reserved for comatose pts esp. with meningitis or pts who are unable to take medication by mouth.

ADVERSE EFFECTS

(1) GIT

Nausea, vomiting, diarrhea, stomatitis.

(2) Liver
Hepatitis, focal or diffuse hepatic necrosis.

(3) Urinary Tract
Acetylated metabolite of sulfonamides may ppt. in urine esp. at neutral or acid pH causing crystalluria, hematuria, or even obstruction; nephrosis & allergic nephritis.

(4) Blood
Hemolytic anemia esp in G-6-P-dehydrogenase deficiency, aplastic anemia, granulocytopenia, thrombocytopenia, sulfhemoglobinemia.

Note: Inc. risk of kernicterus in newborn (if the drug is taken near term).

(5) Allergic Reactions
Drug fever, skin rashes, urticaria, exfoliative dermatitis, polyarteritis nodosa, stevens-johnson synd, eosinophilia, photosensitivity.

CONTRAINDICATIONS

(1) Hypersensitivity.
(2) Pregnancy at term.
(3) Lactation.
(4) Impaired renal function.
(5) Impaired hepatic function.

DOSAGE

(1) Sulfadiazine 2 Initially 4 g, followed by 1g/4 hrs.
(2) Sulfisoxazole 2 Initially 4g, followed by 1g/6 hrs.
(3) Sulfamethoxypyridazine 2 Initially 1 g, followed by 0.5 g/day
(4) Sulfasalazine 2 Initially 4g, followed by 1g/6 hrs.
(5) Sulfacetamide 2 Eye drops (10-30 %) & ointment (6%).

GENERIC & TRADE NAMES

(1) Sulfisoxazole: Pediazole*.
(2) Sulfadiazine: Sulphadiazine.
(3) Sulfamethoxazole: See Unit VIII.
(4) Sulfadoxine: Fansidar*, Favax*, Maladar*, Malarest*, Malarina*, Malidar*.
(5) Sulfasalazine: Salazodine, Salazine, Sulfasal.
(6) Sulfacetamide: Blephamide*, Blephapred, Mydosone*, Panocid, Sulphapred, Sulphamed*.
(7) Silver Sulfadiazine: Dermazin, Flamazin.

Unit VIII

Trimethoprim, & Co - Trimoxazole

TRIMETHOPRIM

MECHANISM OF ACTION
Trimethoprim inhibits the enzyme 'dihydrofolic acid reductase', that converts dihydrofolic acid into tetrahydrofolic acid 2 Synthesis of thymidine is blocked, b/c tetrahydrofolic acid is required for its synthesis 2 This causes inhibition of purine synthesis 2 Leading to inhibition of DNA synthesis.

CLINICAL USES
(1) Urinary tract inf.
(2) Prostatic & vaginal inf.

ADVERSE EFFECTS

(1) CNS
Headache, nervousness.

(2) GIT
Nausea, vomiting, abd cramps, glossitis, stomatitis.

(3) Blood
Leukopenia, agranulocytosis, thrombocytopenia, methemoglobinemia, megaloblastic anemia.

(4) Allergic Reactions
Drug fever, skin rashes, vasculitis.

CONTRAINDICATIONS
(1) Hypersensitivity.
(2) Megaloblastic anemia.

TRIMETHOPRIM PLUS SULFAMETHOXAZOLE (COTRIMOXAZOLE)

MECHANISM OF ACTION
Co-trimoxazole has inhibitory effect on the synthesis of tetrahydrofolic acid at two successive stages;
(1) Sulfamethoxazole inhibits incorporation of PABA into folic acid, by interfering with dihydropteroate synthetase.
(2) Trimethoprim inhibits the next step, ie enzymatic reduction of dihydrofolic acid to tetrahydrofolic acid by dihydrofolic acid reductase.

CLINICAL USES
(1) Respiratory tract inf esp acute exacerbations of chronic bronchitis caused by H. influenzae, & S. pneumoniae.
(2) Complicated urinary tract inf.
(3) Genital tract inf esp of prostate & vagina.
(4) Salmonella inf, eg typhoid & paratyphoid fever.
(5) Symptomatic shigella enteritis.
(6) Serratia sepsis.
(7) Pneumocystis carinii pneumonia (a protozoal inf).
(8) Pharyngeal gonorrhea.
(9) Skin & soft tissue inf, eg boils, carbuncles, abscess, burns, wounds.

ADVERSE EFFECTS

As for sulfonamides & trimethoprim.

CONTRAINDICATIONS

(1) Neonates
(2) Pregnancy
(3) Severe renal insufficiency
(4) Severe hepatic insufficiency
(5) Blood dyscrasias.
(6) Hypersensitivity.

DOSAGE

(1) Oral TMP/SMZ 2 160 mg/800 mg to 320 mg/1600 mg, twice daily.
(2) IM inj 2 160 mg/800 mg, thrice daily.

GENERIC & TRADE NAMES

Co- Trimoxazole: Bacitran, Bactrim, Co-trimax, Colitran, Comax, Cotrim, Mactran, Mazatrim, Mexazol, Nicotrim, Semozol, Septran, Septrozole, Trimoxin.
Trimethoprim: Syraprim.
Trimethoprim + Sulfadimidine: Penetrin.
Trimethoprim + Sulfadiazine: Antrima.

Unit IX

Fluoroquinolones

DRUG CLASSIFICATION

(1) First Generation Fluoroquinolones

These are least active against both gram-negative & gram-positive organisms.
Examples: Norfloxacin.

(2) Second Generation Fluoroquinolones

They have excellent gram-negative activity & moderate to good activity against gram-positive organisms.
Examples: Ciprofloxacin, Enoxacin, Levofloxacin, Lomefloxacin, Ofloxacin, Pefloxacin.

(3) Third Generation Fluoroquinolones

They have improved activity against gram-positive organisms esp. S pneumoniae & staphylococci.
Examples: Gatifloxacin, Gemifloxacin, Moxifloxacin.

MECHANISM OF ACTION

Fluoroquinolones block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA gyrase) & topoisomerase IV;

(1) Inhibition of DNA gyrase prevents the relaxation of supercoiled DNA that is required for normal transcription & replication.
(2) Inhibition of topoisomerase IV interferes with separation of replicated chromosomal DNA into the respective daughter cells during cell division.

RESISTANCE

It is due to;
(1) One or more point mutations in the quinolone binding region of the target enzyme, or
(2) Change in the permeability of organism.

CLINICAL USES

(1) Urinary tract infections (even when caused by multi-drug-resistant bacteria, eg pseudomonas).
(2) Infectious diarrhea (eg, due to shigella, salmonella, toxigenic E coli, campylobacter).
(3) Infections of soft tissues, bones, & joints.
(4) Abdominal & respiratory tract infections.
(5) Prophylaxis & treatment of anthrax.
(6) Sexually transmitted diseases (eg, gonococcal &, chlamydial infections).
(7) Mycobacterial infections.
(8) For eradication of meningococci from carriers.
(9) Prophylaxis of infection in neutropenic pts.

ADVERSE EFFECTS

(1) CNS: Headache, dizziness, insomnia.
(2) GIT: Nausea, vomiting, diarrhea.
(3) Hepatic: Abnormal liver function tests.
(4) Skeletal: Damage to growing cartilage.
(5) Skin: Rashes.
(6) Concomitant administration of theophylline lead to elevated levels of theophylline with the risk of toxic effects, especially seizures.
(7) Superinfection with streptococci & candida.

GENERIC & TRADE NAMES

Norfloxacin: Alenbit, Chibroxine, Nolicin, Norfax, Norocin, Noroxin, Uracin, Urisept, Uritec, Utinor.
Enoxacin: Enoxabid, Enoxa.
Ciprofloxacin: Algocin, Ciplox, Cipacin, Ciprin, Ciprocide, Ciprox, Ciproxin, Nafcin, Novidat, Proflox, Quinoflox.
Levofloxacin: Cravit, Lavilox, Leflox, Qumic, Xeflox.
Lomefloxacin: Floxlome, Lomedin, Loxoflox.
Ofloxacin: Albact, Bactacin, Eracin, Fugacin, Korvid, Oflobid, Oflocin, Oflox, Ofloxin, Tariflox, Tarivid.
Pefloxacin: Abaktal, Euphen, Peflacine, Peflox.
Gatifloxacin: Gati, Gatox, Glax, Quintec.

Gemifloxacin: Grat.
Moxifloxacin: Avelox, Mofilox, Moxiflox.

Unit X

Anti-Tuberculous Drugs

TUBERCULOSIS

It is a communicable chronic granulomatous disease caused by "Mycobacterium tuberculosis". It usually involves the lungs, but may affect any organ or tissue in the body. Typically the centres of granulomas undergo caseous necrosis to create soft tubercles.

Clinical Features

(1) Malaise, anorexia, & weight loss.
(2) Low grade remittent fever (appearing late each after-noon & then subsiding) with night sweating.
(3) Cough with sputum (at first-mucoid & later purulent).
(4) Hemoptysis.
(5) Pleuritic pain.

DRUGS USED IN TUBERCULOSIS

DRUG CLASSIFICATION

(A) First Line Drugs

Isoniazid, Rifampin, Ethambutol, Streptomycin, Pyrazinamide.

(B) Second Line Drugs

Amikacin, Capreomycin, Ciprofloxacin, Clofazimine, Cycloserine, Ethionamide, Levofloxacin, Para-aminosalicylic acid, Rifabutin, Rifapentin, Viomycin.

ISONIAZID

Mechanism of Action

It interferes with cellular metabolism esp. synthesis of mycolic acid (an important constituent of mycobacterial cell wall), thus interfering with the formation of mycobacterial cell wall.

Clinical Uses

(1) Treatment of tuberculosis.
(2) Prophylaxis of tuberculosis.

Note: Nine months of chemotherapy with isoniazid plus rifampin is the treatment of choice for uncomplicated pulmonary tuberculosis.

Adverse Effects

(1) CNS: Peripheral neuritis, insomnia, restlessness, muscle twitching, convulsions, psychosis.
Note: Concomitant administration of pyridoxine prevent these effects..
(2) Liver: Abnormal liver function tests, jaundice, multilobular necrosis, hepatitis.
(3) Urinary tract: Urinary retention.
(4) Blood: Hemolysis in G - 6 - P dehydrogenase deficiency.
(5) Allergic reactions: Fever, skin rashes, hepatitis.

Contraindications

Pts. with previous isoniazid associated hepatic injury, or other severe adverse effects with isoniazid.

Dosage

5 mg/kg/d upto to a max of 300 mg, orally.

RIFAMPIN

Mechanism of Action

It inhibits RNA synthesis in mycobacteria & chlamydiae, by binding to DNA-dependent RNA polymerase.

Clinical Uses

(1) Tuberculosis.
(2) Atypical mycobacterial inf.
(3) Leprosy.
(4) Prophylaxis of H. influenzae type b disease in children.

Adverse Effects

(1) Allergic reactions: Fever, skin rashes.
(2) Blood: Thrombocytopenia, hemolytic anemia.
(3) Kidney: Nephritis, light chain proteinuria.
(4) Immunity: Impaired antibody response.
(5) Hepatotoxicity.
(6) GIT disturbances.
(7) Harmless orange color to urine, sweat, tears, & saliva.

Contraindications

Hypersensitivity.

Dosage

600 mg/d, with isoniazid, ethambutol or other antituberculous drugs.

ETHAMBUTOL

Mechanism of Action

It probably inhibits RNA synthesis.

Clinical Uses

Tuberculosis, in combination with other antituberculous drugs.

Adverse Effects

(1) Eye: Optic neuritis, reduction in visual acquity, retinal damage.
(2) Allergic reactions: Fever, skin rashes.

Dosage

15 - 25 mg/kg/day.

STREPTOMYCIN

See Unit VI 'Aminoglycosides'.

PYRAZINAMIDE

Mechanism of Action

Unknown, but at pH 5.0 it strongly inhibits growth of tubercle bacilli.

Adverse Effects

(1) Liver: Hepatitis.
(2) Joints: Arthralgia associated with hyperuricemia.

PARA-AMINOSALICYLIC ACID (PAS)

Mechanism of Action

PAS compete for the active center of an enzyme involved in converting PABA to dihydropteroic acid, thereby inhibiting purine & ultimately DNA synthesis.

Clinical Uses

Tuberculosis, in combination with INH or streptomycin (in the past).

Adverse Effects

(1) GIT: Anorexia, nausea, diarrhea, epigastric pain, peptic ulcer, GIT bleeding.
(2) Nephrotoxicity.
(3) Hepatotoxicity.
(4) Endo: Goitre with or without myxedema.
(5) Allergic reactions: Fever, skin rashes, granulocytopenia, joint pains, neurologic symptoms.
(6) Acid - Base Balance: Metabolic acidosis.

GENERIC & TRADE NAMES

(1) **Isoniazid (INH):** INH, Isoniazid, Isozide, Niazid, Nydrazide, Polyzide, Sonorex.
(2) **Rifampin:** Abrifam, Lederrif, Rifac, Rifacin, Rifadin, Rifagen, Rifamate, Rifamed, Rifampicin.
(3) **Ethambutol:** Abbutol, Ethambutol, Etibi, Myambutol.
(4) **Pyrazinamide:** Medizinamide, Piramide, Pyrazid, Pyrazinamide, PZA-Ciba, Zinamid.
(5) **Isoniazid Plus Rifampin:** Rifazol junior, Rifamate INH, Riso, Rifazid, Rifinah, Rifazid forte.
(6) **Ethambutol Plus Isoniazid:** Butarex, Myambutol INH.
(7) **Isoniazid, Rifampin Plus Ethambutol:** Cyrex, Myrin, Rifatol, Risen, Tuberin.
(8) **Isoniazid, Rifampin Plus Pyrazinamide:** Pyratar, Rifados, Rifatar.
(9) **Isoniazid, Rifampin, Ethambutol Plus Pyrazinamide:** Cyrex P, Myrin P, Rifa 4, Risen P, Tuberlin P.
(10) **Cycloserine:** Tuberserine.
(11) **Amikacin & Streptomycin:** See Unit VI.
(12) **P-aminosalicylic acid:** PAS tab.
(13) **Fluoroquinolones:** See Unit IX.

Unit XI

Anti-Leprotic Drugs

LEPROSY

It is a chronic communicable disease, caused by 'Mycobacterium leprae', which produces various granulomatous lesions in the skin, mucus memb. & peripheral nervous system.

Principal Types

(1) Lepromatous leprosy.
(2) Tuberculoid leprosy.

DRUGS USED IN LEPROSY

DRUG CLASSIFICATION

(1) Sulfones
Dapsone, Acedapsone, Glucosulfone Na, Sulfoxone Na, Sulfetrone Na, Thiazolesulfone.
(2) Antituberculous Drugs
Rifampin, Ethionamide.
(3) Miscellaneous Drugs
Clofazimine, Thiambutosine.

SULFONES

Mechanism of Action

Similar to sulfonamides.

Clinical Uses

(1) Leprosy.
(2) Pneumocystis pneumonia in AIDS (Dapsone).

Adverse Effects

(1) GIT disturbances.
(2) Blood: Hemolysis esp. in G - 6 - P dehydrogenase deficiency, methemoglobinemia.
(3) Allergic reactions: Fever, skin rashes, pruritus, erythema nodosum leprosum.

Dosage

Begin with 25-50 mg orally per week, inc. by 25 mg weekly until a full dose of 400 - 600 mg per week is reached.

RIFAMPIN

See Unit X, 'Antituberculous Drugs'.

CLOFAZIMINE

Mechanism of Action

Unknown, but it may involve DNA binding.

Clinical Uses

(1) Sulfone-resistant leprosy, or intolerance to sulfone.
(2) Mycobacterium avium - intracellulare inf in pts with AIDS.

Adverse Effects

(1) Gastrointestinal disturbances.
(2) Skin discoloration ranging from red - brown to nearly black.

Dosage

100 - 300 mg/day, orally.

GENERIC & TRADE NAMES

Antituberculous drugs: See Unit X.

Unit XII

Drug Treatment of UTI

URINARY TRACT INFECTIONS (UTI)

Urinary tract inf is a disorder resulting from invasion & multiplication of microorganism in some parts of urinary tract.

Types

(1) Lower Tract Inf (Ascending Inf)
Urethritis, cystitis, prostatitis.

(2) Upper Tract Inf (Descending Inf)
Acute pyelonephritis.

Causative Organisms

(1) Escherichia coli.
(2) Proteus spp.
(3) Klebsiella pneumoniae.
(4) Pseudomonas aeruginosa.
(5) Staphylococcus aureus.
(6) Enterococci.
(7) Micrococci.

DRUGS USED IN UTI

DRUG CLASSIFICATION

(A) Urinary Antiseptics

These exert antibacterial activity in urinary tract, but have little or no systemic antibacterial effect;

(1) Furan derivatives: Nitrofurantoin.
(2) Quinolones: Nalidixic acid, Oxolinic acid, Cinoxacin.
(3) Methenamine mandelate
(4) Methenamine hippurate
(5) Acidifying salts: NH_4Cl, Ascorbic acid, Mandelic acid, Methionine, Hippuric acid, Na acid citrate, Pipedemic acid.

(B) Systemic Drugs

(1) Fluoroquinolones
(2) Sulfonamides.
(3) Trimethoprim.
(4) Co-trimoxazole.
(5) Penicillins.
(6) Cephalosporins.
(7) Tetracyclines.
(8) Streptomycin.
(9) Cycloserine.

NITROFURANTOIN

Mechanism of Action

Unknown, the activity of nitrofurantoin is greatly enhanced at pH 5.5 or below, but dec. by very high conc. of bacteria in urine.

Clinical Uses

Urinary tract inf.

Adverse Effects

(1) CNS: Neuropathies.
(2) GIT: Anorexia, nausea, vomiting.
(3) Blood: Hemolytic anemia is G - 6 - P dehydrogenase deficiency.
(4) Allergic reactions: Skin rashes, pulmonary infiltration.

Contraindications

(1) Impaired renal function.
(2) Pregnant women at term.

Dosage

100 mg, QID, orally, with meals or milk.

Drug Interactions

It antagonizes the action of nalidixic acid.

NALIDIXIC ACID

Mechanism of Action

It blocks bacterial DNA synthesis by inhibiting DNA gyrase.

Clinical Uses

Urinary tract inf. with coliform organisms.

Adverse Effects

(1) CNS: Seizures.
(2) Visual disturbances
(3) GIT disturbances
(4) Metabolism: False - positive test for glucose in urine, hyperglycemia, glycosuria.
(5) Allergic reactions: Skin rashes, photosensitivity.

Contraindications

(1) History of convulsive disorders.
(2) Porphyria.

Dosage

1gm orally, QID, for 1-2 weeks.

METHENAMINE MANDELATE & HIPPURATE

Mechanism of Action

Mandelic acid or hippuric acid taken orally is excreted unchanged in urine, where they are bactericidal for some gram-negative bacteria if the pH can be kept below 5.5. Methenamine releases formaldehyde in the urinary tract, if the pH of urine is below 5.5, which act as bactericidal b/c bacteria can not survive in the presence of high conc. of formaldehyde.

Clinical Uses

Urinary tract inf.

Adverse Effects

(1) GIT disturbances.
(2) Allergic reaction eg, skin rashes.
(3) Bladder irritation.

Contraindications

(1) Severe dehydration.
(2) Severe renal failure.
(3) Metabolic acidosis.

Dosage

(1) Methenamine mandelate 2 1gm, QID, orally.
(2) Methenamine hippurate 2 1gm, BD, orally.

GENERIC & TRADE NAMES

(1) Nitrofurantoin: Furatin, Furadin, Furasol.
(2) Nalidixic acid: Nalacid, Negram, Uriben.
(3) Oxolinic acid: Utibid.
(4) Hexamine hippurate: Urodonal.
(5) Pipedemic acid: Pimic, Urixin, Urotractin.
(6) Ascorbic acid: See Chapter 24.
(7) Na acid citrate: Albacit, Alkacitron, Bliss-Alkali, Citralka, Citrol, Hyocit, Pexocitral, Prosalkali, Sioalkali, Sykol, Ural, Uralka.

Unit XIII

Self - Assessment (T/F)

(See answers on page no. 241)

(135) ***Mechanism of antibacterial action of cephalosporins involves***
(A) Inhibition of peptide synthesis.
(B) Interference with synthesis of ergosterol.
(C) Inhibition of transpeptidase enzymes.
(D) Inhibition of beta-lactamases.
(E) Inhibition of DNA gyrase.

(136) ***All of the following antibiotics are correctly matched with an appropriate clinical use***
(A) Penicillin G 2 Pneumonia caused by Klebsiella pneumoniae.
(B) Carbenicillin 2 Urinary tract infection caused by pseudomonas aeruginosa.
(C) Ampicillin 2 Bacterial meningitis caused by H. influenzae.
(D) Penicillin G 2 Syphilis caused by Treponema pallidum
(E) Cefazolin 2 Osteomyelitis.

(137) ***Following drugs are effective in the treatment of an infection caused by S aureus***
(A) Amoxycillin.
(B) Nafcillin.
(C) Cefazolin.
(D) Oxacillin.
(E) Azlocillin.

(138) ***Third generation cephalosporins***
(A) Show greater activity than first generation cephalosporins against G-ve bacilli.
(B) Include agents that are active against pseudomonas aeruginosa.
(C) Include agents that are effective in treating meningitis.
(D) Are beta-lactamase sensitive.
(E) Have poor CSF penetrability.

(139) ***All of the following drugs interfere with vit K availability, leading to hypoprothrombinemia & bleeding disorders***
(A) Cefoperazone.
(B) Moxalactam.
(C) Nafcillin.
(D) Carbenicillin.
(E) Cefotaxime.

(140) ***All of the following statements about chloramphenicol are correct***
(A) It inhibits peptidyl transferase.
(B) When it is given to neonates, their limited hepatic glucuronyl-transferase activity may result in cyanosis.
(C) It is usually bacteriostatic.
(D) Clinical resistance occurs thru change in structure of bacterial peptidyl-transferase.
(E) Dose should be reduced in pts with hepatic failure.

(141) ***Appropriate clinical uses of chloramphenicol includes***
(A) Typhoid fever.
(B) Topical application for chlamydial infections of eye.
(C) Meningococcal meningitis in a penicillin allergic person.
(D) H influenzae meningitis.
(E) Sepsis.

(142) ***Mechanism of antibacterial action of tetracyclines involves***
(A) Inhibition of conversion of lanosterol to ergosterol.
(B) Inhibition of DNA-dependent RNA polymerase.
(C) Blockade of binding of aminoacyl-tRNA to bacterial ribosomes.
(D) Selective inhibition of ribosomal peptidyl-transferases.
(E) Inhibition of transpeptidase, & endopeptidase.

(143) ***Appropriate clinical uses of tetracyclines includes***
(A) Rickettsial infections.
(B) Pneumonia caused by Mycoplasma pneumoniae.
(C) Osteomyelitis due to methicillin resistant staphylococci.
(D) Gonorrhea.
(E) Inclusion conjunctivitis.

(144) ***Following are recognized adverse effects of tetracyclines***
(A) Hepatic necrosis.
(B) Enamel dysplasia in children.
(C) Gray baby syndrome.
(D) Superinfection.
(E) Dizziness, vertigo.

(145) ***All of the following statements about aminoglycosides are correct***

(A) Antibacterial action involves binding to 50 S ribosomal subunit & subsequent inhibition of peptidyl-transferase.
(B) Clinical resistance occur thru alteration in cell surface, which interfere with drug permeation into cell.
(C) They are bactericidal.
(D) Streptomycin is clinically useful in pulmonary tuberculosis & plague.
(E) Neomycin is usually administered intravenously.

(146) ***Regarding adverse effects of aminoglycosides, following are correct***
(A) Gentamycin is the least nephrotoxic aminoglycoside.
(B) Neuromuscular blockade may be noted with kanamycin.
(C) Streptomycin may cause scotomas.
(D) Amikacin may cause dizziness & vertigo.
(E) Tobramycin may cause fanconi synd.

(147) ***All of the following statements about sulfonamides are correct***
(A) They inhibit bacterial dihydropteroate synthetase.
(B) Acute hemolysis may occur in pts with G-6-P dehydrogenase deficiency.
(C) They are antimetabolites of PABA.
(D) Crystalluria is most likely to occur at high urinary pH.
(E) Clinical resistance may occur thru production of a large excess of PABA.

(148) ***Regarding clinical uses of sulfonamides, following are correct***
(A) Sulfadiazine is effective in acute urinary tract infections due to nonresistant E coli.
(B) Topical sulfacetamide is useful for chlamydial inf of eye.
(C) Sulfamethoxazole is effective in Rocky Mountain spotted fever in pts allergic to tetracyclines.
(D) Sulfasalazine is effective in ulcerative colitis.
(E) Sulfadimidine is useful in burn sepsis.

(149) ***All of the following statements about the combination of trimethoprim plus sulfamethoxazole are correct***
(A) It is effective in the treatment of pneumonia due to pneumocystis carinii.
(B) Drugs produce a sequential blockade of folic acid synthesis.
(C) Fever & pancytopenia can occur.
(D) It is appropriate for the treatment of streptococcal pharyngitis.
(E) It is effective in prostatitis.

(150) ***All of the following statement about erythromycin are correct***
(A) It is often used as a penicillin substitute.
(B) It binds to 50 S ribosomal subunit.
(C) Valid clinical uses include respiratory inf. caused by mycoplasma pneumoniae.
(D) It can cause GIT disturbances.
(E) It is effective in pharyngeal diphtheria.

(151) ***Primary reason for the use of drug combinations in the treatment of tuberculosis is to***
(A) Prolong the plasma half-life of each drug.
(B) Lower the incidence of adverse effects.
(C) Enhance activity against metabolically inactive mycobacteria.
(D) Delay the emergence of resistance.
(E) Provide long-term prophylaxis.

(152) ***Concerning isoniazid, all of the following statements are correct***
(A) It increases phenytoin plasma levels by inhibiting its liver metabolism.
(B) It is not used in children b/c of high risk of Hepatotoxicity.
(C) Pyridoxine protects against peripheral neuritis caused by isoniazid.
(D) It interferes with the synthesis of mycolic acid.
(E) It may cause hemolysis in G-6-P dehydrogenase deficient pts.

(153) ***Concerning rifampin, following statements are correct***
(A) It colors body secretions orange.
(B) It disrupts bacterial lipid metabolism as its major mechanism of action.
(C) Although rare, it can cause serious hepatotoxicity.
(D) When used alone, there is a high risk of emergence of resistant strains of mycobacteria.
(E) It can cause optic neuritis.

(154) ***Regarding anti-leprotic drugs, following are correct***
(A) Mechanism of action of dapsone probably involves inhibition of folic acid synthesis.
(B) Clofazimine should not be given to pts. who are intolerant to dapsone or who fail to respond to treatment with dapsone.
(C) Monthly dosage of rifampin delay the emergence of resistance to dapsone.
(D) Clofazimine can cause discoloration of urine.
(E) Dapsone causes hemolysis in G-6-P-dehydrogenase deficient pts.

(155) ***Following drugs are effective in treating urinary tract infections***
(A) Nitrofurantoin.
(B) Cinoxacin.
(C) Co-trimoxazole.
(D) Chloramphenicol.
(E) *Nalidixic acid.*

19 CHEMOTHERAPY OF FUNGAL INFECTIONS

Unit I

Antifungal Agents

DRUG CLASSIFICATION

(A) According to Chemical Nature

(1) Polyenes

Amphotericin B, Nystatin, Natamycin.

(2) Azole Derivatives

(a) Imidazoles

Ketoconazole, Clotrimazole, Miconazole.

(b) Triazoles

Fluconazole, Itraconazole, Voriconazole.

(3) Echinocandins

Caspofungin, Micafungin, Anidulafungin.

(4) Miscellaneous

Griseofulvin, Flucytosine, Tolnaftate, Haloprogin, Naftifine, Fatty acid (Undecylenic acid & its salts).

(B) According to Site of Action

(1) Systemic Antifungals for Systemic Infections

Amphotericin B, Flucytosine, Ketoconazole, Triazoles, Echinocandins.

(2) Systemic Antifungals for Mucocutaneous Infections

Griseofulvin, Terbinafine.

(3) Topical

Nystatin, Natamycin, Tolnaftate, Azoles (clotrimazole, miconazole, econazole, oxiconazole, sulconazole, butaconazole, terconazole, & tioconazole), Undecylenic acid, Haloprogin, Butenafine, Terbinafine, Naftifine.

POLYENES

AMPHOTERICIN B

Mechanism of Action

It binds firmly to fungal cell memb. in the presence of ergosterol 2 This alters cell memb. thru the formation of amphotericin pores 2 This results in loss of cellular macromolecules & ions, producing irreversible damage.

Resistance

It may results from a dec. in memb. ergosterol or a modification in its structure so that it combines less well with the drug.

Clinical Uses

(1) Pulmonary, cutaneous, & disseminated forms of blastomycosis.
(2) Acute pulmonary coccidioidomycosis.
(3) Pulmonary histoplasmosis.
(4) Cryptococcus neoformans inf.
(5) Candidiasis, including disseminated forms.
(6) Fungal meningitis.
(7) Corneal ulcers caused by fungi.
(8) Naegleria meningo-encephalitis.
(9) Cutaneous & muco-cutaneous lesions of American leishmaniasis.
(10) Injected into joints infected with coccidioidomycosis or sporotrichosis.

Adverse Effects

(1) CNS: A variety of neurologic symptoms.
(2) CVS: Hypotension, cardiac arrest (due to hypokalemia).
(3) Blood: Normochromic normocytic anemia.
(4) Liver: Hepatotoxicity.
(5) Kidney: Impaired renal function causing inc. in K^+ clearance, & dec. in creatinine clearance.
(6) Allergic reactions: Skin rashes, fever, anaphylaxis.
(7) IV inj: Chills, fever, vomiting, headache, thrombophlebitis.

Dosage

(1) Given by slow IV infusion over a period of 4-6 hours.
(2) Initial dose is 1-5 mg/d, inc. daily by 5 mg until a final dose of 0.4-0.7 mg/kg/d is reached.
(3) This is continued for 6-12 weeks with a daily dose not exceeding 60 mg.

NYSTATIN

Mechanism of Action

Similar to Amphotericin B.

Clinical Uses

Candidiasis of skin, mouth, vagina, & intestinal tract.

Adverse Effects

GIT disturbances with oral administration.

NATAMYCIN

Mechanism of Action

Similar to Amphotericin B.

Clinical Uses

(1) Corneal keratitis caused by Fusarium, Cephalosporium or other fungi.
(2) Oral & vaginal candidiasis.

AZOLE DERIVATIVES

KETOCONAZOLE

Mechanism of Action

It alters fungal cell memb. permeability by blocking biosynthesis of fungal lipids esp. ergosterol in cell memb.

Clinical Uses

(1) Oral, vaginal, & muco-cutaneous candidiasis.
(2) Blastomycosis.
(3) Coccidioidomycosis.
(4) Histoplasmosis.
(5) Paracoccidioidomycosis.
(6) Dermatophytosis.

Adverse Effects

(1) GIT: Nausea, vomiting.
(2) Liver: Hepatotoxicity.
(3) Endocrinal abnormalities: Block synthesis of adrenal steroids & androgens, & can cause gynecomastia.
(4) Allergic reactions: Skin rashes, urticaria, anaphylaxis.

Contraindications

(1) Liver disease.
(2) Pregnancy.

Dosage

200 - 400 mg once daily with meals, for at least one week.

MICONAZOLE

Mechanism of Action

Similar to ketoconazole.

Clinical Uses

(1) Topically in vaginal candidiasis, & dermatophytosis.
(2) Systemically in disseminated candidiasis, coccidioido-mycosis, paracoccidioidomycosis, cryptococcis, & blastomycosis.
(3) Intrathecally in fungal meningitis.

Adverse Effects

(1) GIT: Nausea, vomiting.
(2) Blood: Anemia, leukemia, thrombocytosis, hyponatremia.
(3) Allergic reactions
(4) Thrombophlebitis

Dosage

(1) Topical 2 2% cream.
(2) IV inj 2 30 mg/kg/d.
(3) Intrathecal 2 10 - 20 mg/d.

CLOTRIMAZOLE

It is used topically in oral & vaginal candidiasis, & in dermatophytosis.

MISCELLANEOUS

GRISEOFULVIN

Mechanism of Action

It interferes with microtubule function, or with nucleic acid synthesis & polymerization.

Clinical Uses

Severe dermatophytosis involving skin, hair, or nails esp. if caused by Trichophyton rubrum (eg tinea capitis, pedis, cruris & corporis).

Adverse Effects

(1) CNS: Mental confusion, headache.
(2) GIT: Nausea, vomiting, diarrhea.
(3) Liver: Hepatotoxicity.
(4) Allergic reactions: Fever, skin rashes, leukopenia, serum sickness.
(5) Skin: Photosensitivity.

Dosage

0.5 -1 gm daily in divided doses; for 3-6 weeks if only hairs & skin are involved, but for 3-6 months if nails are affected.

FLUCYTOSINE

Mechanism of Action

It is converted within fungal cells to fluorouracil, a metabolic antagonist that ultimately leads to inhibition of thymidylate synthetase & DNA synthesis.

Clinical Uses

Inf. caused by candida albicans & cryptococcus meningitidis.

Adverse Effects

(1) Fatal bone marrow depression.
(2) Gastrointestinal disturbances.
(3) Skin rash.
(4) Hepatic dysfunction.

TOLNAFTATE

Topical antifungal drug, used for the treatment of dermatophytosis.

FATTY ACIDS

Fatty acids esp. Undecylenic acid & its salts are used topically in tinea pedis & corporis.

GENERIC & TRADE NAMES

(1) Polyenes

Nystatin: Davistin, Myconil, Mystate, Nilstat, Nistoral, Nystrin, O-Nystat, Tergynan*.
Natamycin: Ophth-natamycin.

(2) Azole Derivatives

Clotrimazole: Baycuten N*, Canestan, Clotrim, Clotrima, Dermosporin, Gynosporin, Gynosporin-1, Novestin.

Fluconazole: Candican, Diflucan, F-zole, Flucon, Flucozal, Fluderm, Funganil, Fungix, Hiflucan, Zolanix.
Ketoconazole: Conaz, Funginil, Kenzol, Ketacon, Konazole, Nizoral.
Miconazole: Candistat, Daktacort*, Daktarin, Dermicon, Gynostin, Gyno-daktarin, Myconit.
Itraconazole: Itazol, Itracon, Itrazole, Rolac, Sporanox.
Econazole: Econophen, Gyno-Pevaryl*.
Tioconazole: Trosyd.

(3) Miscellaneous

Griseofulvin: Fungivin, Grifin, Griful, Grifulvin, Griseofulvin, Grivin, Gryso.
Naftifine: Exoderil.
Terbinafine: Antifin, Docinaf, Onyfine, Terbiderm, Terbin, Terbino, Terbisan, Terbisil, Terbix, Verticil.

Unit II

Self - Assessment (T/F)

(See answers on page no. 241)

(156) ***Following drugs are used for the treatment of systemic fungal infections***
(A) Amphotericin B.
(B) Flucytosine.
(C) Ketoconazole.
(D) Nystatin.
(E) Clotrimazole.

(157) ***All of the following statements correctly describe Ketoconazole***
(A) It inhibits conversion of lanosterol to ergosterol.
(B) It may produce gastrointestinal upsets.
(C) It can cause gynecomastia in males.
(D) It is useful as systemic antifungal in pts with liver disease.
(E) It is effective in candida infections.

(158) ***Regarding amphotericin B, following are correct***
(A) Its mechanism of action involves formation of amphotericin pores in fungal cell memb.
(B) It is applied topically in oral & vaginal candidiasis.
(C) It is effective in pulmonary coccidioidomycosis & pulmonary histoplasmosis.
(D) It may causes hypertension.
(E) *It may cause an inc. in K clearance & dec. in creatinine clearance.*

20 CHEMOTHERAPY OF VIRAL INFECTIONS

Unit I

Antiviral Drugs

CLASSIFICATION OF ANTIVIRAL DRUGS

(A) Drugs Inhibiting Adsorption & Penetration of Susceptible Cells

(1) Gamma Globulins

(2) Adamantanamines

Amantadine, Rimantadine, Tromantadine.

(3) Aliphatic Alcohol

Docosanol.

(4) Fusion Inhibitors

Enfuvirtide

(B) Drugs Inhibiting Late Protein Synthesis

Methisazone.

(C) Drugs Inhibiting Nucleic Acid Synthesis

(1) Pyrimidine & Purine Analogues

- **(a) Guanosine analog:** Acyclovir, Famciclovir, Ganciclovir, Penciclovir, Valacyclovir, Valganciclovir, Abacavir, Entecavir.
- **(b) Cytosine analog:** Cidofovir, Lamivudine, Emtricitabine, Zalcitabine.
- **(c) Thymidine analog:** Stavudine.
- **(d) Deoxythymidine analog:** Zidovudine.
- **(e) Adenosine analog:** Adefovir, Tenofovir.
- **(f) Deoxyadenosine analog:** Didanosine.
- **(g) Miscellaneous:** Idoxuridine, Cytarabine, Trifluridine, Vidarabine.

(2) Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Delavirdine, Efavirenz, Nevirapine.

(3) Others

Ribavirin, Foscarnet.

(D) Drugs Inhibiting Both Nucleic Acid & Protein Synthesis

Interferon alfa.

(E) Drugs Inhibiting Assembly or Release of Viral Particles

(1) Protease Inhibitors

Amprenavir, Atazanavir, Fosamprenavir, Indinavir, Lopinavir, Ritonavir, Nelfinavir, Saquinavir, Tipranavir.

(2) Neuraminidase Inhibitors

Zanamivir, Oseltamivir.

AMANTADINE

Mechanism of Action

(1) It inhibits penetration of susceptible cells, or uncoating of certain myxoviruses, eg influenza A, rubella & some tumor viruses.

(2) Being a weak base, amantadine may act by buffering the pH of endosomes (memb. bound vacuoles that surround virus particles as they are taken into cell) 2 Prevention of acidification in these vacuoles blocks fusion of virus envelope with endosome memb., thereby preventing transfer of viral genetic material into cell cytoplasm.

Clinical Uses

(1) For prophylaxis during influenza A virus epidemics.

(2) Parkinson's disease (b/c it potentiates the dopaminergic function).

Adverse Effects

(1) CNS: Restlessness, depression, irritability, insomnia, agitation, excitement, hallucinations, confusion, headache.

Note: These effects occur b/c the drug causes release of stored catecholamines.

(2) CVS: Congestive cardiac failure, postural hypotension, peripheral edema.

(3) GIT: Dry mouth, anorexia, nausea, constipation.

(4) Renal: Urinary retention.

Contraindications

(1) Pts. with a history of seizures.

(2) Congestive cardiac failure.

Dosage

200 mg/day, for 2-3 days before & 6-7 days after influenza A infection.

RIBAVIRIN

Mechanism of Action

(1) It may interfere with the formation of viral messenger RNA, & may inhibit viral RNA polymerase.

(2) It may act by interfering with guanidine monophosphate formation & subsequent nucleic acid synthesis.

Clinical Uses
(1) Herpes simplex infection.
(2) Influenza A & B.
(3) Respiratory syncytial viral infection.
(4) Viral hepatitis.
(5) Lassa fever.

Adverse Effects
(1) Rash & conjunctivitis (with aerosol use).
(2) Mutagenic, teratogenic & carcinogenic.

Contraindications
Pts requiring mechanical ventilation b/c small aerosol particles ppt. on the respirator valves & tubing, causing malfunction that can be lethal.

VIDARABINE

Mechanism of Action
It is phosphorylated in the cell to triphosphate derivative, which inhibits viral DNA polymerase (much more effectively than mammalian DNA polymerase).

Clinical Uses
(1) Herpes simplex encephalitis.
(2) Herpes simplex keratoconjunctivitis.
(3) Neonatal disseminated herpes simplex inf.
(4) Viremia in chronic active hepatitis.
(5) Herpes zoster inf. in immunosuppressed pts.

Adverse Effects
(1) CNS toxicity.
(2) GIT disturbances.
(3) Carcinogenic.

Dosage
(1) Topically, 3% ointment.
(2) IV inj, 10-15 mg/kg/d over 12 hours.

ACYCLOVIR

Mechanism of Action
It is converted in vivo into triphosphate form which interferes with viral DNA polymerase & inhibits viral DNA replication. It is incorporated into DNA & leads to premature chain termination.

Clinical Uses
(1) Primary mucocutaneous herpes simplex inf. in immunocompromized pts.
(2) Herpes genitalis inf.
(3) Herpes simplex encephalitis.
(4) Neonatal herpatic dissemination.
(5) Prophylactically before bone marrow transplants to protect against severe herpes lesions during post-transplant immunosuppression.
(6) After heart transplants to prevent dissemination of herpes from existing lesions.
(7) Varicella-Zoster virus inf.

Adverse Effects
(1) Topical application: Local discomfort, pruritus.
(2) Oral therapy: Nausea, vomiting, diarrhea, headache.
(3) IV therapy: Thrombophlebitis, rash, nephrotoxicity, neurologic reactions, hives.

Dosage
(1) Topical 2 5% ointment.
(2) Oral 2 200 mg 5 times daily.
(3) IV 2 15 mg/kg/day.

GANCICLOVIR

Mechanism of Action
It is first phosphorylated to a deoxyguanosine triphosphate (dGTP) analogue. This competitively inhibits the incorporation of dGTP by viral DNA polymerase, resulting in the termination of elongation of viral DNA.

Clinical Uses
(1) CMV retinitis in immuno-compromized pts.
(2) CMV pneumonitis in immunosuppressed pts.
(3) Prevention of CMV disease in bone marrow & solid organ transplant recipients.
(4) Acute CMV colitis in HIV/AIDS.

Adverse Effects
(1) **CNS:** Headache, confusion, hallucination, seizures.
(2) **GIT:** Nausea, vomiting, dyspepsia, diarrhea, abdominal pain, flatulence, anorexia.
(3) **Liver:** Raised liver enzymes.
(4) **Renal:** Increased serum creatinine & blood urea.
(5) **Blood:** Granulocytopenia, neutropenia, anemia, thrombocytopenia.
(6) **Temp:** Fever.
(7) **Skin:** Sweating, rash, itch.
(8) **Local:** Pain & phlebitis at injection site.

Dosage
(1) Acute infections are treated in two phases:
  (a) Induction phase, 5 mg/kg, IV, every 12 hours for 14-21 days.
  (b) Maintenance phase, 5 mg/kg, IV every day.
(2) Stable disease is treated with 1000 mg orally three times daily.
(3) As slow-release formulations for insertion into the vitreous humor of the eye.

ZIDOVUDINE

Mechanism of Action
It is incorporated into retrovirus HIV, & causes termination of DNA polymerase chain synthesis of viral DNA.

Clinical Uses
Acquired immunodeficiency synd. (AIDS) caused by retrovirus HIV.

Adverse Effects
(1) CNS: Headache, agitation, insomnia.
(2) Blood: Severe anemia, granulocytopenia & thrombocytopenia, due to bone marrow depression.

Dosage
200 mg orally per 4 hours.

METHISAZONE

Mechanism of Action
It inhibits viral replication by interfering with the synthesis of a 'late' structural protein.

Clinical Uses
(1) Small pox virus inf.
(2) Vaccinia virus inf.

INTERFERON

Mechanism of Action
Interferon induces host cell ribosomes to produce cellular enzymes that subsequently block viral reproduction by inhibiting transcription of viral mRNA into viral proteins. Three enzymes are known to be induced:

(1) Protein kinase: It leads to phosphorylation of elongation factor 2, resulting in inhibition of peptide chain initiation.
(2) Oligoisoadenylate synthetase: It leads to activation of an RNase & degradation of viral mRNA.
(3) Phosphodiesterase: It degrades the terminal nucleotides of tRNA, inhibiting peptide elongation.

Clinical Uses
(1) Herpes zoster inf. in pts with lymphoma.
(2) Neoplastic diseases, eg Hairy-cell leukemia.
(3) For reducing cytomegalovirus shedding after renal transplantation.
(4) For preventing reactivation of herpes after trigeminal root section.
(5) Viremia with hepatitis B virus.
(6) Warts of condylomata acuminata.
(7) Rabies.
(8) Hemorrhagic fever.

Adverse Effects
(1) CNS: Fatigue, weakness.
(2) GIT: Gastrointestinal disturbances.
(3) Blood: Anemia.

GENERIC & TRADE NAMES

(1) Gamma globulin: Allerglobulin, Gamma-16 vaccine.
(2) **Amantadine:** PK-Merz, Virofral.
(3) **Tromantadine:** Viru-Merz.
(4) **Ribavirin:** Virazole.
(5) **Acyclovir:** Acylex, Cycloz, Elovir, Lovir, Ophthcyclovir, Santovir, Verox, Virucid, Zaclovir, Zovirax.
(6) **Famiclovir:** Famvir.
(7) **Lamivudine:** Lamudine, Zeffix.
(8) **Zalcitabine:** Hivid.
(9) **Adefovir:** Hepovir, Hepsera.
(10) **Idoxuridine:** Herpidu.
(11) **Cytarabine:** Alexan, Cytocin.
(12) **Interferons:** Alphaferoi, Anferon, Ceron-alfa, Ceron-alpha, Heberon-alpha, Infron-alpha, Intron-A, Roferon-A, Viteron-A.
(13) **Lopinavir/Ritonavir:** Kaletra.
(14) **Oseltamivir:** Influ-rid, Oselta, Pronto, Tamiflu.

Unit II

Self - Assessment (T/F)

(See answers on page no. 241)

(159) ***All of the following statements about the mechanism of action of antiviral drugs is correct***
(A) Vidarabine inhibits viral DNA polymerase.
(B) Inc. activity of host cell phosphodiesterase that degrade tRNA is one of the antiviral actions of interferons.
(C) Acyclovir is incorporated into viral RNA causing premature chain termination.
(D) Ribavirin interfere with the formation of viral messenger RNA.
(E) Methisazone interfere with the synthesis of a 'late' structural protein.

(160) ***All of the following statements about amantadine are correct***
(A) It is effective in prophylaxis of influenza A inf.
(B) It causes CNS disturbances at high doses.
(C) It is contraindicated in pts. with Parkinsonism.
(D) It may cause diarrhea.
(E) It is used topically in herpes genitalis inf.

(161) ***Each of the following statements about anti-viral agents is correct***
(A) Interferons may prevent dissemination of herpes zoster virus in cancer pts & reduce CMV shedding after renal transplantation.
(B) Ribavirin is useful in viral hepatitis.
(C) Blood dyscrasias may be noted with azidothymidine.
(D) Amantadine is contraindicated in pts with a history of seizures.
(E) *Vidarabine in effective in rabies.*

21 CHEMOTHERAPY OF PROTOZOAL INFECTIONS

Unit I

Drug Treatment of Malaria

MALARIA

It is an infectious febrile disease caused by protozoa of genus 'Plasmodium', which are transmitted to humans by the bites of infected female mosquitoes of genus 'Anopheles'.

Causative Organisms

Four species of plasmodium are responsible:

(1) Plasmodium vivax.
(2) Plasmodium ovale.
(3) Plasmodium malariae.
(4) Plasmodium falciparum.

Clinical Features

(1) Attacks of chills, fever, sweating, anemia, & splenomegaly, occurring at intervals which depend on time required for the development of a new generation of parasites in body.
(2) After recovery from acute attack, disease has a tendency to become chronic, with occasional relapses.

Types of Malaria

(1) Tertian Malaria

It is produced by P. vivax & P. ovale with fever every third day ie at 48 hour intervals. Disease produced by P. vivax tends to be chronic with frequent relapses, while P. ovale infection is milder.

(2) Quartan Malaria

It is produced by P. malariae with fever every fourth day, ie at 72 hour intervals, & relapses at long intervals.

(3) Malignant Tertian Malaria

It is produced by P. falciparum with fever every third day, & more serious infection. It does not relapse so frequently.

DRUG CLASSIFICATION

(A) According to Chemical Nature

(1) 4 - Aminoquinolines
Chloroquine, Amodiaquine.

(2) 8 - Aminoquinolines
Primaquine.

(3) Quinoline Methanol (Cinchona Alkaloids)
Quinine, Quinidine, Mefloquine.

(4) 2,4 - Diaminopyrimidines
Pyrimethamine.

(5) Biguanides
Proguanil.

(6) Phenanthrene Methanol
Halofantrine.

(7) Amyl Alcohol
Lumefantrine.

(8) 9 - Aminoacridine
Quinacrine.

(9) Sulfonamides
Sulfadoxine, Sulfadiazine, Sulfalene (Sulfametopyrazine), Sulfamethoxazole.

(10) Sulfones
Dapsone

(11) Tetracyclines
Doxycycline.

(12) Sesquiterpene Lactone
Artemisinins (Qinghaosu), Artesunate, Artemether.

(13) Combinations
Fansidar (Pyrimethamine + Sulfadoxine), Maloprim (Pyrimethamine + Dapsone), Chlorproguanil + Dapsone, Malarone (Atovaquone + Proguanil).

(B) According to Site of Action

(1) Drugs Acting on Erythrocytic Stage
Chloroquine, Amodiaquine, Quinine, Quinacrine, Mefloquine, Halofantrine, Lumefantrine, Artemisinins.

(2) Drugs Acting on Exo-erythrocyte Stage
Primaquine, Sulfonamides, Sulfones.

(3) Drugs Acting on Both Stages
Proguanil, Pyrimethamine.

CHLOROQUINE & AMODIAQUINE

MECHANISM OF ACTION

They block enzymatic synthesis of DNA & RNA in both mammalian & protozoal cells, & form a complex with DNA that prevents replication or transcription to RNA. Selective toxicity for malarial parasites depends on chloroquine concentrating mech. in parasitized cells.

PHARMACOLOGICAL EFFECTS

(A) Antimalarial Action

(1) They are effective blood schizonticide, & used to prevent or terminate attacks of vivax, ovale, malariae or sensitive falciparum malaria.
(2) They are also moderately effective against gametocytes of P. vivax, P. ovale, & P. malariae.

(B) Cardiovascular System

Chloroquine has a low-level quinidine-like effect on CVS, which may cause noticeable change in the T wave of ECG during therapy.

CLINICAL USES

(1) Acute malaria attacks.
(2) Chemoprophylaxis of malaria.
(3) Amebic liver abscess.
(4) Giardiasis.
(5) Lupus erythematosus.
(6) Rheumatoid arthritis.

ADVERSE EFFECTS

(1) CNS: Mild headache, confusion, psychosis, convulsions, impaired hearing.
(2) Eye: Retinal & reversible corneal damage.
(3) CVS: Hypotension.
(4) GIT: Anorexia, nausea, vomiting.
(5) Blood: Hemolysis in G-6-P dehydrogenase deficiency.
(6) Skin: Exfoliative dermatitis, urticaria, pruritus (esp. in black persons).

CONTRAINDICATIONS

(1) Pts. with psoriasis.
(2) Porphyria.
(3) With drugs known to cause dermatitis.
(4) Concomitantly with gold or phenylbutazone therapy.
(5) Liver damage.
(6) Alcoholism.
(7) Blood dyscrasias.
(8) Neurologic disorders.

DOSAGE

(1) Chloroquine phosphate 2 1000 mg initially, then 500 mg daily, orally.
(2) Amodiaquine HCl 2 600 mg initially, followed by 300 mg 6, 24 & 48 hours later, orally.

QUININE

MECHANISM OF ACTION

(1) It forms a hydrogen-bonded complex with double-stranded DNA that inhibits protein synthesis by preventing strand separation & therefore DNA replication & transcription to RNA.
(2) It depresses many enzyme systems.

PHARMACOLOGICAL EFFECTS

(A) Antimalarial Action

(1) It is an effective blood schizonticide, eliminating the asexual stages of all 4 parasites.
(2) It is also gametocidal against P. vivax & P. malariae.

(B) Others Effects

(1) On cardiac muscle, it has quinidine like effects (but less intense).
(2) On gravid uterus, it has a slight oxytocic action, esp. during the third trimester of pregnancy.
(3) In skeletal muscle, it has a curare like effect.
(4) It has a minor antipyretic action.
(5) When given IV, it may cause severe hypotension, or hypoglycemia.

CLINICAL USES

(1) Malaria esp. due to P. falciparum.
(2) Chemoprophylaxis of malaria.
(3) Babesiosis.

ADVERSE EFFECTS

(1) Cinchonism

Symptoms include flushed & sweaty skin, headache, blurred vision, impaired hearing, tinnitus, dizziness, nausea, vomiting, abd. pain, & diarrhea.
Severe cinchonism is associated with papular or urticarial skin rashes, deafness, somnolence, blindness, & disturbance in cardiac rhythm & conduction.

(2) Blood Dyscrasias

Hemolytic anemia in G- 6-P dehydrogenase deficiency, leukopenia, agranulocytosis, thrombocytopenic purpura, Henoch-Schonlein purpura, hypoprothrombinemia.

(3) Blackwater Fever

Characterized by massive intravascular hemolysis; followed by hemoglobinuria, dark urine, azotemia, intravascular sludging & coagulation, renal failure, & uremia.

(4) IV Inj

Thrombophlebitis, moderate to marked hypotension which may progress to shock.

(5) IM Inj

Pain & sterile abscesses at the site of inj.

CONTRAINDICATIONS

(1) Subcutaneous or IM inj.
(2) Tinnitus.
(3) Optic neuritis.
(4) Myasthenia gravis.
(5) Hypersensitivity to quinine or quinidine.
(6) Pregnancy.

DOSAGE

650 mg TDS for 3 -7 days, orally.

PRIMAQUINE

MECHANISM OF ACTION

Unknown; quinoline- quinone intermediates derived from it are electron carrying redox compounds that can act as oxidants. These probably cause hemolysis & methemoglobinemia.

ANTIMALARIAL ACTIONS

(1) It is active against late hepatic stages of P. vivax & P. ovale.
(2) It is also highly active against primary exoerythrocytic stages of P. falciparum.
(3) It is gametocidal against all 4 malaria parasites.

CLINICAL USES

(1) Radical cure of vivax & ovale malarias.
(2) Chemoprophylaxis of malaria.
(3) Pneumocystosis (pneumocystis jiroveci inf).

ADVERSE EFFECTS

(1) CNS: Headache.
(2) GIT: Nausea, epigastric pain, abd. cramps.
(3) Blood: Leukopenia, agranulocytosis, hemolysis in G- 6- P dehydrogenase deficiency, methemoglobinemia.

CONTRAINDICATIONS

(1) Pts. with connective tissue disorders.
(2) Pregnancy.
(3) Parenterally (b/c it may induce marked hypotension).
(4) With other potentially hemolytic drugs.
(5) With drugs that depress bone marrow.

DOSAGE

26.3 mg daily, orally for 14 days, usually with chloroquine.

PYRIMETHAMINE

Mechanism of Action

Similar to trimethoprim by inhibiting dihydrofolate reductase. (See chapter '18').

Antimalarial Actions

(1) It is an effective blood schizonticide.
(2) It is also gametocidal, & active against primary exo-erythrocytic stages of P. falciparum.

Clinical Uses

(1) For prophylaxis of 4 - Aminoquinoline resistant falciparum malaria (with sulfonamides or sulfones).
(2) Treatment of 4 - Aminoquinoline resistant falciparum malaria (with sulfonamides & quinine).
(3) Treatment of toxoplasmosis.
(4) Pneumocystosis.

Adverse Effects

(1) GIT: Mild upsets.
(2) Skin: Rashes.
(3) Blood: Megaloblastic anemia.

Contraindications

Pregnancy.

Dosage

75 mg/day, orally.

PROGUANIL

Mechanism of Action

It is a prodrug, which is converted into active metabolite 'cycloguanil'. It acts by inhibiting dihydrofolate reductase.

Antimalarial Actions

(1) It has a marked effect on primary exoerythrocytic stages of P. falciparum & P. vivax.
(2) It is an effective blood schizonticide.

Clinical Uses

For prophylaxis & treatment of falciparum & vivax malarias.
Note: It is considered safe in pregnancy.

Adverse Effects

(1) GIT: Vomiting, diarrhea, abd. pain.
(2) Blood: Megaloblastic anemia, leukopenia, granulocytopenia.

FANSIDAR

It is a combination of Pyrimethamine & Sulfadoxine (a sulfonamide).

Mechanism of Action

Similar to 'Cotrimoxazole'. (See chapter '18').

Antimalarial Actions

(1) It is an effective blood schizonticide against P. falciparum.
(2) It also has a marked effect on primary exoerythrocytic stages of P. falciparum.

Clinical Uses

For prophylaxis & treatment of falciparum malaria.

Adverse Effects

(1) GIT: Mild upsets.
(2) Blood: Megaloblastic anemia.
(3) Skin: Erythema multiforme, Stevens-Johnson Synd., toxic epidermal necrolysis.

Contraindications

(1) Pts. who have had adverse reactions to either of its components.
(2) Pregnant or nursing women.
(3) Children under 2 months of age.
(4) Impaired renal function.
(5) Impaired hepatic function.
(6) G-6-P dehydrogenase deficiency.
(7) Pts. with severe allergic disorders, bronchial asthma or poor nutritional status.

MEFLOQUINE

Mechanism of Action

Unknown.

Antimalarial Actions

It has strong schizonticidal activity against all malarial parasites.

Clinical Uses

P. falciparum malaria resistant to chloroquine & Fansidar.

Adverse Effects

(1) CNS: Dizziness, headache, confusion, hallucinations, depression.
(2) CVS: Sinus bradycardia.
(3) GIT: Nausea, vomiting, diarrhea, abd. pain.
(4) Skin: Rashes, itching.

QUINACRINE

Antimalarial Actions

It is an effective blood schizonticide that suppresses all 4 types of malarial parasites.

Clinical Uses

(1) P. malariae & P. falciparum malarias (the drug is now obsolete for malaria).
(2) Giardiasis.

Adverse Effects

(1) CNS: Dizziness, headache, restlessness, confusion, anxiety, euphoria.
(2) GIT: Vomiting, diarrhea.

QINGHAOSU

(1) It is an effective blood schizonticide against all 4 types of malaria.
(2) It is esp. useful in the treatment of falciparum cerebral malaria, including that due to chloroquine resistant strains.

GENERIC & TRADE NAMES

(1) **Chloroquine phosphate:** Binaquin, Cloquin, Efroquin, Kciquin, Proquine, Resochin, Wilquin, Chloroquine phosphate tab.
(2) **Amodiaquine HCl:** Amdaquin, Amoquine, Basoquin, Semoquine.
(3) **Primaquine:** Primaquine.
(4) **Quinine:** Hydroquine.
(5) **Mefloquine:** Fansimate, Fansimef.
(6) **Halofantrine:** Halfan.
(7) **Artemether:** Artem, Artemal, Artemex, Artemose, Entum, Hitecxin, Malamether.
(8) **Pyrimethamine:** Fansidar*, Fansimef*, Maladar*, Metafin*, Malarina*, Malidar.
(9) **Sulfonamides & Tetracyclines :** See Chapter 18.

Unit II

Drug Treatment of Amebiasis

AMEBIASIS

It is an infectious disease caused by Entameba histolytica. It may produce ulceration of large intestine, & also abscess of liver & rarely of other organs.

Clinical Features

(1) An acute stage with frequent passage of motions containing blood & mucus, & accompanied by abdominal pain & tenesmus.
(2) A chronic stage in which symptoms may entirely disappear, & diarrhea may even give place to constipation.

DRUG CLASSIFICATION

(A) Tissue Amebicides

(1) Nitroimidazoles: Metronidazole, Tinidazole, Ornidazole.
(2) Emetines: Emetine HCl, Emetine bismuth iodide, Dehydroemetine HCl.
(3) 4 - Aminoquinolines: Chloroquine.

(B) Luminal Amebicides

(1) Dichloroacetamides: Diloxanide furoate, Clefamide, Etofamide, Teclozan.
(2) Halogenated 8-OH quinolines: Iodoquinol (Diiodohydroxyquin), Clioquinol (Iodochloro-hydroxyquin).
(3) Antibiotics: Tetracycline, Paromomycin, Erythromycin.

DRUGS USED IN DIFFERENT AMEBIC INFECTIONS

(1) Asymptomatic Intestinal Infection

Drug of Choice: Diloxanide furoate.
Alternative Drug: Iodoquinol, Paromomycin.

(2) Mild to Moderate Intestinal Infection

Dg/Ch: Metronidazole or Tinidazole, Plus Diloxanide furoate, Iodoquinol or Paromomycin.
Alt. drugs: Diloxanide furoate, Iodoquinol or Paromomycin, plus Tetracycline or Erythromycin.

(3) Severe Intestinal Inf. (Dysentery)

Dg/Ch: Metronidazole or Tinidazole, Plus Diloxanide furoate, Iodoquinol or Paromomycin.
Alt. drugs: Diloxanide furoate, Iodoquinol or Paromomycin, plus Tetracycline, Emetine or Dehydroemetine.

(4) Hepatic Abscess

Dg/Ch: Metronidazole or Tinidazole, Plus Diloxanide furoate, Iodoquinol or Paromomycin.
Alt. drugs: Dehydroemetine or emetine followed by Chlroquine + Diloxanide furoate, Iodoquinol or Paromomycin.

(5) Ameboma or Extraintestinal Inf.
Dg/Ch: As for hepatic abscess.
Alt. drugs: As for hepatic abscess but excluding chloroquine.

METRONIDAZOLE & TINIDAZOLE

MECHANISM OF ACTION
Within sensitive protozoal cells, the nitro group of metronidazole is chemically reduced by ferrodoxin & the reduction product appears to be responsible for killing organisms by reacting with various intracellular macromolecules.

CLINICAL USES
(1) Amebiasis.
  (a) Mild to moderate & severe intestinal inf.
  (b) Hepatic abscess.
  (c) Ameboma.
(2) Urogenital trichomoniasis.
(3) Giardiasis.
(4) Balantidiasis.
(5) Gardnerella vaginalis.
(6) Anaerobic infections.
(7) Phagedenic leg ulcers (topically).
(8) Acute ulcerative gingivitis (topically).
(9) Cancrum oris (topically).
(10) Decubitus ulcers (topically).

ADVERSE EFFECTS
(1) CNS: Headache, insomnia, weakness, paresthesias, vertigo, seizures, ataxia, encephalopathy.
(2) GIT: Nausea, vomiting, diarrhea, dry mouth, metallic taste, stomatitis, pseudomembranous colitis.
(3) Renal: Urethral burning, dark or reddish-brown urine.
(4) Blood: Leukopenia.
(5) Skin: Rashes.
(6) IV Inj: Thrombophlebitis.

DOSAGE
400-800 mg 3 times daily, for 5 days.

EMETINE & DEHYDROEMETINE

MECHANISM OF ACTION
They irreversibly block the synthesis of protein by inhibiting movement of ribosome along mRNA. DNA synthesis is secondarily blocked.
Note: They act only against trophozoites.

CLINICAL USES
(1) Amebic dysentery.
(2) Fasciola hepatica inf.
(3) Balantidiasis.
(4) Paragonimus westermani inf.

ADVERSE EFFECTS
(1) CNS: Headache, fatigue, dizziness, paresthesias, polyneuritis.
(2) CVS: Tachycardia, arrhythmias, precordial pain, congestive cardiac failure with dyspnea & hypotension.
(3) GIT: Nausea, vomiting, diarrhea.
(4) Renal: Proteinuria.
(5) Blood: Hypokalemia, elevated transaminase level.
(6) Skeletal muscles: Generalized muscular weakness associated with tenderness, stiffness, aching, tremors.
(7) Skin: Urticaria, eczema, purpura.
(8) Local: Pain, tenderness, muscular weakness, sterile abscess in the area of inj.

CONTRAINDICATIONS
(1) Cardiac disease.
(2) Renal disease.
(3) Polyneuritis.
(4) Young children.
(5) Pregnancy.

DOSAGE
1 mg/kg/d, SC or IM for 3-5 days; max. daily dose for dehydroemetine is 90 mg, & for emetine 65 mg.

DILOXANIDE FUROATE

Mechanism of Action
Probably directly amebicidal, but the exact mech. is unknown.

Clinical Uses
All forms of amebiasis.

Adverse Effects
(1) GIT: Flatulence, nausea, vomiting, diarrhea, esophagitis, dryness of mouth, abd. cramps.
(2) Renal: Proteinuria.
(3) Skin: Pruritus, urticaria, tingling sensation.

Contraindications
(1) Pregnancy.
(2) Children under 2 years of age.

Dosage
500 mg 3 times daily with meals, for 10 days.

IODOQUINOL (DIIODOHYDROXYQUIN)

Mechanism of Action
Unknown; but it is probably due to its iodine content.

Clinical Uses
(1) Asymptomatic & mild to moderate intestinal amebiasis.

(2) Giardiasis.
(3) Dientameba fragilis inf.

Adverse Effects

(1) CNS: Headache, peripheral neuropathy.
(2) Eye: Optic atrophy, visual loss.
(3) GIT: Nausea, vomiting, diarrhea, constipation, gastritis, abd. discomfort.
(4) Endo: Slight enlargement of thyroid gland.
(5) Blood: Agranulocytosis.
(6) Skin: Pruritus ani, discoloration of hairs or nails, hair loss.
(7) Iodine sensitivity: Characterized by furunculosis, chills, fever, various skin reactions.

Contraindications

(1) Pts. with intolerance to iodine.
(2) Renal disease.
(3) Thyroid disease.

Dosage

650 mg 3 times daily, for 21 days.

GENERIC & TRADE NAMES

(1) **Metronidazole:** Abozole, Amibazol, Candizole-M, Dependal M, Diloxamet, Diloxazole, Entamizole, Flagyl, Klint, Merizole, Metgyl, Metodine, Metomet, Metronidazole, Resgyl, Trivizol, Zolen, Zolint.
(2) **Tinidazole:** Fasigyn, Trichogin.
(3) **Diloxanide furoate:** Amibazole*, Diloxazole*, Zolen*, Entamizole*.
(4) **Clioquinol:** Clioquinol.

Unit III

Drug Treatment of Leishmaniasis

LEISHMANIASIS

It is a human disorder produced by flagellated tissue protozoa of genus leishmania, transmitted to humans by the bites of sandflies of genera phlebotomus & lutzomyia.

Types of Leishmaniasis

(1) Visceral Leishmaniasis (Kala-azar)

It is caused by leishmania donovani, & is characterized by continuous or remittent fever, hepato-splenomegaly, lymphadenopathy, epistaxis, emaciation, anemia, & dry, rough, harsh skin with occasional warty eruption & mucocutaneous lesions.

(2) Cutaneous Leishmaniasis

It is caused by leishmania tropica, which produces cutaneous lesion called tropical sore. This begins as a raised nodule which then ulcerates, & is distributed on exposed parts of body esp. on face & extremities.

(3) Mucocutaneous Leishmaniasis

It is caused by leishmania braziliensis, & is characterized by a specific ulcerative granuloma of skin, followed by involvement of mucocutaneous area in some cases.

DRUG CLASSIFICATION

(1) For Kala-azar

(a) Drugs of Choice: Pentavalent antimonials eg sodium stibogluconate.
(b) Alternative drug: Meglumine antimonate, Pentamidine, Amphotericin B, Mitefosine.

(2) For Cutaneous Leishmaniasis

(a) Drugs of choice: Sodium stibogluconate.
(b) Alternative drugs: Meglumine antimonate, Pentamidine, Ketoconazole.

(3) For Mucocutaneous Leishmaniasis

(a) Drugs of Choice: Sodium stibogluconate.
(b) Alternative drugs: Meglumine antimonate, Pentamidine, Amphotericin B, Mitefosine

SODIUM STIBOGLUCONATE

MECHANISM OF ACTION

Pentavalent antimonials are first broken in vivo into trivalent compounds. Trivalent antimonials than inhibit the enzyme phosphofructokinase, which prevent protozoa from completing anaerobic metabolism of glucose essential for their survival.

CLINICAL USES

All forms of leishmaniasis.

ADVERSE EFFECTS

(1) CNS: Headache.
(2) CVS: Bradycardia, arrhythmias, circulatory collapse.
(3) Resp. tract: Lobar pneumonia.
(4) GIT: Nausea, vomiting, abd. pain.
(5) Liver: Hepatitis.
(6) Blood: Hemolytic anemia.
(7) Musculo - skeletal system: Joint & muscle pain.
(8) Skin: Maculo-papular rash, pruritus.

DOSAGE

Na stibogluconate 2 10 mg/kg body wt. for 10 days, IM or IV; 3 courses with interval of a week b/w each course.

PENTAMIDINE

MECHANISM OF ACTION

Unknown; parasite may take up more of the drug than mammalian tissue does, & probably function of mitochondria & respiration of intact parasites are depressed.

CLINICAL USES

(1) Kala-azar.
(2) African trypanosomiasis.
(3) Pneumocystosis.
(4) Blastomycosis.

ADVERSE EFFECTS

(1) CVS: Hypotension.
(2) Endo: Hypoglycemia, hyperglycemia, diabetes mellitus.
(3) Liver: Abnormal liver function tests.
(4) Pancreas: Acute pancreatitis, selective toxicity to B cells of pancreatic islets causing first insulin release & then insulin deficiency.
(5) Renal: Kidney dysfunction, azotemia.
(6) Blood: Megaloblastic anemia, thrombocytopenia (leading to purpura).
(7) Electrolytes: Hyperkalemia, Hypocalcemia.
(8) Skin: Toxic epidermal necrolysis.
(9) IM inj: Pain, sterile abscess.
(10) IV inj: Severe hypotension, tachycardia, dizziness, fainting, itching.

CONTRAINDICATIONS

(1) Diabetes mellitus.
(2) Liver disease.
(3) Kidney disease.
(4) Megaloblastic anemia.

DOSAGE

2 - 4 mg/kg/d, IM for upto 15 doses.

Unit IV

Drug Treatment of Trypanosomiasis

INTRODUCTION

AFRICAN TRYPANOSOMIASIS

African trypanosomiasis or sleeping sickness is a disease caused by 'Trypanosoma brucei', & is transmitted to humans by flies of genus glossina.

Clinical Features

Rapid pulse, irregular fever, rashes, glandular enlargement, & after CNS becomes involved, severe headache, insanity, emaciation, lethargy, coma which may end in death.

AMERICAN TRYPANOSOMIASIS

It is caused by 'Trypanosoma cruzi'.

Clinical Features

Anemia, enlarged glands, & irregular fever.

DRUG CLASSIFICATION

(A) For African Trypanosomiasis
- ***(1) For Hemolymphatic Stage***
  - (a) Suramin (Dg/Ch).
  - (b) Pentamidine, Eflornithine (Alt. drug).
- ***(2) For Late Disease with CNS Involvement***
  - (a) Trivalent arsenicals (Dg/Ch) eg Melarsoprol.
  - (b) Eflornithine (Alt. drug).

(B) For American Trypanosomiasis
- (1) Nifurtimox (Dg/Ch).
- (2) Benznidazole (Alt. drug).

SURAMIN

MECHANISM OF ACTION

It is a non - specific inhibitor of many enzymes.

CLINICAL USES

(1) Hemolymphatic stage of African trypanosomiasis.
(2) Onchoceriasis.

ADVERSE EFFECTS

(1) CNS: Peripheral neuritis.
(2) GIT: Nausea, vomiting.
(3) Liver: Jaundice.
(4) Renal: Nephrotoxicity.
(5) Blood: Anemia.
(6) Temp: Fever.
(7) Skin: Urticaria, exfoliative dermatitis.

MELARSOPROL

Mechanism of Action

(1) It may act by inhibiting trypanothione reductase.
(2) It may act by inhibiting sulfhydryl enzymes.

Clinical Uses

African trypanosomiasis with CNS involvement.

Adverse Effects

(1) CNS: Encephalopathy, crippling sensory neuropathy.
(2) CVS: Capillary damage causing inc. permeability, dehydration & shock.
(3) Resp. tract: Bronchitis, laryngitis.
(4) GIT: Nausea, vomiting, abd. pain.
(5) Bone marrow: Bone marrow depression.

NIFURTIMOX

Mechanism of Action

It induces hydrogen per oxide production in Trypanosoma cruzi, which may result in its trypanosomicidal action.

Clinical Uses

American trypanosomiasis.

Unit V

Self - Assessment (T/F)

(See answers on page no. 241)

(162) ***All of the following statements about anti-malarial drugs are correct***

(A) Chloroquine is a blood schizonticide but does not affect secondary tissue schizonts.
(B) Proguanil is converted to a reactive metabolite that is effective blood schizonticide.
(C) Primaquine acts primarily on exoerythrocytic stages of malarial life cycle.
(D) Mefloquine destroys secondary exoerythrocytic schizonts.
(E) Pyrimethamine destroys both erythrocytic & exoerythrocytic stages of malarial parasites.

(163) ***Following antimalarial drugs causes hemolysis in G - 6 - P - dehydrogenase deficiency***

(A) Chloroquine.
(B) Quinine.
(C) Primaquine.
(D) Pyrimethamine.
(E) Proguanil.

(164) ***All of the following statements about amebicides are correct***

(A) Paromomycin is effective in extraintestinal amebiasis.
(B) Diloxanide furoate is a luminal amebicide.
(C) Metronidazole has little activity in gut lumen.
(D) Systemic use of iodoquinol may cause thyroid enlargement & peripheral neuropathy.
(E) Emetine can cause arrhythmias & precordial pain.

(165) ***Drugs effective in Kala-azar includes***

(A) Amphotericin B.
(B) Na Stibogluconate.
(C) Dehydroemetine.
(D) Neostibosan.
(E) Pyrimethamine.

(166) ***Following drugs are used in late CNS stages of African sleeping sickness***

(A) *Melarsoprol.*
(B) *Suramin.*
(C) *Nifurtimox.*
(D) *Tryparsamide.*
(E) *Pentamidine.*

22 CHEMOTHERAPY OF HELMINTIC INFECTIONS

Unit I

Drug Treatment of Schistosomiasis

SCHISTOSOMIASIS

It is a trematode or fluke infection of blood, caused by 3 species of family Schistosomitidae ie S. Mansoni, S. Hematobium, & S. Japonicum, that gain access thru intact skin when human baths in water infected with cercariae of Schistosomitidae.

Habitat

(1) S. Hematobium in the pelvic venous plexus.
(2) S. Mansoni in the mesenteric veins of sigmoido-rectal area, & in the brs. of portal vein.
(3) S. Japonicum in veins of large intestine esp. in hemorrhoidal plexuses, & also in gastric & mesenteric veins.

Pathogenesis

They lay large number of eggs in circulatory system which causes lesion primarily at the sites of habitat, & secondarily to other areas (eg in lungs, brain, & spinal cord) due to overflow phenomenon.

(1) Terminal-spined eggs erode blood vessels causing hemorrhages.
(2) Deposited eggs act like foreign protein having irritant effect, leading to round cell infiltration & connective tissue hyperplasia.

Clinical Features

(1) S. Hematobium Infection (Bilharziasis)

Hematuria, pain in the bladder region, back & on passing urine, frequency of micturition, hepatosplenomegaly, & dysentery with passage of blood & mucus in feces if rectum is involved.

(2) S. Mansoni Infection

Urticaria, pulmonary signs, abd. pain, dysentery, blood & mucus in feces, prolapse of rectum, hepatosplenomegaly, cirrhosis.

(3) S. Japonicum Infection

Fever, cough, profuse perspiration during night, vomiting, urticaria, dysentery with blood & mucus in feces, hepatosplenomegaly, cirrhosis.

DRUG CLASSIFICATION

(1) Praziquantal
(Drug of choice against all 3 species).
(2) Metrifonate
(Alt. drug in S. hematobium inf).
(3) Oxamniquine
(Alt. drug in S. mansoni inf).

PRAZIQUANTAL

Mechanism of Action

It inc. cell memb. permeability to Ca ions, resulting in marked contraction followed by paralysis of worm musculature. Vacuolization & disintegration of tegmen occurs & parasite death follows.

Clinical Uses

(1) Schistosomiasis.
(2) Clonorchiasis.
(3) Opisthorchiasis.
(4) Paragonimiasis.
(5) Cysticercosis.
(6) Beef tape worm inf.
(7) Fish tape worm inf.
(8) Dwarf tape worm inf.
(9) Pork tape worm inf.
(10) Rat tape worm inf.
(11) Hydatid disease

Adverse Effects

(1) CNS: Headache, dizziness, drowsiness, lassitude.
(2) GIT: Nausea, vomiting, abd. pain, loose to mushy stools.
(3) Musculo-skeletal system: Arthralgia, myalgia.
(4) Blood: Eosinophilia.
(5) Temp: Low grade fever.
(6) Skin: Pruritus, macular & urticarial skin rashes.

Contraindication

Ocular cysticercosis.

Dosage

20 mg/kg TDS, for 1 day.

METRIFONATE

Mechanism of Action
It is converted into active metabolite 'dichlorvos' which functions as a cholinesterase inhibitor 2 This results in temporary paralysis of adult worms, leading in their shift from bladder venous plexus to small arterioles of lungs where they are trapped & encased, & then die.

Clinical Uses
Bilharziasis (S. hematobium inf).

Adverse Effects
(1) CNS: Headache, fatigue, weakness, vertigo.
(2) GIT: Nausea, vomiting, diarrhea, abd. pain.
(3) Resp. tract: Bronchospasm.
(4) Skin: Sweating.

OXAMNIQUINE

Mechanism of Action
It may act by DNA binding.

Clinical Uses
S. mansoni inf.

Adverse Effects
(1) CNS: Headache, dizziness, drowsiness, seizures, hallucinations.
(2) Resp. tract: Cough, ronchi.
(3) GIT: Nausea, vomiting, diarrhea, abd. colic.
(4) Liver: Liver enzyme abnormalities.
(5) Renal: Orange to red discoloration of urine, proteinuria, hematuria.
(6) Blood: Leukopenia, lymphopenia, eosinophilia.
(7) Temp: Low grade fever.
(8) Skin: Urticaria, pruritus.

Unit II

Drug Treatment of Tapeworm (Cestode) Infestations

DRUG CLASSIFICATION

(1) For Taenia Saginata (Beef TW) Infection
(a) Drug of choice 2 Praziquantal, Niclosamide.
(b) Alternative drugs 2Mebendazole.

(2) For Taenia Solium (Pork TW) Infection
(a) Drug of choice 2 Praziquantal.
(b) Alt. drug 2 Niclosamide.

(3) For Hymenolepis Nana (Dwarf TW) Infection
(a) Drug of choice 2 Praziquantal.
(b) Alt. drug 2 Niclosamide.

(4) For Diphyllobothrium Latum (Fish TW) Infection
(a) Drug of choice 2 Praziquantal.
(b) Alt. drug 2 Niclosamide.

(5) For Hymenolepis Diminuta (Rat TW) Infection
(a) Drug of choice 2 Praziquantal.
(b) Alt. drug 2 Niclosamide.

(6) For Cysticercosis (Pork TW Larval Infection)
(a) Drug of choice 2 Albendazole.
(b) Alt. drug 2 Praziquantal.

(7) For Echinococcus Granulosus Inf. (Hydatid Disease)
(a) Drug of choice 2 Albendazole.
(b) Alt. drug 2 Mebendazole.

NICLOSAMIDE

Mechanism of Action
Scoleces & segments of tapeworm are rapidly killed on contact with niclosamide, due to drug's inhibition of oxidative phosphorylation or due to its ATPase stimulating property.

Clinical Uses
(1) Beep TW inf.
(2) Pork TW inf.
(3) Dwarf TW inf.
(4) Fish TW inf.
(5) Rat TW inf.
(6) Fasciolopsis buski inf.
(7) Heterophyes inf.
(8) Metagonimus yokogawai inf.

Adverse Effects
(1) CNS: Headache, vertigo.
(2) GIT: Nausea, vomiting, diarrhea, abd. pain.
(3) Skin: Skin rashes, urticaria, pruritus ani.

Contraindications
Consumption of alcohol.

Dosage
2 gm orally.

OTHER DRUGS

Praziquantal
See Unit I.

Mebendazole & Albendazole
See Unit III.

GENERIC & TRADE NAMES

(1) Mebendazole: Deworm, Erizole, Meben, Nemazole, Vermin, Vermol, Vermox, Wormizole, Zeworm,
(2) Albendazole: Alben, Albendix, Albenza, Bendazol, Polyworm, Wormgo, Wormocid, Zentel.

(3) Niclosamide: Yomesan.

Unit III

Drug Treatment of Roundworm (Nematode) Infestations

DRUG CLASSIFICATION

(1) For Ascaris Lumbricoides (Round Worm) Inf.
- (a) Drug of choice 2 Albendazole, Pyrantal pamoate, Mebendazole.
- (b) Alt. drug 2Piperazine.

(2) For Nector Americanos & Ankylostoma Duodenale (Hook Worm) Inf.
- (a) Drug of choice 2 Pyrantal pamoate, Mebendazole.
- (b) Alt. drug 2 Albendazole.

(3) For Enterobius Vermicularis (Pin Worm) Inf.
- (a) Drug of choice 2 Pyrantal pamoate, Mebendazole.
- (b) Alt. drug 2 Albendazole.

(4) For Trichuris Trichura (Whip Worm) Inf.
- (a) Drug of choice 2 Mebendazole, Albendazole.
- (b) Alt. drug 2 Pyrantal pamoate, Oxantel pamoate.

(5) For Strongyloides Stercoralis (Thread Worm) Inf.
- (a) Drug of choice 2Ivermectin.
- (b) Alt. drug 2 Thiabendazole, Albendazole.

(6) For Trichinella Spiralis (Trichina Worm) Inf.
- (a) Drug of choice 2 Mebendazole, & ACTH or Corticosteroids (for severe inf).
- (b) Alt. drug 2 Albendazole, & Corticosteroids (for severe inf).

(7) For Wuchereria Bancrofti Inf. (Filariasis)
- (a) Drug of choice 2Diethylcarbamazine citrate.
- (b) Alt. drug 2 Ivermectin.

PYRANTAL PAMOATE

Mechanism of Action
(1) It causes inhibition of neuromuscular transmission resulting in spastic neuromuscular paralysis with subsequent expulsion of worm from host's intestinal tract.
(2) It also inhibit cholinesterase.

Clinical Uses
(1) Round worm inf.
(2) Hook worm inf.
(3) Pin worm inf.
(4) Whip worm inf.

Adverse Effects
(1) CNS: Headache, dizziness, drowsiness, insomnia.
(2) GIT: Nausea, vomiting, diarrhea, abd. cramps.
(3) Skin: Rashes.
(4) Temp: Fever.

Dosage
20 mg/kg body weight in a single dose, on two successive days with a max. of 1 gm.

MEBENDAZOLE

Mechanism of Action
It inhibits microtubule synthesis in nematodes, & impair their uptake of glucose. As a result, intestinal parasites are immobilized or die slowly.

Clinical Uses
(1) Round worm inf.
(2) Hook worm inf.
(3) Pin worm inf.
(4) Whip worm inf.
(5) Thread worm inf.
(6) Trichina worm inf.
(7) Hydatid disease.
(8) Beef tape worm inf.
(9) Pork tape worm inf.
(10) Intestinal capillariasis.
(11) Visceral larva migrans inf.

Adverse Effects
(1) CNS: Headache, dizziness.
(2) GIT: Nausea, vomiting, diarrhea, abd. pain.

Contraindications
(1) Hepatic parenchymal disease.
(2) Pregnancy.
(3) Children under 2 years of age.

Dosage
(1) Thread worms 2 100 mg, dose is repeated after 2 or 3 weeks if required.
(2) Other worms 2 100 mg morning & evening, for 3 days.

ALBENDAZOLE

Mechanism of Action
It blocks glucose uptake by larval & adult stages of susceptible parasites, depleting their glycogen stores & dec. formation of ATP. As a result parasites are immobilized & dies.

Clinical Uses
(1) Round worm inf.
(2) Hook worm inf.
(3) Pin worm inf.
(4) Whip worm inf.
(5) Thread worm inf.
(6) Hydatid disease.
(7) Cutaneous larva migrans inf.

Adverse Effects
(1) CNS: Headache, dizziness, insomnia.

(2) GIT: Nausea, diarrhea, epigastric distress.
(3) Blood: Leukopenia.
(4) Skin: Alopecia.

Contraindications
(1) Pregnancy.
(2) Children under 2 years of age.
(3) Cirrhosis.

Dosage
400 mg in a single dose, orally.

PIPERAZINE

Mechanism of Action
It causes paralysis of ascaris by blocking acetylcholine at myoneural junction, which is then expelled live by normal peristalsis.

Clinical Uses
Ascariasis (round worm inf.)

Adverse Effects
(1) CNS: Headache, exacerbation of seizures.
(2) GIT: Nausea, vomiting, diarrhea, abd. pain.
(3) Allergic reactions: Serum sickness like-synd.

Contraindications
(1) Impaired renal function.
(2) Impaired hepatic function.
(3) Chronic neurologic disease.

Dosage
75 mg/kg orally, for 2 successive days.

THIABENDAZOLE

Mechanism of Action
It may act on parasites by interfering with microtubule aggregation, & thru inhibition of enzyme fumarate reductase.

Clinical Uses
(1) Thread worm inf.
(2) Trichina worm inf.
(3) Cutaneous larva migrans inf.
(4) Visceral larva migrans inf.
(5) Intestinal capillariasis.
(6) Dracontiasis.
(7) Scabies (topically).
(8) Tinea nigra palmaris (topically).

Adverse Effect
(1) CNS: Headache, dizziness, drowsiness, giddiness, tinnitus, paresthesias, visual disturbances.
(2) CVS: Bradycardia, hypotension.
(3) GIT: Anorexia, nausea, vomiting, epigastric pain, abd. cramps.
(4) Liver: Liver function abnormalities.
(5) Skin: Pruritus, skin rashes esp. perianal, erythema multiforme, toxic epidermal necrolysis.
(7) Blood: Leukopenia.
(8) Temp: Fever with chills.
(9) Lymphatics: Lymphadenopathy.

Contraindications
(1) Hepatic dysfunction.
(2) Renal dysfunction.

Dosage
25 mg/kg orally after meals with a max. of 1.5 gm.

DIETHYLCARBAMAZINE CITRATE

Mechanism of Action
It is an inhibitor of arachidonic acid metabolism in filarial microfilaria. This makes the microfilaria more susceptible to immune attack.

Clinical Uses
(1) Lymphatic filariasis caused by infection with Wuchereria bancrofti, Brugia malayi, or Brugia timori.
(2) Tropical pulmonary eosinophilia.
(3) Loiasis.

Adverse Effects
(1) CNS: Headache, malaise, weakness, dizziness.
(2) GIT: Anorexia, nausea, vomiting.
(3) Reactions to dying microfilariae: Fever, malaise, popular rash, headache, gastrointestinal symptoms, cough, chest pain, muscle or joint pain, leukocytosis, eosinophilia, proteinuria, retinal hemorrhages, encephalopathy.
(4) Reactions to dying adult worms: Lymphangitis, wheals, papules.

GENERIC & TRADE NAMES

(1) Pyrantal pamoate: Anthelmin, Blissworm, Combantrin.
(2) Mebendazole & Albendazole: See Unit II..
(3) Piperazine: Engpar, Piperazine elixir, Pipragen, Remipar.
(4) Levamisole: Antiworm, Geomisole, Nilpar.
(5) ACTH & corticosteroids: See Chapter 17.

Unit IV

Self - Assessment (T/F)

(See answers on page no. 241)

(167) ***All of the following statements concerning niclosamide are correct***
(A) It is effective in many tapeworm infections.
(B) It kills parasitic ova.
(C) Its effects include inhibition or uncoupling of oxidative phosphorylation.
(D) It can cause pruritus ani.
(E) It is usually administered intravenously.

(168) ***All of the following statements are correct, regarding drug treatment of round worm infestations***

(A) Mebendazole inhibits microtubule synthesis in nematodes.
(B) Pyrantal pamoate inhibits neuromuscular transmission, resulting in spastic neuromuscular paralysis of parasites.
(C) Albendazole can cause alopecia.
(D) Piperazine is effective in most round worm infestations.
(E) Albendazole is contraindicated in children under 2 years of age.

(169) ***All of the following drugs are effective in schistosomiasis***
(A) Praziquantal.
(B) Niridazole.
(C) Stibocaptate.
(D) Mebendazole.
(E) Na Stibogluconate.

23 CANCER CHEMOTHERAPY

Unit I

Anti - Cancers

CANCER (NEOPLASIA)

It is a disease of uncontrolled cell division, invasion & metastasis, & is due to clonal expansion of a single neoplastic cell (however, there may be additional somatic mutations, leading to heterogeneous cell population).

Characteristics of Cancer

(1) Some lack of differentiation with anaplasia; structure is often atypical.
(2) Rate of growth is erratic, & may be slow to rapid; mitotic figures usually numerous & abnormal.
(3) Invasion without encapsulation; usually infiltrative, but may be cohesive & expansile.
(4) Metastasis is frequently present.

DRUG CLASSIFICATION

(A) Alkylating Agents

(1) Bis-Chloroethyl Amines
Cyclophosphamide, Mechlorethamine (Nitrogen mustard), Chlorambucil, Melphalan.

(2) Nitrosoureas
Carmustine, Lomustine, Semustine.

(3) Aziridines
Triethylenemelamine, Thiotepa (Triethylenethiophosphoramide), Altretamine (Hexamethylmelamine).

(4) Alkylsulfonates
Busulfan.

(5) Triazenes
Dacarbazine.

(6) Plantinum Analogs
Cisplatin, Carboplatin, Oxaliplatin, Transplatin.

(7) Miscellaneous
Procarbazine, Pentamethylmelamine, Ifosfamide, Temozolomide.

(B) Antimetabolites

(1) Folate Antagonists
Methotrexate, Pemetrexed.

(2) Purine Antagonists
6-Mercaptopurine, 6-Thioguanine, Fludarabine, Cladribine.

(3) Pyrimidine Antagonists
5-Fluorouracil, Capecitabine, Cytarabine, Gemcitabine.

(C) Plant Alkaloids

(1) Vinca Alkaloids
Vinblastine, Vincristine, Vinorelbine.

(2) Epipodophyllotoxins
Etoposide, Teniposide.

(3) Camptothecins
Topotecan, Irinotecan.

(4) Taxanes
Paclitaxel, Docetaxel.

(D) Anticancer Antibiotics

(1) Anthracyclines
Daunorubicin, Doxorubicin, Idarubicin, Epirubicin.

(2) Miscellaneous
Bleomycin, Dactinomycin, Mitomycin, Mitoxantrone.

(E) Hormonal Agents

(1) Antiandrogens
Flutamide, Bicalutamide, Cyproterone.

(2) Antiestrogen
Tamoxifen.

(3) Progestins
Megestrol acetate.

(4) Adrenocorticosteroids
Hydrocortisone, Prednisone.

(5) Gonadotropin-Releasing Hormone Agonists
Leuprolide, Goserelin acetate.

(6) Aromatase Inhibitors
Aminoglutethimide, Anastrozole, Letrozole, Exemestane.

(F) Miscellaneous Anticancer Drugs
Arsenic trioxide, Asparaginase, Bevacizumab, Cetuximab, Dasatinib, Erlotinib, Gefitinib, Imatinib, Hydroxyurea, Trastuzumab, Retinoic acid derivatives.

BIS-CHLOROETHYL AMINES

MECHANISM OF ACTION

(1) Kill rapidly proliferating cells as well as non-proliferating cells, as a result of alkylation of RNA, DNA & essential proteins.
(2) Antitumor activity results from alkylation of DNA, most favored sites for alkylation being 7-nitrogen & 6-oxygen of guanine 2 This results in ;
   (a) Cross linking, resulting in inhibition of DNA replication.
   (b) Mispairing of bases, resulting in miscoding of gene, & production of defective proteins.
   (c) Depurination of DNA resulting in weakened sugar-phosphate backbone of DNA & strand breakage.

Note: Enzyme exist which can repair DNA damage caused by alkylation, & they may limit responsiveness of some tumors.

CLINICAL USES

(1) Cyclophosphamide
(a) Hodgkin's disease.
(b) Burkitt's lymphoma.
(c) Ovarian & breast carcinoma.
(d) Oat cell lung cancer.
(e) Neuroblastoma.
(f) As immunosuppressive agent.

(2) Mechlorethamine
(a) Hodgkin's disease.
(b) Mycosis fungoides.

(3) Chlorambucil
(a) Chronic lymphocytic leukemia.
(b) Waldenstrom's macroglobulinemia.

(4) Melphalan
Multiple myeloma.

ADVERSE EFFECTS

(1) Acute Toxicity
GIT: Nausea, vomiting (with cyclophosphamide & mechlorethamine).

(2) Delayed Toxicity
(a) Renal: Hemorrhagic cystitis with cyclophosphamide.
(b) Blood: Moderate depression of peripheral blood cell count.
(c) Bone marrow: Depression with leukopenia, thrombocytopenia & bleeding.
(d) Skin: Alopecia.

DOSAGE

(1) Cyclophosphamide 2 3.5 - 5 mg/kg/d orally, for 10 days.
(2) Mechlorethamine 2 0.4 mg/kg IV in single or divided doses.
(3) Chlorambucil 2 0.1 - 0.2 mg/kg/d orally, for 10 days.
(4) Melphalan 2 0.25 mg/kg/d orally, for 4 days every 4 - 6 weeks.

NITROSOUREAS

Mechanism of Action
(1) They decompose into alkylating & carbamylating intermediates in aqueous environments.
(2) Cause alkylation of DNA & other nucleophiles, & carbamylation of lysine residues on proteins.
(3) Consequences of DNA alkylation are similar to nitrogen mustards.

Clinical Uses

(1) Carmustine
(a) Hodgkin's disease.
(b) Meningeal leukemia.
(c) Tumor of brain.
(d) Acute lymphocytic leukemia.
(e) Non-Hodgkin lymphomas.
(f) Multiple myeloma.

(2) Lomustine
(a) Hodgkin's disease.
(b) Non-Hodgkin lymphomas.
(c) Carcinoma of cervix.
(d) Carcinoma of stomach & pancreas.
(e) Melanoma.

Adverse Effects

(1) Acute Toxicity
GIT: Nausea, vomiting.

(2) Delayed Toxicity
(a) Blood : Leukopenia, thrombocytopenia.
(b) Liver: Hepatitis.

PLATINUM ANALOGS

MECHANISM OF ACTION
Platinum complexes are formed in cells, which binds DNA thru formation of intrastrand & interstrand cross-links, ultimately inhibiting DNA synthesis & function & triggering apoptosis, or programmed cell death.

CLINICAL USES

(1) Cisplatin & Carboplatin
Solid tumors eg sarcomas, some carcinomas (eg small cell lung cancer, & ovarian cancer), lymphomas & germ cell tumors.

(2) Oxaliplatin
Metastatic colorecatal cancer; it is typically administered in combination with fluorouracil & leucovorin in a combination known as FOLFOX for the treatment of colorectal cancer.

ADVERSE EFFECTS

Cisplatin & Carboplatin
(1) **CNS:** Neuropathy (nerve damage).
(2) **GIT:** Nausea, vomiting.
(3) **Renal:** Nephrotoxicity (kidney damage).
(4) **ENT:** Ototoxicity (hearing loss).
(5) **Skin:** Alopecia (hair loss).
(6) **Body fluids:** Electrolyte disturbances include hypomagnesemia, hypokalemia & hypocalcemia.

Oxaliplatin

(1) **CNS:** Neuropathy (both an acute reversible sensitivity to cold & numbness in the hands & feet, & a chronic irreversible foot/leg, hand/arm numbness, often with deficits in proprioception), fatigue.
(2) **GIT:** Nausea, vomiting, diarrhea.
(3) **Skin:** Alopecia (hair loss).
(4) **Blood:** Neutropenia.

Note: Oxaliplatin has less ototoxicity & nephrotoxicity than cisplatin & carboplatin

METHOTREXATE

MECHANISM OF ACTION

(1) It is folic acid analog that competitively inhibits dihydrofolate reductase, which catalyzes formation of tetrahydrofolate from dihydrofolate.
(2) Tetrahydrofolate is required for biosynthesis of thymidylate & purines which are essential for DNA synthesis; thus methotrexate block DNA synthesis resulting in inhibition of mitosis.
(3) It also inhibits RNA & protein synthesis (b/c tetrahydrofolate is required also for synthesis of methionine & glycine) which results in slow entry of cells into DNA synthesis phase.

CLINICAL USES

(1) Acute lymphocytic leukemia.
(2) Acute myelocytic & myelomonocytic leukemia.
(3) Carcinomas of head & neck.
(4) Carcinoma of cervix.
(5) Breast carcinoma.
(6) Choriocarcinoma.
(7) Carcinoma of testis.
(8) Wilm's tumor.
(9) Osteogenic sarcoma.
(10) Burkitt's lymphoma.
(11) Mycosis fungoides.
(12) Psoriasis.

ADVERSE EFFECTS

(1) CNS: Necrotizing leuko-encephalopathy (when given with radiation therapy).
(2) GIT: Ulcerative stomatitis, nausea, vomiting, diarrhea.
(3) Liver: Hepatic dysfunction, cirrhosis.
(4) Renal: Renal failure.
(5) Blood: Myelosuppression with leukopenia, thrombocytopenia.
(6) Skin: Dermatitis.

DOSAGE

2.5 - 5 mg/d orally; 10 mg intrathecally 1-2 times weekly.

MERCAPTOPURINE

MECHANISM OF ACTION

(1) It is first converted intracellularly into 6-mercaptopurine ribose-phosphate & also into 6-methylmercaptopurine ribonucleotide 2 Both block aminotransferase that is responsible for formation of 5-phosphoribosylamine (first step in purine biosynthesis) 2 Thus purine & ultimately DNA synthesis in inhibited.
(2) 6- mercaptopurine ribose-phosphate also inhibits both adenylosuccinate synthetase (that converts inosinic acid to adenylosuccinic acid), & inosinate dehydrogenase (that converts inosinic acid to xanthylic acid).

CLINICAL USES

(1) Acute lymphocytic leukemia.
(2) Acute myelocytic & myelomonocytic leukemia.
(3) Chronic myelogenous leukemia.
(4) Choriocarcinoma.

ADVERSE EFFECTS

(1) GIT: Anorexia, nausea.
(2) Liver: Jaundice, hepatic necrosis, bile stasis.
(3) Blood: Myelosuppression, hyperuricemia.
(4) Renal: Hyperuricosuria.

DOSAGE

2.5 mg / kg /d orally.

FLUOROURACIL

MECHANISM OF ACTION

First it is activated to 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP) 2 This block thymidylate synthetase which transfers a methylene group from reduced folic acid to deoxyuridylate monophosphate to form thymidylate, essential for DNA synthesis 2 Thus DNA synthesis is inhibited.

CLINICAL USES

(1) Carcinomas of head & neck.
(2) Carcinoma of endometrium.
(3) Carcinoma of ovary.
(4) Carcinoma of breast.
(5) Carcinoma of prostate.
(6) Carcinoma of thyroid.
(7) Carcinoma of stomach.
(8) Carcinoma of pancreas.
(9) Carcinoma of colon.
(10) Insulinoma.

ADVERSE EFFECTS

(1) CNS: Neurologic toxicity.
(2) GIT: Stomatitis, nausea, diarrhea.
(3) Blood: Leukopenia.
(4) Skin: Alopecia.

DOSAGE

15 mg/kg/d IV for 5 days by 24-hour infusion; 15 mg / kg weekly IV.

VINCRISTINE

MECHANISM OF ACTION

It binds to tubulin dimers, inhibiting assembly of microtubule structures. Disruption of the microtubules arrests mitosis in metaphase.

Note: Vinca alkaloids affect all rapidly dividing cell types including cancer cells, but also intestinal epithelium & bone marrow.

CLINICAL USES

(1) Non-Hodgkin's lymphoma as part of the chemotherapy regimen CHOP.
(2) Hodgkin's lymphoma as part of MOPP, COPP, BEACOPP.
(3) Acute lymphoblastic leukemia.
(4) Nephroblastoma (Wilms tumor).
(5) As immunosuppressant, in thrombotic thrombocytopenic purpura (TTP).

ADVERSE EFFECTS

(1) CNS: Peripheral neuropathy (eg foot drop).
(2) GIT: Constipation.
(3) Body fluids: Hyponatremia.
(4) Skin: Alopecia.

PACLITAXEL

MECHANISM OF ACTION

(1) Paclitaxel binds to the β subunit of tubulin (the "building block" of microtubules), & the binding of paclitaxel locks these building blocks in place. The resulting microtubule/paclitaxel complex does not have the ability to disassemble. This adversely affects cell function because the shortening & lengthening of microtubules (termed dynamic instability) is necessary for their function as a mechanism to transport other cellular components.
(2) It also induces programmed cell death (apoptosis) in cancer cells by binding to an apoptosis stopping protein called Bcl-2 (B-cell leukemia 2) & thus arresting its function.

CLINICAL USES

(1) Ovarian cancer.
(2) Breast cancer.
(3) Lung cancer.
(4) Head & neck cancer.
(5) Kaposi's sarcoma.
(6) Restenosis (recurrent narrowing of coronary stents).
(7) In biological & biomedical research as a microtubule stabilizer.

ADVERSE EFFECTS

(1) CNS: Tingling in the hands or toes, dizziness.
(2) GIT: Nausea, vomiting, anorexia, change in taste, change in normal bowel habits.
(3) Resp: Cough, shortness of breath, chest pain.
(4) ENT: Sore throat, dysphagia.
(5) Temp: Fever, chills.
(6) Skin: Thinned or brittle hair, changes in nail color, skin rash, facial flushing.
(7) Joints: Pain in the joints of arms or legs.
(8) Local: Bruising, pain/redness/swelling at injection site.

GENERIC & TRADE NAMES

(1) Alkylating Agents

Cyclophosphamide: Cyclomide, Endoxan, Shandoxan.
Melphalan: Melpha.
Busulfan: Busulf.
Dacarbazine: Dacarbazine, Darbazine.
Cisplatin: Blastolem, Ceplatin, Cisplasol, Cisplatin, Cisplatino, Cisplatinum, Platidiam, Lachema, Platimit, Platinil, Platosin, Unistin.
Carboplatin: Carboplatin, Carbotinol, Carpsol, Cycloplatin, Neoplatine, Pharmaplatin.
Oxaliplatin: Oxaltie.
Procarbazine: Natulan, P-carbazine.
Ifosfamide: Holoxan.

(2) Antimetabolites

Methotrexate: Cytotrexate, Emthexate, Methotrexat lachema, Methotrexate, Metotrexato gador, MTX, Pharmatrexate, Unitrexate.
Thioguanine: Thioguanine.
Fludarabine: Fludara.
Fluorouracil: Pharmauracil.
Capecitabine: Xeloda.
Cytarabine: Alexan, Cytocin.
Gemcitabine: Gemzar.

(3) Plant Alkaloids

Vinblastine: Velbe, Vinblas.
Vincristine: Oncovin, Pharmacristine, Vincristina Gador, Vincritine, Vinracine.
Vinorelbine: Navelbine.
Etoposide: Etoposide, Etopul, Oncoside, Toposide, Vepesid.
Paclitaxel: Anzafax, Ebetaxel, Taxol, Unitaxel.
Docetaxel: Donataxel, Taxotere.

(4) Anticancer Antibiotics

Daunorubicin: Donobin.
Doxorubicin Adriblastina, D-Rubicin, Deldoxin, Doxobin, Doxolem, Doxorubicin, Doxorubin, Rubicin.
Idarubicin: Zavedos.
Epirubicin: Epirubicin.
Bleomycin: Bleomycin.
Dactinomycin: Cosmegen.

(5) Hormonal Agents

See chapter 17, unit V.

(6) Miscellaneous Agents

Imatinib: Glivec.

Unit II

Self - Assessment (T/F)

(See answers on page no 241)

(170) ***Concerning mechanism of action of anticancer drugs, all of the following statements are correct***

(A) Alkylating agents commonly attack nucleophilic N-7 position in guanine.

(B) Fluorouracil can cause thymineless death of cancer cells.

(C) Mercaptopurine is an irreversible inhibitor of HGPRTase.

(D) Lomustine causes alkylation of DNA that results in inhibition of DNA replication.

(E) Methotrexate competitively inhibits dihydrofolate reductase.

(171) ***Characteristic adverse effects of anticancer drugs include***

(A) Hemorrhagic cystitis with cyclophosphamide.

(B) Myelosuppression with methotrexate.

(C) Hepatic necrosis with mercaptopurine.

(D) Alopecia with nitrogen mustards.

(E) *CNS toxicity with lomustine.*

24 VITAMINS & MINERALS

VITAMINS

VITAMIN A

Mechanism of Action

(1) Provides prosthetic group for photosensitive pigment "rhodopsin" (essential for dark vision).
(2) Concerned with growth & differentiation of epithelia.
(3) Plays a role in synthesis of adrenal steroids.

Clinical Uses

(1) Prophylaxis & treatment of deficiency diseases of vit. A;
  (a) Hyperkeratosis.
  (b) Night blindness (Nyctalopia).
  (c) Xerophthalmia, Bitot spots, & keratomalacia.
  (d) Respiratory tract infections.
  (e) Squamous metaplasia of epithelium of renal pelvis, ureters, & urinary bladder.
  (f) Urinary calculi.
(2) Impaired absorption of vit. A, eg in steatorrhea & biliary tract obstruction.
(3) During infancy, pregnancy, & lactation.
(4) Certain skin diseases, eg keratosis follicularis.

Adverse Effects

Hypervitaminosis A

Chronic ingestion of 25,000 to 500,000 IU daily causes chronic vit. A toxicity or hypervitaminosis A. It is manifested by;

(1) Painful tender swellings over bones.
(2) Anorexia.
(3) Hepatosplenomegaly, & lymphadenopathy.
(4) General malaise.
(5) Skin lesions.
(6) Inc. liability of biological membranes & outer layer of skin, to peel off.

Dosage

(1) Men: 5000 IU/day.
(2) Women: Normally 4000 IU/day; during pregnancy & lactation 6000 IU/day.

VITAMIN B_1 (THIAMIN)

Mechanism of Action

Thiamin pyrophosphate (TPP) is a co-enzyme for "carboxylase", & is required for carbohydrate metabolism.

Clinical Uses

(1) Beriberi.
(2) Alcoholic neuritis.
(3) Wernicke- Korsakoff syndrome.
(4) Herpes zoster & neuralgias.
(5) Diabetes mellitus.
(6) Severe mental & physical work.

Adverse effects

Rare; occasionally allergic reactions.

Dosage

100-300 mg orally, SC or IM.

VITAMIN B_2 (RIBOFLAVIN)

Mechanism of Action

It forms co-enzymes flavin adenine dinucleotide (FAD) & flavin mononucleotide (FMN); which act as hydrogen carriers.

Clinical Uses

Ariboflavinosis (consisting of angular stomatitis, cheilosis, glossitis, seborrheic dermatitis, & corneal vascularization, photophobia & lacrimation).

Dosage

2-10 mg/day orally, SC or IM.

NICOTINAMIDE & NICOTINIC ACID

Mechanism of Action

It forms co-enzymes nicotinamide adenine dinucleotide (NAD), & nicotinamide adenine dinucleotide phosphate (NADP); which act as hydrogen carriers.

Clinical Uses

(1) Pellagra.
(2) Meniere's disease.

Adverse Effects

Nicotinic acid (which is converted to nicotinamide) causes:

(1) CVS: Peripheral vasodilation, unpleasant flushing, fainting
(2) Skin: Itching.

Dosage

(1) 100 mg 5 times/day orally.
(2) 20 mg 2-3 times/day IV.

VITAMIN B_6 (PYRIDOXINE)

Mechanism of Action

It forms co-enzyme 'pyridoxal-5-phosphate', that catabolize a number of reactions in amino acids metabolism.

Clinical Uses

(1) Vomiting of pregnancy.
(2) In combination with isoniazid to prevent peripheral neuritis.
(3) Agranulocytosis & anemia.
(4) Seborrheic dermatitis.

(5) Radiation sickness.
(6) With oral contraceptives (b/c the latter lowers its serum level).

Dosage
25 - 100 mg orally, IM or IV.

VITAMIN C (ASCORBIC ACID)

Mechanism of Action
(1) Acts as a powerful reducing or anti -oxidant agent, eg it prevent oxidation of epinephrine in adrenal medulla.
(2) Partakes in collagen biosynthesis.
(3) Partakes in tyrosine metabolism.
(4) Converts folic acid to folinic acid.

Clinical Uses
(1) Prevention & treatment of scurvy.
(2) Urinary acidification.
(3) Methemoglobinemia (as a reducing agent).
(4) Severe infections, dental caries, gum infections, anemia, & hemorrhagic states.

Adverse Effects
High doses cause sleep disturbances.

Dosage
0.5 -1 gm daily, orally.

VITAMIN D_3 (CHOLECALCIFEROL)

Mechanism of Action
Cholecalciferol is converted in liver to 25-hydroxycholecalciferol, & then in kidney to 1,25-dihydroxycholecalciferol under the influence of parathyroid hormone 2 1,25-dihydroxycholecalciferol causes;
(1) Inc. Ca^{++} & PO_4^- absorption from GIT & renal tubules.
(2) Inc. maturation & calcification of epiphyseal cartilages.

Clinical Uses
(1) Prophylaxis & treatment of rickets & osteomalacia.
(2) Hypoparathyroidism.
(3) Lupus vulgaris & tuberculosis of lymph nodes.

Adverse Effects
Hypervitaminosis D
Occurs due to excessive intake of vit. D, manifested by;
(1) CNS: Headache.
(2) GIT: Abdominal pain, vomiting, diarrhea.
(3) Kidney: Impairment of renal function.
(4) Others: Weakness, wt. loss.

Dosage
(1) 3000 - 4000 units/day.
(2) 600,000 units as a single dose IM.

VITAMIN E

Mechanism of Action
It is antioxidant, that prevents oxidation of essential cellular constituents or prevents formation of toxic oxidation products.

Clinical Uses
(1) Habitual abortion & sterility.
(2) Muscular dystrophies.
(3) Coronary & peripheral vascular diseases.
(4) Certain types of anemia.
(5) Liver cirrhosis.

Adverse Effects
Overdose causes;
(1) CNS: Headache.
(2) Eye: Blurred vision.

Dosage
15 IU/day, orally.

VIT. B_{12}, FOLIC ACID, & VIT. K

See Chapter 10, 'Drugs Affecting Blood'.

GENERIC & TRADE NAMES

(1) Vitamin A: Adexolin*, Geloit AD*, Rovigon*, Sclerobion*, Seven Seas*.
(2) Vitamin B_1: Alinamin - F*, Benerva, Berin, Bevidox*, Thiamine.
(3) Vitamin B_2: Alinamin - F*, Bevidox*, Neurofort*.
(4) Nicotinic acid: Nicosur, Nicotinic acid.
(5) Vitamin B_6: Navidoxine*, Sclerobion*, Vita 6, Vit B_6 inj.
(6) Vitamin B_{12}, Folic acid, & Vitamin K: See Chapter 10.
(7) Vitamin B_1, B_6, & B_{12}: Cyanorin Forte, Cytamen Comp, Dilconeurine, Elkoneurin, Neurobedoxine*, Neurobion, Neurofort*, Neurovit, Novobion, Nuramine Forte, Tabrovit, Thiavit, Triovit, Trividox, Uneskobion, Vioneurine Forte, Vitrobion.
(5) Vitamin C: Ascorbon, Ascorlet, Ascorvit, Atcocee - 500, CaC 1000*, C-Cor, Cebon, Cecon, Cecovit, Celimo, Citrovit - C, Efferalgen*, Energy - C*, Redoxan, Semo - C, Vitacimin.
(6) Vitamin D: Adexolin*, Calcee D*, Calcico*, Calcidron*, Calci-Ostelin*, Calcium P*, Calcivit*, Caltrate*, Calvid*, De-calc*, Gelvit AD*, Ostocalcium*, Seven Seas*.
(7) Vitamin E: Bliss E, Ephynal, Evion, Rovigon*, Sclerobion*, Seven Seas*, Vit E.
(8) Multivitamins without minerals: ABDEC, ACE - BEX, Camovit L, Hexavit, Multibionta, Polyvit, Theraplex, Vi-Daylin, Vidaylin F.....
(9) Multivitamins with minerals: Becadexamin, Centrum, Dayalets, Genatosan, Nutrisan, Optilets-M, Panvitan-M, Polyvit-M, Stresstabs 600, Theragran-M, Unicap M, Vi-Daylin M.....

MINERALS

CALCIUM

Mechanism of Action
(1) Constituent of bone & teeth.
(2) Regulates nerve & muscle function.

Clinical Uses
(1) Rickets.
(2) Osteomalacia.
(3) Tetanus.

Adverse Effects

(1) CNS: Irritability.
(2) GIT: Nausea, vomiting, diarrhea.

Contraindications

Renal calculi.

Dosage

(1) For tetanus: 10-20 ml 10% sol. at rate of 2 ml/min IV.
(2) For rickets & osteomalacia: 500 -1000 mg/day.

Generic & Trade Names

CaC 1000*, Calcee*, Calcee - D*, Calcico*, Calcidron*, Calci-ostelin*, Calcium P*, Calcium Sandoz, Calcivit*, Caltrate*, Calvid*, De Calc*, Energy C*, Ossopan 800*, Ostocalcium*, Qalsan, Vitacal 1000 + C*, Upsa - C*.

IRON

See Chapter 10, 'Drugs Affecting Blood'.

25 DRUG INTERACTIONS

DRUG INTERACTIONS

It refers to alteration in pharmacological effects of a drug, due to concomitant administration of another drug.

Types

(1) Pharmacokinetic Drug Interactions

It is the alteration in plasma level for a given dose of a drug.

(2) Pharmacodynamic Drug Interactions

It is the alteration in pharmacological effects at a given plasma level of a drug.

PHARMACOKINETIC DRUG INTERACTIONS

INTERACTIONS AFFECTING DRUG ABSORPTION

(1) After Oral Administration

(a) Drug Binding

Cholestyramine binds drugs in GIT, decreasing their absorption, eg of acetaminophen, digitalis glycosides, thiazides, thyroid hormones.

(b) Drug Adsorption

Certain drugs with large surface areas, eg antacids, adsorbs drugs in GIT & dec. their absorption eg, of digoxin, iron, ketoconazole, quinolones, salicylates, tetracyclines.

(c) Alter GI Motility

(i) Antimuscarinics decreases GI motility 2 Inc. bioavailability of poor soluble drugs, & dec. bioavailability of drugs degraded in gut eg levodopa.

(ii) Metoclopramide inc. gastric emptying 2 Dec. absorption of drug that is absorbed in stomach, eg cimetidine.

(d) Absorption Blockade

(i) Phenytoin & oral contraceptives inhibit folic acid hydrolysis, & so its absorption.

(ii) Colchicine causes vit B_{12} malabsorption.

(e) Dietary Influence

(i) Presence of food in stomach decreases absorption of some drugs.

(ii) Fatty meal increases absorption of lipid-soluble drugs, eg griseofulvin.

(f) Alter Gastric pH

Weak acids, eg salicylates, are not absorbed well when gastric pH is inc. with antacids.

(g) Alter Gut Flora

Antimicrobials may potentiate oral anti-coagulant by dec. bacterial synthesis of vit K in large gut.

(2) After Parenteral Administration

(a) Concomitant SC or IM injection of a drug with epinephrine decreases its absorption (b/c epinephrine causes local vasoconstriction).

(b) Concomitant SC or IM injection of a drug with methacholine, increases its absorption (b/c of methacholine's local vasodilating effect).

INTERACTIONS AFFECTING DRUG DISTRIBUTION

(1) Competition for Plasma Protein Binding

Drugs compete for plasma protein binding sites 2 Inc. free conc. & effect of displaced drug, eg;

Phenylbutazone potentiates anticoagulant actions of warfarin.

(2) Displacement from Tissue Binding Sites

It inc. blood conc. & effect of displaced drug, eg of digoxin by concurrent quinidine therapy.

INTERACTIONS AFFECTING METABOLISM

(1) Induction or Inhibition of Microsomal Enzymes

(a) Induction

It results in accelerated metabolism of drugs.

Example of inducers: Barbiturates, carbamazepine, glutethimide, phenytoin, primidone, rifampin.

Example of drugs whose metabolism is increased: Ca^{+2} channel blockers, corticosteroids, cyclosporine, doxycycline, estrogens, phenothiazines, quinidine, theophylline.

(b) Inhibition

It results in decreased metabolism of drugs.

Example of inhibitors: Allopurinol, chloramphenicol, cimetidine, ciprofloxacin, clarithromycin, diltiazem, enoxacin, erythromycin, fluconazole, isoniazid, ketoconazole, metronidazole, miconazole, omeprazole, phenylbutazone, verapamil.

Example of drugs whose metabolism is decreased: Oral anticoagulants, azathioprine, mercaptopurine, carbamazepine, cyclosporine, phenytoin, sulfonylurea, benzodiazepines, lidocaine, quinidine, theophylline.

(2) Inhibition of Nonmicrosomal Enzymes

(a) MAO inhibitors dec. metabolism of various drugs, eg barbiturates, benzodiazepines, serotonin, norepinephrine.

(b) Xanthine oxidase inhibitors eg allopurinol results in accumulation of 6-mercaptupurine.

INTERACTIONS AFFECTING DRUG EXCRETION

(1) Competition for Transport System in Proximal Tubule

It results in dec. urinary elimination of competing drugs, eg;

(a) Probenecid blocks excretion of penicillin, indomethacin, cefazolin, & methotrexate.

(b) Aspirin blocks excretion of methotrexate.

(2) Changes in Urinary pH

(a) Drugs that alkalinize urine, eg acetazolamide or $NaHCO_3$, increases excretion of weak acids.

(b) Drugs that acidify urine, eg ammonium chloride, increases elimination of weak bases.

PHARMACODYNAMIC DRUG INTERACTIONS

(1) Drug interactions can occur at the level of drug receptors, eg;
H_2 - receptor antagonist cimetidine blocks action of histamine - like agonists, eg betazole.

(2) Drugs can dec. the effects of other drugs by acting via different cellular mechanisms, eg;
Acetylcholine & norepinephrine have opposing effects on heart rate.

(3) Drugs can inc. the effects of other drugs although they act via different cellular mechanisms, eg;
Ethanol increases CNS depression caused by opioids, or sedative - hypnotics.

(4) Effect of one drug can be influenced by changes in intracellular or extracellular environment that are caused by another drug, eg;
Diuretic-induced hypokalemia increases digitalis-induced cardiac toxicity.

(5) Chemical inactivation can occur systemically to reduce a drug's action, eg;
Protamine binds heparin, thereby neutralizing it.

26 ANTIDOTES

Antidotes: It refers to drugs that prevent absorption, inactivate, or antagonize the actions of poisons.

ANTIDOTE	POISONING	MECHANISM OF ACTION
Acetylcysteine	Paracetamol, Chloroform, Carbon tetrachloride	Replenish depleted glutathione stores
Acids	Alkalies	Buffer
Alkalies	Acids	Buffer
Atropine	Cholinesterase inhibitors eg, Organophosphorus insecticides	Blocks muscarinic cholinoceptors
Benztropine	Drug - causing movement disorders	Blocks muscarinic cholinoceptors
Benzyl-penicillin	Amatoxin (Amanita phalloides)	Displaces toxin from plasma albumin, & enhances urinary excretion
Bicarbonate, sodium	Membrane-depressant cardiotoxic drugs (tricyclic antidepressants, quinidine)	Provides a rapid increase in extracellular sodium that helps overcome sodium channel blockade.
Calcium edetate	Lead	Chelates lead ions
Calcium gluconate	Hydrofluoric acid, Fluorides	Binds or precipitates fluoride ions
Desferoxamine	Iron	Iron Chelates ferrous ions
Dicobalt edetate	Cyanide & derivatives eg, Acrylonitrile	Chelates to form non-toxic cobalti - & cobalto – cyanides
Digoxin-specific Antibody fragments (FAB)	Digitalis glycosides	Binds free glycoside in plasma, & complex excreted in urine
Dimercaprol (BAL)	Arsenic, Copper, Gold, Lead, Inorganic mercury	Chelates metal ions
Esmolol	Theophylline, caffeine, metaproterenol	Short acting β-blocker reverses β1-induced tachycardia & β2-induced vasodilation
Ethanol	Ethylene glycol, Methanol	Competitively inhibits alcohol & acetaldehyde dehydrogenases, preventing formation of toxic metabolites
Flumazenil	Benzodiazepines	Competes for benzodiazepine receptors
Fomepizole	Ethylene glycol, Methanol	More convenient & easier to use than ethanol
Glucagon	β - adrenoceptor antagonists	Bypasses blockade of β - adrenoceptor; stimulates cAMP formation with positive cardiac inotropic effect
Isoprenaline	β - adrenoceptor antagonists	Competes for β - adrenoceptors
Methionine	Paracetamol	Replenish depleted glutathione stores
Naloxone	Opioids	Competes for opioid receptors
Neostigmine	Antimuscarinic drugs, Tubocurarine	Inhibits acetylcholinesterase, causing acetylcholine to accumulate at cholinergic receptor sites

Oxygen	Carbon monoxide (CO)	Competitively displaces CO from binding sites on hemoglobin
Penicillamine	Copper, Gold, Lead, Zinc, Elemental mercury (vapor)	Chelates metal ions
Phenoxybenzamine	Hypertensive drugs eg, α - adrenoceptor agonists, with MAOI, clonidine, ergotamine	Competes for α - adrenoceptors (long - acting)
Phentolamine	As above	Competes for α - adrenoceptors (short- acting)
Phytonadione (vitamin K1)	Coumarin (warfarin) & Indandione anticoagulants	Replenishes vitamin K
Physostigmine	Antimuscarinic drugs	Inhibits acetylcholinesterase, causing acetylcholine to accumulate at cholinergic receptor sites
Pralidoxime	Cholinesterase inhibitors, eg Organophosphorus insecticides	Competitively reactivates cholinesterase
Propranolol	β - adrenoceptor agonists, Ephedrine, Theophylline, Thyroxine	Competes for β – adrenoceptors
Protamine	Heparin	Binds ionically to neutralize
Prussian blue (ferric ferrocyanide)	Thallium (in rodenticides)	Exchanges for thallium
Unithiol	Lead, Elemental & organic mercury	Chelates metal ions

27 COMPARATIVE PHARMACOLOGY

PHYSOSTIGMINE	NEOSTIGMINE
(1) Nature Natural alkaloid. **(2) Chemistry** (a) Carbamic acid ester of alcohol with tertiary ammonium group. (b) Yellow crystalline compound. **(3) Mechanism of Action** Reversible inhibitor of cholinesterase. **(4) Pharmacological Effects** No direct effect on nicotinic receptors. **(5) Pharmacokinetics** Well absorbed from GIT. **(6) Clinical Uses** (a) Used as antidote in atropine, phenothiazine & tricyclic antidepressant intoxication. (b) Used in glaucoma. (c) No such use. (d) No such use. **(7) Adverse Effects** Produces CNS toxicity b/c it is capable of penetration of lipid barrier.	**(1) Nature** Synthetic drug. **(2) Chemistry** (a) Also carbamic acid ester of alcohol but with quaternary ammonium group. (b) White crystalline compound. **(3) Mechanism of Action** Same. **(4) Pharmacological Effects** Has direct nicotinic agonist effect at neuromuscular junction. **(5) Pharmacokinetics** Not well absorbed from GIT. **(6) Clinical Uses** (a) No such use. (b) No such use. (c) Used as antidote in paralysis induced by non-depolarizing neuromuscular blockers. (d) Used in treatment of myasthenia gravis, paralytic ileus & atony of urinary bladder. **(7) Adverse Effects** Does not cross blood brain barrier, so no CNS toxicity.

TUBOCURARINE	SUXAMETHONIUM
(1) Chemistry (a) Quaternary alkaloid obtained from curare. (b) It is a rigid bulky molecule known as Pachycurare.	**(1) Chemistry** (a) Synthetic quaternary amine compound. (b) It has a molecule which is slender & flexible known as Leptocurare.
(2) Pharmacokinetics Metabolism is negligible, is excreted unchanged in urine.	**(2) Pharmacokinetics** Rapidly metabolized by pseudocholinesterase.
(3) Mechanism of Action (a) It has both affinity for receptor, but no intrinsic activity. (b) Competitively block nicotinic receptors at muscle endplate.	**(3) Mechanism of Action** (a) It has both affinity for receptor as well as intrinsic activity. (b) React with nicotinic receptors at muscle endplate leading to depolarization (Phase I), but with prolonged exposure flaccid paralysis occur due to reduction in receptor sensitivity (Phase II).
(4) Pharmacological Effects (a) No fasciculations are seen prior to paralysis. (b) Block autonomic ganglia. (c) No such effect. (d) Causes moderate inc. in histamine release. (e) No such effect. (f) No such effect. (g) No such effect.	**(4) Pharmacological Effects** (a) Fasciculations are seen esp. over chest & abdomen prior to onset of paralysis. (b) Stimulates autonomic ganglia. (c) Stimulates cardiac muscarinic receptors. (d) Causes slight inc. in histamine release. (e) Causes hyperkalemia. (f) Causes inc. in intraocular pressure. (g) Causes inc. in intragastric pressure.
(5) Effect on Paralysis (a) **Tubocurarine Administration** Additive. **(b) Suxamethonium Administration** Antagonistic. **(c) Effect of Cholinesterase Inhibitors** Antagonistic. **(d) Response to Tetanic Stimulation** Unsustained. **(e) Posttetanic Facilitation** Present. **(f) Effect of Procaine & Propanidid** No effect. **(g) Effect of Hypothermia** Additive. **(h) Effect of Diazepam** Antagonistic. **(i) No effect.** **(j) Myasthenia Gravis** Causes initial strengthening of muscle tone.	**(5) Effect on Paralysis** **(a) Tubocurarine Administration** Antagonistic in phase I, but augment phase II. **(b) Suxamethonium Administration** Additive in phase I, but augment phase II. **(c) Effect of Cholinesterase Inhibitors** Augment phase I, but antagonizes phase II. **(d) Response to Tetanic Stimulation** Sustained in phase I, but unsustained in phase II. **(e) Posttetanic Facilitation** Absent in phase I, but present in phase II. **(f) Effect of Procaine & Propanidid** Prolong paralysis, b/c they are also metabolized by pseudocholinesterase. **(g) Effect of Hypothermia** Antagonistic. **(h) Effect of Diazepam** Additive. **(i) Streptomycin, neomycin, local anesthetics, & quinidine has additive effects.** **(j) Myasthenia Gravis** Augments.

MORPHINE	CODEINE
(1) Chemistry Member of phenanthrene series of opium alkaloids.	**(1) Chemistry** Also a member of phenanthrene series of opium alkaloids.
(2) Mechanism of Action By mimicking actions of opiopeptins, it stimulates opioidreceptors causing inhibition of release of excitatory neurotransmitters.	**(2) Mechanism of Action** Same.
(3) Pharmacological Effects **(a) CNS** (i) Potent analgesic. (ii) Causes euphoria, & sedation. (iii) Causes respiratory depression. (iv) Causes cough suppression. (v) Causes miosis, truncal rigidity, & emesis. **(b) GIT** Causes constipation, & dec. gastric acid secretion. **(c) Biliary Tract** Constriction of biliary smooth muscle, & sphincter of oddi. **(d) Genitourinary Tract** (i) Dec. renal plasma flow. (ii) Inc. ureteral, bladder, & urethral sphincter tone. **(e) Uterus** Prolong labor by reducing uterine tone. **(f) Neuroendocrine** (i) Stimulate ADH, prolactin, & somatotropin release. (ii) Inhibit luteinizing hormone release.	**(3) Pharmacological Effects** **(a) CNS** (i) Analgesic potency is $1/12^{th}$ that of morphine. (ii) Less euphoriant, & sedative than morphine. (iii) Less resp. depression that morphine. (iv) More potent cough suppressant. (v) Same. **(b) GIT** Same, but only mild effect. **(c) Biliary Tract** Same. **(d) Genitourinary Tract** (i) Same. (ii) Same. **(e) Uterus** Causes less reduction of uterine tone. **(f) Neuroendocrine** (i) Same. (ii) Same.
(4) Clinical Uses (a) Relief of mild to severe visceral & somatic pains. (b) For relief of dyspnea in pulmonary edema. (c) Cough. (d) Diarrhea, & it is prefer over codeine. (e) As premedicant drugs before anesthesia & surgery.	**(4) Clinical Uses** (a) Relief of only milder pain. (b) No such use. (c) Cough, & it is prefer over morphine. (d) Diarrhea. (e) No such use.
(5) Adverse Effects (a) **CNS:** Inc. intracranial pressure, behavioral restlessness, tremor, hyperactivity. (b) **CVS:** Postural hypotension esp. in hypovolemia. (c) **GIT:** Nausea, vomiting, constipation. (d) **Renal:** Urinary retention. (e) **Skin:** Urticaria, itching. (f) Great addiction liability. (g) Severe withdrawal symptoms.	**(5) Adverse Effects** (a) **CNS:** Same but less effect on intracranial pressure. (b) **CVS:** Same but less intense. (c) **GIT:** Less effect than morphine. (d) **Renal:** Same. (e) **Skin:** Less so. (f) Addiction liability is less. (g) Less severe withdrawal symptoms.

CHLORPROMAZINE	MEPROBAMATE
(1) Chemistry Aliphatic phenothiazine. **(2) Drug Category** Anti - psychotic drug or major tranquilizers. **(3) Pharmacological Effects** **(a) CNS** (i) Produces neuroleptic effects consisting of emotional quieting & reduced physical movement. (ii) Produces extrapyramidal effects & parkinsonism. (iii) No such effect. (iv) Does not impair consciousness. (v) No such effect. (vi) Has antiemetic effect due to direct depression of medullary vomiting centre. **(b) Anesthetic Property** Has local anesthetic effect. **(c) ANS** (i) Has alpha-adrenergic blocking activity causing hypotension. (ii) Has anticholinergic effect. (iii) Has ganglionic blocking activity. **(d) CVS** (i) Has quinidine like antiarrhythmic effect. (ii) Causes hypotension. **(e) Endo** (i) Inhibit ADH secretion. (ii) Stimulate release of lactogenic hormone causing lactation, galactorrhea, & gynecomastia. **(f) Temp** Normally produces hypothermia, but in hot climate causes hyperthermia. **(g) Autacoids** Has antihistamine & anti-tryptamine effects. **(4) Clinical Uses** Used in psychotic disorders, in treatment of nausea & vomiting, & as antipruritics. **(5) Adverse Effects** (a) **CNS:** Parkinsonism, acute dystonic reactions, tardive dyskinesia, lethargy, drowsiness. (b) **CVS:** Orthostatic hypotension, reflex tachycardia. (c) **Allergic reactions:** Cholestatic jaundice, dermatitis, photosensitivity. (d) **Blood:** Agranulocytosis, eosinophilia.	**(1) Chemistry** Propyl alcohol derivative (propanediol carbamate). **(2) Drug Category** Anti - anxiety drug or minor tranquilizers. **(3) Pharmacological Effects** **(a) CNS** (i) No such effect but it is useful in pt. suffering from anxiety, worry & tension. (ii) No such effects. (iii) Has anticonvulsant property. (iv) Produces hypnosis. (v) Central muscle relaxant effect thru inhibitionof interneurons in polysynaptic reflex pathways. (vi) No such effect. **(b) Anesthetic Property** No such effect. **(c) ANS** (i) No such effect. (ii) No such effect. (iii) No such effect. **(d) CVS** (i) No such effect. (ii) No such effect. **(e) Endo** (i) No such effect. (ii) No such effect. **(f) Temp** No such effect. **(g) Autacoids** No such effect. **(4) Clinical Uses** Used in anxiety, insomnia, & skeletal muscle spasms. **(5) Adverse Effects** (a) **CNS:** Drowsiness, ataxia. (b) **CVS:** No effect. (c) **Allergic reactions:** Urticaria, skin rashes, pruritus. (d) **Blood:** Thrombocytopenia, leukopenia.

COCAINE	PROCAINE
(1) Chemistry Ester of benzoic acid.	**(1) Chemistry** Ester of diethylaminoethanol & para-aminobenzoic acid.
(2) Mechanism of Action Block Na channels, causing inc. threshold for excitation slow impulse conduction, declining of rate of rise of action potential, dec. action potential amplitude, & finally abolished ability to generate action potential.	**(2) Mechanism of Action** Same mechanism.
(3) Pharmacological Effects **(a) Peripheral Nerves** Causes differential nerve block. **(b) Neuromuscular Junction** Slows or block impulse transmission. **(c) CNS** Initially produces euphoria & some times dysphoria, followed by post-stimulatory depression. **(d) CVS** (i) Depress abnormal cardiac pacemaker activity, excitability, & conduction. (ii) Causes tachycardia, & vasoconstriction. **(e) Eye** Causes mydriasis. **(f) ANS** Blocks uptake of catecholamines at adrenergic nerve terminals. (g) No such effect. (h) Can be used topically. (i) It has double the potency of procaine. (j) Has intermediate duration of action.	**(3) Pharmacological Effects** **(a) Peripheral Nerves** Also causes differential nerve block. **(b) Neuromuscular Junction** Same effect. **(c) CNS** Same effect. **(d) CVS** (i) Same effect. (ii) Depresses myocardial contractility & causes arteriolar dilatation. **(e) Eye** No effect. **(f) ANS** Prevent release of acetylcholine from motor nerve endings. (g) Antagonizes action of sulfonamides thru its hydrolysis to para-aminobenzoic acid. (h) It lacks topical activity. (i) It has potency half that of cocaine. (j) Has short duration of action.
(4) Pharmacokinetics Degraded by pseudo-cholinesterases.	**(4) Pharmacokinetics** Degraded by pseudo-cholinesterases.
(5) Clinical Uses For topical anesthesia of nose, pharynx, & tracheobronchial tree.	**(5) Clinical Uses** For nerve block, infiltration, & spinal anesthesia.
(6) Adverse Effects (a) **CNS:** Euphoria, sleepiness, lightheadedness, nystagmus, shivering, visual & auditory disturbances, convulsions, depression. (b) **CVS:** No significant effect. (c) **Temp:** Hyperpyrexia. (d) **Allergic reactions**	**(6) Adverse Effects** (a) **CNS:** Same effects. (b) **CVS:** Hypotension, collapse. (c) **Temp:** No effect. (d) **Allergic reactions**

GUANETHIDINE	RESERPINE
(1) Occurrence Synthetic compound.	**(1) Occurrence** Natural alkaloid derived from Rauwolfia compound.
(2) Pharmacokinetics (a) Absorption from GIT is low & variable (3% to 30%). (b) Given orally. (c) Metabolized by hepatic enzymes.	**(2) Pharmacokinetics** (a) Well absorbed from GIT. (b) Given orally or parenterally. (c) Metabolism involves hydrolysis of ester linkage, & demethylation.
(3) Mechanism of Action It is taken up & stored in adrenergic nerve terminals, where it acts (presynaptically) to inhibit release of norepinephrine, thus reducing response to sympathetic nerve activation.	**(3) Mechanism of Action** It blocks ability of adrenergic transmitter vesicles to take up & store biogenic amines 2 This results in depletion of norepinephrine, dopamine & serotonin in both central & peripheral neurons.
(4) Pharmacological Effects (a) Initially, it displaces & releases enough unchanged norepinephrine to cause mild, transient hypertension & cardiac stimulation. (b) Hypotension & bradycardia follows. (c) Depresses vasoconstrictor reflexes, so postural hypotension is marked. (d) No such effect. (e) Has a direct inhibitory effect on skeletal muscle contraction. (f) Inc. sensitivity of tissues to catecholamines (g) No central actions, as it does not cross blood brain barrier.	**(4) Pharmacological Effects** (a) No initial hypertension & cardiac stimulation. (b) Hypotension & bradycardia occur as initial effects. (c) Only partially inhibits cardiovascular reflexes, so less postural hypotension. (d) Has direct vasodilating effect on vascular smooth muscle when administered intra-arterially. (e) No such effect. (f) Not so. (g) It exerts central actions that produce sedation.
(5) Clinical Uses Moderate to severe hypertension.	**(5) Clinical Uses** Moderate hypertension.
(6) Adverse Effects (a) **CNS:** No effects. (b) **CVS:** Postural & exercise-induced hypotension, hypertensive crises in pheochromocytoma. (c) **GIT:** Diarrhea. (d) **Skeletal muscles:** Ache & weakness. (e) **Repro:** No effect. (f) Tolerance occurs.	**(6) Adverse Effects** (a) **CNS:** Sedation, lassitude, nightmares, depression, extrapyramidal signs. (b) **CVS:** Hypotension, bradycardia, nasal congestion. (c) **GIT:** Diarrhea, abd. cramps, inc. gastric acid secretion. (d) **Skeletal muscles:** No effect. (e) **Repro:** Delayed or retrograde ejaculation. (f) No tolerance.

DIGOXIN	DIGITOXIN
(1) Chemistry A cardiac glycoside, obtained from dried leaves of Digitalis lanata & from seeds of strophanthus gratus.	**(1) Chemistry** A cardiac glycoside, obtained from dried leaves of Digitalis purpurea & Digitalis lanata, & from seeds of strophanthus gratus.
(2) Pharmacokinetics (a) Variable intestinal absorption (40% - 70%). (b) Less than 30% bound to plasma proteins. (c) Plasma half life is 36 hrs. (d) Principal metabolic route is kidney. (e) Has moderate lipid solubility. (f) Volume of distribution is 6.3 L / Kg. (g) Therapeutic plasma conc. is 0.5-2 ng /ml. (h) Toxic plasma conc. is greater than 2 ng /ml. (i) Rapid digitalizing dose is 0.5-0.75 mg every 8 hrs, for 3 doses. (j) Daily maintenance dose is 0.125-0.5 mg. (k) Time to peak effect is 3-6 hrs.	**(2) Pharmacokinetics** (a) Well absorbed from GIT (90% - 100%). (b) About 97% bound to plasma albumin. (c) Plasma half life is 5-7 days. (d) Principal metabolic route is liver. (e) Has high lipid solubility. (f) Volume of distribution is 0.6 L / Kg. (g) Therapeutic plasma conc. is 10-25 ng /ml. (h) Toxic plasma conc. is greater than 35 ng /ml. (i) Rapid digitalizing dose is 0.2-0.4 mg every 12 hrs, for 3 doses. (j) Daily maintenance dose is 0.05-0.2 mg. (k) Time to peak effect is 6-12 hrs.
(3) Pharmacological Effects **(a) Cardiac Effects** (i) Inc. myocardial contractility. (ii) Prolong refractory period & dec. conduction velocity of AV-node. (iii) Dec. atrial & ventricular refractory periods. (iv) Inc. abnormal automaticity in ventricles & Purkinje system. (v) Bradycardia in pts with CCF. (vi) Prolong P-R interval. (vii) ST depression, & T wave inversion. **(b) Extracardiac Effects** (i) In CCF, reduces peripheral vascular resistance & venomotor tone. (ii) Systolic BP inc., but diastolic BP falls.	**(3) Pharmacological Effects** **(a) Cardiac Effects** (i) Same effect. (ii) Same effects. (iii) Same effects. (iv) Same effects. (v) Same effects. (vi) Same effect. (vii) Same effects. **(b) Extracardiac Effects** (i) Same effects. (ii) Same effects.
(4) Clinical Uses (a) Congestive cardiac failure. (b) Atrial flutter & fibrillation, paroxysmal supraventricular tachycardia.	**(4) Clinical Uses** (a) Same use. (b) Same uses.
(5) Adverse Effects (a) **CNS:** Headache, fatigue, neuralgia, delirium, visual impairment. (b) **CVS:** Premature ventricular beats, ventricular tachycardia & fibrillation, AV block, SA block, sinus arrhythmia, atrial tachycardia. (c) **GIT:** Anorexia, nausea, vomiting.	**(5) Adverse Effects** (a) **CNS:** Same effects. (b) **CVS:** Same effects. (c) **GIT:** Same effects.

ACTH	CORTICOSTEROIDS
(1) Chemistry (a) Human ACTH is a polypeptide hormone consisting of 39 amino acids. (b) Synthetic preparations are available.	**(1) Chemistry** (a) Steroid compounds, composed of a cyclopentano-perhydrophenanthrene ring. (b) Same.
(2) Pharmacokinetics (a) Being a polypeptide, it is not administered orally. (b) Given only parenterally.	**(2) Pharmacokinetics** (a) Readily absorbed from GIT. (b) Can be given parenterally.
(3) Mechanism of Action Stimulate specific protein receptor sites on adrenal cortical cell memb. 2 cAMP system is activated & synthesis of corticosteroids is initiated.	**(3) Mechanism of Action** Traverses target cell memb. & binds to nuclear receptor forming a complex which then binds to chromatin 2 mRNA formation is stimulated which stimulates synthesis of various enzymes.
(4) Pharmacological Effects (a) Stimulates growth of adrenal cortex, & secretion of corticosteroids (mainly glucocorticoids). (b) Administration of exogenous ACTH inhibits release of endogenous pituitary ACTH, but has stimulatory effect on adrenal cortex. (c) Has some melanotropic activity. **(d) Carbohydrate Metabolism** Effects (same) are mediated thru glucocorticoids release. **(e) Protein Metabolism** Effect (same) are mediated thru glucocorticoids release. **(f) Fat Metabolism** Effects (same) are mediated thru glucocorticoids release. **(g) Water & Electrolyte Metabolism** Effects (same) are mediated thru corticosteroids release. **(h) Inflammation** Effects (same) are mediated thru glucocorticoids release.	**(4) Pharmacological Effects** (a) Inhibit ACTH secretion by feed-back inhibition, leading to inhibition & atrophy of adrenal cortex. (b) Administration of exogenous corticosteroids inhibits release of both endogenous ACTH & corticosteroids. (c) No such effect. **(d) Carbohydrate Metabolism** Inc. gluconeogenesis, dec. peripheral carbohydrate utilization, & promote glycogen storage in liver. **(e) Protein Metabolism** Inhibit protein synthesis, & inc. protein catabolism. **(f) Fat Metabolism** Inc. lipolysis, & cause characteristic fat deposition in neck & supraclavicular area (buffalo hump) & in face (moon face) & trunk. **(g) Water & Electrolyte Metabolism** Causes sodium retention, & inc. potassium excretion. **(h) Inflammation** Has anti-inflammatory & antiallergic effects resulting from inhibition of PG & leukotriene synthesis.
(5) Clinical Uses For diagnosis of Addison's disease, & secondary adrenal insufficiency.	**(5) Clinical Uses** As replacement therapy in adrenal insufficiency, & in management of rheumatoid arthritis & other inflammatory disorders.
(6) Adverse Effects (a) Suppression of pituitary function. (b) Inc. susceptibility to infection. (c) Peptic ulceration. (d) Less myopathy. (e) Less osteoporosis. (f) Hyperglycemia. (g) Psychological disturbances. (h) Allergic reactions	**(6) Adverse Effects** (a) Suppression of pituitary-adrenal function. (b) Same. (c) Same. (d) Myopathy characterized by proximal arm & leg weakness. (e) More osteoporosis. (f) Hyperglycemia. (g) Same. (h) Not so.

HALOTHANE	ETHER
(1) Chemistry (a) Colorless volatile liquid with chloroform like odor. (b) Non-inflammable, & non-explosive. (c) Boiling point is 50°C.	**(1) Chemistry** (a) Colorless volatile liquid with a pungent irritant odor. (b) Inflammable & explosive. (c) Boiling point is 35°C.
(2) Mechanism of Action Inc. threshold of cells to firing, resulting in dec. activity & also reduce rate of rise of action potential by blocking Na channels.	**(2) Mechanism of Action** Same mechanism.
(3) Pharmacological Effects **(a) CNS** (i) Potent general anesthetic with rapid induction, & rapid recovery. (ii) Dilate cerebral blood vessels resulting in inc. blood flow & CSF pressure. (iii) Causes shivering during recovery. **(b) CVS** (i) Dec. arterial BP. (ii) Depressed myocardial contractility. (iii) Bradycardia. (iv) Dilation of cutaneous blood vessels causing flushing. (v) Interferes with norepinephrine action, & thus antagonizes sympathetic response to arterial hypotension. (vi) Inc. automaticity of heart. **(c) Respiratory System** (i) Rapid & shallow respiration. (ii) Causes a reduction in ventilatory response to CO_2. (iii) Produces bronchiolar dilatation. **(d) Renal** (i) Dec. renal blood flow & glomerular filtration rate. (ii) No such effect. **(e) Hepatic** Causes halothane hepatitis. **(f) Skeletal Muscle** Causes relaxation by both central & peripheral mechanisms. **(g) Uterus** Relaxes uterine smooth muscle.	**(3) Pharmacological Effects** **(a) CNS** (i) Potent general anesthetic with slow induction, & delayed recovery. (ii) Same effect. (iii) No such effect. **(b) CVS** (i) BP maintained b/c of sympathetic activation. (ii) Myocardial contractility remains near normal. (iii) Tachycardia. (iv) Same effect. (v) No such effect. (vi) No such effect. **(c) Respiratory System** (i) Also rapid & shallow respiration. (ii) Ventilatory response to CO_2, although reduced, is maintained spontaneously by reflex excitation at peripheral sites. (iii) Same effect. **(d) Renal** (i) Same effect. (ii) Dec. urinary output as it is a strong stimulant of ADH. **(e) Hepatic** Liver functions are only minimally depressed. **(f) Skeletal Muscle** Same effect, but it is more effective relaxant than halothane. **(g) Uterus** Same effect.
(4) Clinical Uses For general anesthesia.	**(4) Clinical Uses** For general anesthesia.
(5) Adverse Effects Hepatotoxicity, respiratory depression.	**(5) Adverse Effects** Inc. salivary secretion, vomiting, laryngospasm

OPIOID (NARCOTIC) ANALGESICS	NONOPIOID (NON-NARCOTIC) ANALGESICS
(1) Site of Analgesic Action Both cortical, & subcortical (thalamus). **(2) Type of Pain Relieved** Adequate doses can relieve any type of pain (except itching). **(3) Relief of Pain Accompanied By** Euphoria, stupor, or drowsiness. **(4) Addiction** Addictive. **(5) Inflammatory Reaction** No effect.	**(1) Site of Analgesic Action** Subcortical on thalamus. **(2) Type of Pain Relieved** Low intensity pain eg, headache, neuralgia, myalgia, arthralgia, dysmenorrhea. **(3) Relief of Pain Accompanied By** No euphoria, or drowsiness. **(4) Addiction** Non-addictive. **(5) Inflammatory Reaction** Has peripheral anti-inflammatory effects which may contribute to relief of pain (except aniline derivatives).

CODEINE	ASPIRIN
(1) Chemistry Phenanthrene derivative of opium alkaloid. **(2) Pharmacological Effects** (a) Powerful analgesic. (b) Not so. (c) Not so. (d) Has hypnotic effects, & causes drowsiness, clouding of thoughts, euphoria, reduced mental activity & inc. in reaction time. (e) No such effect. (f) No such effect. (g) Respiratory depressant thru depression of medullary respiratory centre. (h) Causes vasodilation, & postural hypotension. (i) No such effect (j) Stimulates chemoreceptor trigger zone, causing nausea & vomiting. (k) No such effect (l) Produces miosis by stimulating Edinger-Westphal nucleus. (m) Potent cough suppressant. **(3) Clinical Uses** (a) Relieving visceral & somatic pains. (b) No such use. (c) No such use. (d) Useful in diarrhea due to spasmogenic activity. (e) For suppressing cough. (f) No such use. **(4) Adverse Effects** (a) No such effect. (b) High doses cause respiratory acidosis, & respiratory failure. (c) Tolerance & addiction with chronic use. (d) Retention of urine. (e) Causes respiratory failure, biliary colic, constipation, prolonged labor, pruritus, sweating, & pin point pupil.	**(1) Chemistry** Acetylsalicylic acid, a synthetic substance. **(2) Pharmacological Effects** (a) Weak analgesic. (b) Anti-inflammatory. (c) Anti-pyretic. (d) No such effects. (e) Inhibits biosynthesis of prostaglandins. (f) Inhibits hyaluronidase activity. (g) Respiratory stimulant, acting directly by increasing amount of CO_2 peripherally. (h) No significant effect. (i) Inc. clotting & prothrombin time. (j) Also stimulates chemoreceptor trigger zone. (k) Inc. gastric acid secretion. (l) No such effect. (m) Not so. **(3) Clinical Uses** (a) Relieving mild & superficial pain eg, headache. (b) Relieving pain of dysmenorrhea. (c) Used in rheumatoid arthritis & acute rheumatic fever. (d) No such use. (e) No such use. (f) Used in gout due to its uricosuric effect. **(4) Adverse Effects** (a) Gastric ulceration & hemorrhage. (b) High doses cause respiratory alkalosis. (c) No such effects. (d) No such effect. (e) Causes salicylism characterized by headache, confusion, drowsiness, tinnitus, difficulty in hearing, thirst & diarrhea.

QUINIDINE	DIGITALIS
(1) Chemistry An alkaloid isolated from cinchona bark.	**(1) Chemistry** Obtained from dried leaves of foxglove, Digitalis purpurea & from seeds of Strophanthus gratus.
(2) Pharmacokinetics Well absorbed from GIT, & is usually given orally.	**(2) Pharmacokinetics** Absorption from GIT varies (70%-100%) & is given orally or parenterally.
(3) Pharmacological Effects **(a) Cardiac Effects** (i) Depresses myocardial contractility by direct myocardial depression & indirect anticholinergic effects. (ii) Prolong refractory period in AV-node, & dec. conduction velocity in AV-node. (iii) Dec. refractory period in Purkinje fibres. (iv) Dec. automaticity in ventricles. (v) Dec. heart rate. (vi) Inc. PR interval. (vii) Inc. Q-T interval. **(b) Extracardiac Effects** (i) Dec. peripheral vascular resistance due to a - receptor blockade. (ii) Not so, but instead hypotension occur. (iii) Not so. (iv) Has antimalarial, antipyretic, & oxytocic properties.	**(3) Pharmacological Effects** **(a) Cardiac Effects** (i) Inc. myocardial contractility by inhibiting Na+ - K+ - ATPase, & making more Ca++ available intracellularly. (ii) Prolong refractory period of AV-node, & dec. conduction velocity thru AV-node. (iii) Dec. ventricular refractory period. (iv) Inc. automaticity in ventricles. (v) Bradycardia in pts with CCF. (vi) Same. (vii) Dec. Q-T interval, with S-T depression. **(b) Extracardiac Effects** (i) In CCF, a reduction in peripheral vascular resistance & venomotor tone occurs. (ii) Systolic BP may inc. due to inc. stroke volume. (iii) Diastolic BP may fall due to improved circulation & dec. reflex vasoconstriction. (iv) No such properties.
(4) Clinical Uses (a) Atrial flutter & fibrillation, & paroxysmal supra-ventricular tachycardia. (b) No such use. (c) Ventricular arrhythmias.	**(4) Clinical Uses** (a) Same. (b) Congestive cardiac failure. (c) No such use.
(5) Adverse Effects (a) **CNS:** Cinchonism characterized by tinnitus, hearing loss, headache, diplopia, photophobia, confusion, psychosis. (b) **CVS:** Ventricular tachyarrhythmias, AV block, myocardial depression, quinidine syncope, inc. digitalis toxicity, hypotension. (c) **GIT:** Anorexia, nausea, vomiting, diarrhea. (d) **Blood:** Thrombocytopenia.	**(5) Adverse Effects** (a) **CNS:** Headache, fatigue, neuralgias, delirium, visual impairment. (b) **CVS:** Premature ventricular beats, ventricular tachycardia & fibrillation, AV block, SA block, sinus arrhythmia, atrial tachycardia. (c) **GIT:** Anorexia, nausea, vomiting. (d) **Blood:** No effect

ATROPINE	HYOSCINE (SCOPOLAMINE)
(1) Occurrence An alkaloid obtained from Atropa belladona.	**(1) Occurrence** Also an alkaloid obtained from Hyoscyamus niger.
(2) Chemistry An ester composed of tropic acid & organic base tropine.	**(2) Chemistry** Also an ester composed of tropic acid & organic base scopine.
(3) Mechanism of Action Competes reversibly with acetylcholine at muscarinic receptors.	**(3) Mechanism of Action** Same.
(4) Pharmacological Effects (a) Has more potent antimuscarinic effect on heart, bronchial muscles, & intestines. (b) Less potent in producing mydriasis, & cycloplegia. (c) Less potent in decreasing bronchial, salivary, & sweat gland secretions. (d) Has mild stimulant effect on medullary centres, & a slower longer lasting sedative effect. (e) Has longer duration of action. (f) Reduces tremor of Parkinson's disease.	**(4) Pharmacological Effects** (a) Less potent. (b) More potent. (c) More potent. (d) Has more marked sedative effects, producing drowsiness & amnesia. (e) Has shorter duration of action. (f) Same.
(5) Clinical Uses Not so.	**(5) Clinical Uses** Excellent for motion sickness.
(6) Adverse Effects CNS stimulant effect produces restlessness, insomnia, & excitement.	**(6) Adverse Effects** CNS depressant effect produces sedation, drowsiness, euphoria, amnesia, fatigue, & dreamless sleep.

EPINEPHRINE	NOREPINEPHRINE
(1) Chemistry Methylated norepinephrine. **(2) Mechanism of Action** Stimulate both alpha & beta receptors. **(3) Pharmacological Effects** **(a) Heart** (i) Tachycardia. (ii) Inc. force of contraction. (iii) Greatly inc. excitability & conductivity. (iv) Inc. cardiac output. **(b) Blood Vessels** (i) Skeletal muscle blood vessels are dilated. (ii) Skin & mucous memb. blood vessels are constricted. (iii) Coronary vessels are dilated. (iv) Total peripheral resistance is decreased. **(c) Blood Pressure** (i) Systolic BP rises. (ii) Diastolic BP falls. **(d) Smooth Muscle** (i) Bronchial smooth muscles relaxed. (ii) Intestinal smooth muscles relaxed. (iii) Uterine smooth muscle may be inhibited or stimulated, depending on menstrual phase or state of gestation. **(e) Metabolic Effects** (i) Inc. glucose & lactate production, via liver & muscle glycogenolysis. (ii) Inhibit insulin secretion causing hyperglycemia. (iii) Causes lipolysis resulting in inc. in free fatty acids. **(4) Clinical Uses** Used to treat bronchospasm, hypersensitivity reactions, anaphylaxis; to prolong the duration of infiltrative anesthesia; to restore cardiac activity in cardiac arrest; & to facilitate aqueous drainage in chronic open-angle glaucoma.	**(1) Chemistry** Hydroxylated dopamine. **(2) Mechanism of Action** Stimulate alpha & beta-1 receptors. **(3) Pharmacological Effects** **(a) Heart** (i) Reflex bradycardia due to vagal stimulation as BP rises. (ii) Same. (iii) Less inc. in excitability & conductivity. (iv) Dec. cardiac output or insignificant change. **(b) Blood Vessels** (i) Constricted. (ii) Same. (iii) Same. (iv) Increased. **(c) Blood Pressure** (i) Same. (ii) Rises. **(d) Smooth Muscle** (i) No effect. (ii) Same. (iii) Uterine smooth muscle is stimulated only. **(e) Metabolic Effects** (i) No such effects. (ii) Also inhibit insulin secretion & causes hyperglycemia. (iii) Also causes lipolysis resulting in inc. in free fatty acids. **(4) Clinical Uses** Used for treating hypotension during anesthesia when tissue perfusion is good.

ERGOTAMINE	ERGOMETRINE
(1) Chemistry (a) Lysergic acid derivative. (b) Amino acid alkaloid. (c) Sparingly soluble in water, & readily soluble in organic solvents.	**(1) Chemistry** (a) Also lysergic acid derivative. (b) Amine alkaloid. (c) Soluble in water & chloroform, but insoluble in alcohol.
(2) Pharmacokinetics Poorly & irregularly absorbed from GIT.	**(2) Pharmacokinetics** Completely absorbed from GIT.
(3) Pharmacological Effects (a) Onset of action is delayed even after parenteral inj. (b) Prolong duration of action. (c) Competitively block alpha adrenergic receptors. (d) Causes direct vasoconstriction of blood vessels leading to elevation of BP. (e) Has active oxytocic action, but of delayed onset. (f) Stimulates cardioinhibitory centre, & chemoreceptor trigger zone. (g) Depresses vasomotor centre, psychomotor activity, & respiratory centre.	**(3) Pharmacological Effects** (a) Onset of action is rapid. (b) Short duration of action. (c) No such effect. (d) Cause slight vasoconstriction. (e) Also has active oxytocic action, with rapid onset & short duration. (f) No such effect. (g) No such effect.
(4) Clinical Uses Migraine.	**(4) Clinical Uses** In obstetrics for the treatment & prevention of postpartum hemorrhage, & for helping involution of uterus.
(5) Adverse Effects May produce gangrene of finger & toes, & also convulsions.	**(5) Adverse Effects** May causes rupture of uterus.

MORPHINE	MEPERIDINE (PETHIDINE)
(1) Chemistry Phenanthrene derivative of opium alkaloid.	**(1) Chemistry** Phenylpiperidine derivative, a synthetic substance.
(2) Pharmacological Effects (a) Powerful analgesic. (b) Potent sedative. (c) Devoid of any local action. (d) Produces severe depression of respiratory centre. (e) Produces miosis due to stimulation of Edinger - Westphal nucleus. (f) Block intestinal propulsive peristalsis, & stomach motility. (g) Potent cough suppressant.	**(2) Pharmacological Effects** (a) Weak analgesic. (b) Weak sedative. (c) Produces mild local anesthesia. (d) Produces slight depression of respiratory centre. (e) Produces mydriasis due to weak atropine-like activity. (f) No such effect. (g) No such effect.
(3) Clinical Uses (a) Relieving both visceral & somatic pains. (b) Used as anti-tussive. (c) Useful in diarrhea.	**(3) Clinical Uses** (a) Relief of (only) visceral pains. (b) No such use. (c) No such use.
(4) Adverse Effects (a) More addiction liability. (b) More severe withdrawal effects. (c) More respiratory depression.	**(4) Adverse Effects** (a) Less addiction liability. (b) Less withdrawal effects. (c) Less respiratory depression.

HEPARIN	WARFARIN
(1) Occurrence (a) Naturally found in association with histamine in mast cells. (b) Commercially obtained from lungs of domestic animals.	**(1) Occurrence** (a) Naturally found in spoiled sweet clover. (b) Also prepared synthetically.
(2) Chemistry Mucopolysaccharide composed of sulfated D-glucosamine & D-glucoronic acid.	**(2) Chemistry** Bis-hydroxycoumarin.
(3) Pharmacokinetics (a) Not effective orally, & so must be given parenterally. (b) Not so. (c) Metabolize in liver by heparinase.	**(3) Pharmacokinetics** (a) Well absorbed orally. (b) 99% bound to plasma proteins. (c) Also metabolize in liver, & undergo enterohepatic circulation.
(4) Pharmacological Effects (a) Prolong clotting time both in vivo & in vitro. (b) Prevents fibrin formation in coagulation process by increasing activity of antithrombin III. (c) No such effect. (d) Produces a clearing effect on postprandial turbid lipemic plasma, by causing release of lipoprotein lipase. (e) Dec. aldosterone secretion & inc. conc. of free thyroxin. (f) Slows wound healing, & also depresses cell mediated immunity. (g) Onset of action is immediate after intravenous inj., & 30 - 60 min. after intramuscular inj. (h) Duration of action is short (2-4 hrs after IV inj).	**(4) Pharmacological Effects** (a) Prolong clotting time only in vivo. (b) No such effect. (c) Interfere with vit. K dependent synthesis of active coagulation factors II, VII, IX & X. (d) No such effect. (e) No such effect. (f) No such effect. (g) Onset of action is delayed, taking 1 - 2 days. (h) Duration of action is long (4 - 7 days).
(5) Adverse Effects (a) **GIT:** No effect. (b) **Blood:** Hemorrhages from any site, transient thrombocytopenia. (c) **Skin:** No effect. (d) Allergic reactions. (e) Transient alopecia.	**(5) Adverse Effects** (a) **GIT:** Anorexia, nausea, vomiting, diarrhea. (b) **Blood:** Hemorrhages from any site. (c) **Skin:** Urticaria, purpura, painful erythematous patch, purple-toe syndrome. (d) Not so. (e) Same.
(6) Antidotes Protamine sulfate, fresh blood transfusion, hexadimethrine (polybrene), toluidine blue.	**(6) Antidotes** Vitamin K_1 (phytonadione), fresh blood transfusion.
(7) Contraindications Hypersensitivity, bacterial endocarditis, TB, recent head trauma, recent major surgery.	**(7) Contraindications** Same.

28 PRACTICAL PHARMACOLOGY

Unit I

Pharmacy

DEFINITIONS

Pharmacy
It refers to the branch of health sciences that deals with preparation, dispensing, & proper utilization of drugs.

Materia Medica
It refers to the branch of health sciences that deals with drugs, their sources, preparations, & uses.

Pharmacopoeia
It is an authorative treatise on drugs & their preparations; a book containing a list of products used in medicine, with descriptions, chemical tests for determining identity & purity, & formulas for certain mixtures of these substances.

Examples
(1) British Pharmacopoeia (BP).
(2) United States pharmacopoeia (USP).

MEASUREMENT SYSTEMS

(A) Weight Measurement

(1) British (Imperial) System

(a) Avoirdupois Weight
(i) 1 Grain (gr) = 0.0366 Dram.
(ii) 1 Dram = 0.0625 Ounce (oz) = 27.34 gr.
(iii) 1 Ounce = 0.0625 Pound (lb) = 16 Dram = 437.5 gr.
(iv) 1 Pound = 16 oz = 256 Dram = 7000 gr.

(b) Apothecaries' Weight
(i) 1 Grain (gr) = 0.05 Scruple.
(ii) 1 Scruple = 0.333 Dram = 20 gr.
(ii) 1 Dram = 0.125 Ounce (oz) = 60 gr.
(iii) 1 Ounce = 0.0833 Pound (lb) = 8 Dram = 24 Scruple = 480 gr.
(iv) 1 Pound = 12 oz = 96 Dram = 288 Scruple = 5760 gr.

(2) Metric System
(a) 10^3 Microgram (μg) = 1 Milligram (mg).
(b) 10 mg = 1 Centigram (cg).
(c) 1000 mg = 100 cg = 10 Decigram = 1 Gram (gm).
(d) 1000 gm = 100 Decagram = 10 Hectogram = 1 Kilogram (Kg) = 0.001 Metric Ton.

(B) Capacity (Vol) Measurements

(1) British (Imperial) System
(a) 1 Minim = 1 drop = 0.0166 Fluid dram.
(b) 1 Fluid dram = 0.125 Fluid ounce = 60 minims.
(c) 1 Fluid ounce = 0.25 Gill = 0.0625 Pint = 480 minims.
(d) 1 Pint = 0.5 Quart = 0.125 Gallon = 16 Fluid ounces.
(e) 1 Gallon = 8 pint = 128 Fluid ounce.

(2) Metric System
(a) 10^3 Microliter (μl) = 1 Milliliter (ml).
(b) 10 ml = 1 Centiliter (cl).
(c) 1000 ml = 100 cl = 10 Deciliter = 1 liter (L).
(d) 1000 L = 100 Decaliter = 10 Hectoliter = 1 Kiloliter (Kl) = 0.001 Megaliter.

(C) Domestic Measures
(1) l Teaspoonful = 5 ml.
(2) l Desert spoonful = 10 ml.
(3) l Table spoonful = 15 ml.
(4) l Teacupful = 5 fluid oz.

(D) Conversion of Measures

(1) Weight Conversion
(a) l gram = 15 grains (Apothecaries).
(b) l kilogram = 2.68 pound (Apothecaries).
(c) l pound (Avoirdupois) = 453.59 grams.
(d) l ounce (Avoirdupois) = 28.35 grams.

(2) Volume Conversion
(a) 1 Minim = 0.06 milliliter.
(b) 1 Fluid dram = 3.70 milliliters.
(c) 1 Fluid ounce = 29.57 milliliters.
(d) 1 milliliter = 16.231 minims.

LOTION

Definition
It is a liquid suspension or dispersion (ie an aqueous sol. of an active drug) with alcohol or glycerine, for external application to the body.

Calamine Lotion

(1) BP Formula
(a) Calamine (Z n carbonate) = 150 gm.
(b) Zn oxide = 50 gm.

(c) Bentonite = 30 gm.
(d) Sodium citrate = 5 gm.
(e) Liquid phenol = 5 ml.
(f) Glycerine = 50 ml.
(g) Distilled water added upto 100 ml.

(2) Uses

(a) As mild astringent.
(b) To allay itching & burning.
(c) As antiseptic.

Viva Questions

(1) Astringent ?

These are substances which when applied to wet skin precipitates & coagulates the proteins of exudates, eg silver nitrate, zinc oxide, & alcohol.

(2) Purpose of adding alcohol or glycerine to lotion ?

(a) Alcohol, to accentuate the cooling effect of lotion.
(b) Glycerine, to maintain the surface to which lotion is applied in a moist condition.

LINIMENT

Definition

It is an oily liquid or semiliquid preparation in the form of emulsion, intended for application to skin with friction.

Official Liniments

(1) Liniment of turpentine.
(2) Liniment of camphor.

Liniment of Turpentine

(A) BP Formula

(1) Soft soap = 75 gm.
(2) Camphor = 50 gm.
(3) Turpentine oil = 650 ml.
(4) Water = 225 ml.

(B) Uses

(1) As counter-irritant for myalgia, neuralgia, sprains, pleurisy, pneumonia, & bronchitis.
(2) As rubefacient.

Viva Questions

(1) Counter-irritants ?

These are substances which when applied to the skin cause stimulation, followed by paralysis of sensory nerve endings (eg turpentine, camphor, menthol, mustard, capsicum).

(2) Rubefacients ?

These are substances that cause redness of skin by local vasodilation.

OINTMENT

Definition

It is a semi-solid preparation for topical applications, that usually contain a medicinal substance.

Base or Vehicle: It is a substance in which active ingredient is dispersed, eg paraffin, wax, fat.

BP Formula of Simple Ointment

(1) Wool fat = 50 gm.
(2) Hard paraffin = 50 gm.
(3) Alcohol = 50 gm.
(4) Soft paraffin = 850 gm.

Sulphur Ointment

(A) BP Formula

(1) Sulphur = 100 gm.
(2) Soft paraffin = 900 gm.

(B) Uses

(1) Scabies.
(2) Acne.
(3) Psoriasis.
(4) Chronic eczema.

Zinc Oxide Ointment

(A) BP Formula

(1) ZnO = 150 gm.
(2) Soft paraffin = 850 gm.

(B) Uses

As astringent & antiseptic in dry eczema, acne, & dermatitis.

Viva Questions

(1) Functions of base ?

(a) To produce stable ointment.
(b) To lubricate the skin.
(c) To reduce water evaporation from skin, thus to keep it moist.
(d) To protect skin from external moisture.
(e) To disperse the active ingredient.

(2) pH of an ointment ?

Should be neutral.

(3) Creams ?

These are semi-solid emulsions, either oil in water (eg vanishing cream) or water in oil (eg cold cream), intended for topical application.

(4) Scabies ?

It is an itching skin infection caused by a mite called sarcoptes scabiei.

SOLUTION

Definition

It is a liquid preparation containing one or more soluble chemical substances usually dissolved in water.

Types

(1) Simple solution: A solution prepared by dissolving solute in a suitable solvent eg, $Ca(OH)_2$.

(2) Compound solution: A solution prepared by reacting two or more solutes in a suitable solvent eg, Lugol's iodine sol.

% of Solution

Certain part of solute is dissolved in such a quantity of solvent that produces 100 parts of solution, eg 1% sol. means 1 gm of solute dissolved in 100 ml of water.

Lugol's Iodine

(A) BP Formula

(1) Iodine = 50 gm.
(2) KI = 100 gm.

(3) Water = 1000 ml.

(B) Uses

(1) Iodine deficiency goiter.
(2) Thyrotoxicosis (pre-operatively to make it euthyroid).

Viva Questions

(1) Solute ?

Substance which is dispersed in a continuous phase.

(2) Solvent ?

Medium in which dispersion takes place.

EMULSION

Definition

It is a preparation of two immiscible liquids one of which is dispersed as fine globules (dispersed phase liquid) thru-out the other (continuous phase liquid).

Types

(1) Oil in water: Oil is dispersed phase & water is continuous phase.
(2) Water in oil: Water is dispersed phase & oil is continuous phase.

Emulsifying Agents

These are substances which lower surface tension of one of the liquid which is thus divided into fine globules.

Classification

(A) Agents Producing Oil in Water Emulsion

(1) Polymeric carbohydrates: Gum acacia, sodium alginate, methyl cellulose, Irish mosh.
(2) Proteins: Gelatin, lecithin, soluble casein.
(3) Alkalies: Potassium hydroxide.
(4) Soaps: Soaps of long chain fatty acids eg, stearic acid.
(5) Cationic substances: Amines of quaternary ammonium compounds eg, cetrimide.
(6) Finely divided solids: Bentonite, kaolin.

(B) Agents Producing Water in Oil Emulsion

(1) Polyvalent soaps: Soaps of Ca, Mg, & Zn.
(2) Waxes: Bees wax, wool alcohol.
(3) Finely divided solids: Zinc oxide, talc.

Cod Liver Oil Emulsion

(A) BP Formula

Oil : Water : Gum = 4 : 2 : 1

(B) Uses

Vit. A & D deficiency diseases eg, osteomalacia, rickets, night blindness.

Viva Questions

(1) Properties of oil in water emulsion ?

(a) White in color.
(b) Non-greasy.
(c) Conducts electricity.

(2) Properties of water in oil emulsion ?

(a) Takes on color of oil.
(b) Greasy.
(c) Poor conductor.

POWDERS

Definition

These are solid medicines in finely divided form.

Types

(1) Simple powders: Contain one active ingredient eg, calomel powder.
(2) Compound powders: Contain more than one active ingredients eg, powder containing hyoscine hydro-bromide & pilocarpine nitrate.
(3) Systemic powders: For internal use in the form of tablets or capsules eg, antacids, antiemetics, purgatives, vitamins, antibiotics.
(4) Topical powders: For external use eg, dusting powders, snuff, tooth powders.

Viva Questions

(1) Dry lubricants ?

A type of dusting powder that reduces friction b/w two opposing skin surfaces eg, talc (hydrated Mg silicate).

(2) Drying agents ?

A type of dusting powder that absorb water & are used in moist skin lesions eg, starch, zinc oxide.

MIXTURE

Definition

It is a combination of different drugs as a fluid, resulting from mixing a fluid with other fluids or with solids, or a suspension of a solid in a liquid.

Carminative Mixture

(A) BP Formula

(1) $NaHCO_3$ = 0.6 gm
(2) Spirit aromatic ammonia = 0.6 ml
(3) Spirit chloroform = 0.3 ml
(4) Tinc. cardamon compound = 2 ml
(5) Aqua added upto 30 ml

(B) Uses

(1) As antiflatulent.
(2) In indigestion.

SUSPENSION

Definition

It is a preparation of finely divided drug intended to be suspended in some suitable liquid vehicle (eg water) before it is used, or already suspended in such a vehicle (eg gum, kaolin).

Example

Alumina & magnesia oral suspension.

PRESCRIPTION

Definition
It is a physician's written order to a pharmacist to dispense certain drugs in a particular form, including directions for its use.

Constituents
(1) Superscription: Consists of the symbol ℞ (recipe = take).
(2) Inscription: Body of prescription consisting the name & quantity of the drugs ordered.
(3) Subscription: Directions to the dispenser.
(4) Directions to the patient.
(5) Pt's name & age are written at the top.
(6) Signature: Dr's initial is in the end.

Abbreviations
(1) HS (Hora somni) = At bed time.
(2) QS (Quantum sufficient) = A sufficient quantity.
(3) ℞ (Recipe) = Take.
(4) SOS (Si opus sit) = If necessary.
(5) Mist (Mistura) = Mixture.
(6) ac (Anti cibus) = Before meal.
(7) pc (Post cibus) = After meal.
(8) CM (Cras mane) = Tomorrow morning.
(9) CN (Cras nocte) = Tomorrow night.
(10) OD (Omni die) = Once daily.
(11) BID or BD (Bis in die) = Twice daily.
(12) TID or TDS (Ter in die) = Thrice daily.
(13) QID (Quarter in die) = Four times a day.
(14) Stat (Statum) = Immediately.

Unit II

Pharmacodynamics

EXPERIMENT OF FROG'S LEG TO DIFFERENTIATE B/W SURFACE & INFILTRATION ANESTHETICS

Observations
(1) Check normal reflexes of frog by dipping both of its legs in hot water at 60°C 2 +ve withdrawal response in both legs.
(2) Dip right leg in lignocaine sol. & left leg in procaine for 5 minutes, & then dip both legs in hot water at 60°C 2 No response in right leg, & +ve withdrawal response in left leg.
(3) Inject 0.25 ml of procaine in left leg, & then dip both legs in hot water at 60°C ↕ No response in both legs.

Inference
Lignocaine is a surface anesthetic, whereas procaine is an infiltration anesthetic.

Viva Questions
(1) Surface anesthetics act on human leg ?
No, b/c they are unable to penetrate keratin layer present on human skin.

(2) Ethyl chloride act on human skin ?
Yes, b/c it is keratolytic.

(3) Local anesthetics given with epinephrine at base of finger or ear lobes ?
No, b/c epinephrine causes vasoconstriction that can lead to local ischemic necrosis.

(4) Sequence of loss of sensations ?
Touch 2 Pain 2 Temperature.

(5) Symptoms & signs of cocaine addiction ?
(a) CNS: Euphoria, tremors, hyperexcitability, convulsions.
(b) Eye: Dilated pupils.
(c) Cocaine bugs.
(d) Cocaine chills.

EXPERIMENT TO STUDY ANALEPTICS ON CNS OF FROG

Observations
(A) Frog A
Inj. 0.25 ml of strychnine sol. intraperitoneally;
(1) Prodromal phase: Rapid respiration, twitching, restlessness.
(2) Convulsion phase: Tonic, reflexed, & symmetrical convulsions.
(3) Effect of after pithing: Convulsions persist.

(B) Frog B
Inj. 0.5 ml of picrotoxin sol. intraperitoneally;
(1) Prodromal phase: Rapid respiration, twitching, restlessness.
(2) Convulsion phase: Clonic, non-reflexed, & asymmetrical convulsions.
(3) Effect of after pithing: Convulsions are abolished.

Inference
Strychnine is spinal stimulant, whereas picrotoxin is higher centre (medullary) stimulant.

Viva Questions
(1) Clonic convulsion ?
Contractions are intermittent ie muscle alternately contracts & relaxes, eg in epilepsy & eclampsia.

(2) Tonic (tetanic) convulsions ?
Muscle contraction is sustained, eg in strychnine poisoning & tetanus.

(3) Mechanism of action of picrotoxin ?
Antagonizes GABA (an inhibitory neurotransmitter) 2 Increased motor activity.

(4) Mechanism of action of strychnine ?
Reduces the inhibitory influence exerted by Renshaw cells in spinal cord 2 Increased motor activity.

(5) Level of pithing ?
B/w C_1 & C_2 of frog.

(6) Treatment of convulsions ?
(a) Diazepam IV.
(b) Clonazepam IV.
(c) Pentothal IV.

EXPERIMENT TO STUDY ACTIONS OF DRUGS ON A PIECE OF INTESTINE OF RABBIT

Observations

(A) Identification of Stimulants

(1) On stimulation by unknown drug, anti-histamine is put in the tissue tube 2 If the graph is reversed, then the unknown drug is histamine; if the graph is not reversed, then the unknown drug is cholinergic (acetylcholine) or $BaCl_2$.

(2) Second antagonist atropine is used 2 If graph is reversed, then unknown drug is cholinergic; if the graph is not reversed, the unknown drug is $BaCl_2$.

Note: $BaCl_2$ kills the tissue in stimulation.

(B) Identification of Depressant

On depression with an unknown drug, pilocarpine/ acetylcholine is put into the test tube 2

(1) An immediate rise in amplitude means that sites for cholinergic drugs are empty (ie unknown drug is not anticholinergic), & so, the unknown drug is an adrenergic drug, ie ephedrine.

(2) No immediate rise in amplitude means that sites for cholinergic drugs are occupied, then unknown drug is anticholinergic, ie atropine.

Viva Questions

(1) Classification of GIT stimulant ?

(a) Parasympathomimetics, eg acetylcholine, pilocarpine, muscarine.
(b) Sympatholytics, eg propranolol.
(c) Direct stimulants, eg histamine, $BaCl_2$.

(2) Classification of GIT depressants ?

(1) Parasympatholytics, eg atropine, scopolamine.
(2) Sympathomimetics, eg epinephrine, ephedrine.
(3) Direct depressants, eg papaverine, chloral hydrate.

(3) Composition of Tyrode solution ?

(a) Tyrode A
(i) NaCl = 160 gm.
(ii) KCl = 4 gm.
(iii) $CaCl_2$ = 4 gm.
(iv) $MgCl_2$ = 2 gm.
(v) Water = upto 1000 ml.

(b) Tyrode B
(i) $NaHCO_3$ = 20 gm.
(ii) Dextrose = 20 gm.
(iii) Na_2HPO_4 = 0.05 gm.
(iv) Water = upto 1000 ml.

(c) Final solution
Tyrode A 50 ml + Tyrode B 50 ml + 900 ml water.

(4) Significance of Tyrode Sol?

Tissue is kept alive & in working condition by providing proper ionic atmospheric, O_2 , & temp. of 37°C.

(5) Define tone & peristalsis?

(a) Tone is the tension present in resting muscle.
(b) Peristalsis is the movement of intestine in the form of a constrictive ring that moves analward.

EXPERIMENT TO STUDY DRUG'S EFFECTS ON RABBIT'S EYE

Observations

(A) Mydriatics

(1) Ephedrine & Epinephrine
(a) Pupil 2 Dilatation.
(b) Light reflex 2 Remain +ve.
(c) Conjunctival reflex 2 Remain +ve.
(d) Color of conjunctiva 2 Pale.

(2) Atropine
(a) Pupil 2 Dilatation.
(b) Light reflex 2 Become -ve.
(c) Conjunctival reflex 2 Remain +ve.
(d) Color of conjunctiva 2 Pink.

(3) Cocaine
(a) Pupil 2 Dilatation.
(b) Light reflex 2 Remain +ve.
(c) Conjunctival reflex 2 Become -ve.
(d) Color of conjunctiva 2 Pink.

(B) Miotics

Pilocarpine & Physostigmine
(a) Pupil 2 Constriction.
(b) Light reflex 2 Remain +ve.
(c) Conjunctival reflex 2 Remain +ve.
(d) Color of conjunctiva 2 Pink.

Viva Questions

(1) Mechanism of action of cocaine ?

It stimulates sympathetic nerve endings.

(2) Morphine causes miosis or mydriasis ?

Miosis by central action.

(3) Pupils during 2nd & 4th stages of general anesthesia?

(a) Pupils dilated with intact reflexes during 2nd stage.
(b) Pupils dilated with abolished reflexes during 4th stage.

(4) Why atropine's action is short in rabbit's eye ?

Because, rabbits eye produces enzyme atropinase that destroys atropine.

(5) Light reflex ?

If light is thrown on eye(s), then pupil(s) constrict.

(6) Consensual light reflex ?

If light is thrown on one eye, pupil of other eye constricts.

(7) Corneal reflex ?

If cornea is touched or irritated, eyelids are closed.

(8) Conjunctival reflex ?

If conjunctiva is touched or irritated, eyelids are closed.

29 TRUE / FALSE TYPE MCQs

(1) Nalorphine
T = (A) Dilate pupil in patients with morphine toxicity.
T = (B) Is almost inert at therapeutic doses in the absence of opioid agonists.
T = (C) Shows no tolerance.
F = (D) Depresses respiration in patients with acute opioid overdosage.
F = (E) Also shows partial agonist activity.

(2) Therapeutic causes of gynecomastia include
F = (A) Androgens.
T = (B) Estrogens.
T = (C) Cimetidine.
T = (D) Digoxin.
F = (E) Griseofulvin .

(3) Barbiturates
T = (A) Depress the respiratory centre.
F = (B) Inhibits the activity of certain liver enzyme.
T = (C) Are usually metabolized in liver.
T = (D) Have anti-convulsant properties.
F = (E) Are rapidly excreted in acidic urine.

(4) Chloramphenicol
F = (A) Does not penetrate the blood brain barrier.
F = (B) Must be administered parenterally.
F = (C) Can be safely used in premature infants.
T = (D) Can cause depression of bone marrow.
F = (E) Can cause discoloration of developing teeth when given to children.

(5) Tetracycline
F = (A) Is bactericidal.
F = (B) Causes aplastic anemia in toxic doses.
F = (C) In over-dosage causes depression of bone marrow.
T = (D) Excreted in bile.
T = (E) Excreted in urine.

(6) Recognized features of acute paracetamol poisoning include
F = (A) Hyperventilation.
F = (B) Early onset of coma.
T = (C) Hypoglycemia.
T = (D) Prolongation of prothrombin time.
T = (E) Nephrotoxicity.

(7) Adverse effects following prolonged administration of corticosteroids include
F = (A) Dehydration & weight loss.
T = (B) Osteoporosis & spontaneous fractures.
F = (C) Hypotensive episodes.
T = (D) Reduced glucose tolerance & worsening of diabetes mellitus.
T = (E) Suppression of ACTH secretion.

(8) Thiazides can cause
F = (A) Hypoglycemia.
T = (B) Hypokalemia.
F = (C) Hypouricemia.
F = (D) Hypocalcemia.
T = (E) Hypophosphatemia.

(9) Chronic use of estrogen causes
F = (A) Increased incidence of MI.
F = (B) Increased incidence of ovarian tumors.
T = (C) Increased incidence of cancer of breast.
T = (D) Increased incidence of venous thrombosis.
T = (E) Increased incidence of cholelithiasis.

(10) Following drugs are contraindicated in 3rd trimester
T = (A) Tetracycline.
F = (B) Ampicillin.
F = (C) Erythromycin.
F = (D) Cephalosporin.
T = (E) Sulfonamides.

(11) Atropine
F = (A) Promotes salivation.
T = (B) Increases resting heart rate.
F = (C) Induces bronchiolar constriction.
T = (D) Administration results in constipation.
T = (E) Causes loss of accommodation.

(12) Methyldopa causes following side effects
F = (A) Visual disturbances.
F = (B) Weight gain.
T = (C) Fever.
T = (D) Hemolytic anemia.
F = (E) Urinary retention.

(13) Drugs having short plasma half life
F = (A) Have low therepeutic index.
F = (B) Are extensively bound to plasma proteins.
T = (C) Reach steady state concentration (C_{ss}) quickly.
F = (D) Have low volume of distribution.
F = (E) Are usually weak bases.

(14) Morphine use is better avoided in patients with
F = (A) Myocardial infarction.
T = (B) Head injury.
T = (C) Cor pulmonale.
F = (D) Diabetes mellitus.
T = (E) Acute biliary colic.

(15) Diazepam
T = (A) Is anxiolytic.
T = (B) Is hypnotic.
F = (C) Does not cause dependence.
T = (D) Is anti-epileptic.
T = (E) May causes paradoxically increased anxiety.

(16) Atropine is given before anesthesia
F = (A) For good induction.
F = (B) For rapid recovery.
F = (C) For full muscle relaxation.
T = (D) To decrease respiratory secretion.
F = (E) To decrease incidence of cardiac arrest.

(17) Dopamine
T = (A) Is given in infusion form.
T = (B) Has inotropic effect an heart.
T = (C) Is given in cardiogenic shock.
F = (D) Causes constriction of renal vessels.
T = (E) Overdosage results in excessive sympathomimetic effects.

(18) Propranolol can be give safely in
F = (A) Asthma.
F = (B) CCF.
F = (C) Heart block.
T = (D) Exertional angina.
T = (E) Hypertension.

(19) In chronic renal failure following drugs can be given safely
F = (A) Gentamycin.
T = (B) Erythromycin.
F = (C) Sulfonamides.
F = (D) Rifampin.
T = (E) Digoxin.

(20) Morphine can be given in
F = (A) Head injury.
F = (B) Diabetes mellitus.
T = (C) Myocardial infarction.
T = (D) Biliary colic.
F = (E) Right ventricular hypertrophy.

(21) Neostigmine reverses skeletal muscle relaxation caused by
T = (A) Gallamine.
T = (B) Tubocurarine.
F = (C) Diazepam.
F = (D) Suxamethonium.
T = (E) Pancuronium.

(22) Rifampicin
F = (A) Has antimicrobial activity only aganist M. tuberculosis.
T = (B) Induces hepatic microsomal enzymes.
F = (C) Acts by inhibiting microbial cell wall synthesis.
F = (D) Resistance has not been observed in mycobacteria.
T = (E) Attains clinically effective concentration in CSF following oral administration.

(23) Compared to morphine pethidine is
T = (A) Mydriatic.
T = (B) Less potent analgesic.
F = (C) More potent antitussive.
F = (D) Not liable to produce dependence.
T = (E) Less constipating.

(24) Most of the H_1 histamine receptor blockers produce
T = (A) Dry mouth.
T = (B) Drowsiness.
F = (C) Decrease in gastric acid secretion.
T = (D) Relief in bronchial asthma.
T = (E) Symptomatic relief in allergic conditions.

(25) Nitroglycerine
F = (A) Produces mainly venodilatation.
F = (B) Decreases heart rate.
T = (C) Decreases venous return.
T = (D) Undergoes extensive first pass metabolizm.
T = (E) Decreases oxygen requirement of heart.

(26) Clinically useful actions of diazepam include
F = (A) Analgesic.
T = (B) Hypnotic.
T = (C) Anxiolytic.
F = (D) Local anesthetic.
T = (E) Skeletal muscle relaxant.

(27) Captopril produces its antihypertensive effects by inhibition of
F = (A) Noradrenaline formation.
T = (B) Angiotensin-II formation.
F = (C) Angiotensin-II receptors.
F = (D) Bradykinin inactivation.
F = (E) Renin release.

(28) Drugs which mainly block beta-1 adrenoceptors include
F = (A) Timolol.
T = (B) Atenolol.
F = (C) Propranolol.
F = (D) Pindolol.
T = (E) Metoprolol.

(29) Aminoglycoside antibiotics are
F = (A) Well absorbed from GIT.
T = (B) Nephrotoxic.
T = (C) Bactericidal.
T = (D) Ototoxic.
F = (E) Eliminated mainly by hepatic inactivation.

(30) Drug actions which have been attributed to genetic polymorphism include
T = (A) Prolonged apnea with suxamethonium.
T = (B) Peripheral neuritis with isoniazid.
F = (C) Gingival hyperplasia with phenytoin.
F = (D) Hemolysis with primaquine.
T = (E) Lupus erythematosus like syndrome with hydralazine.

(31) Oxytetracycline
T = (A) Absorption from GIT is decreased by antacids.
T = (B) Stains & damages teeth if used in children.
F = (C) Is bactericidal in usual doses.
F = (D) Resistant micro-organisms do not show resistance to other tetracyclines.
T = (E) Is liable to cause superinfections in GIT.

(32) Renal excretion of drugs by glomerular filtration is reduced by
T = (A) Extensive binding of the drug to plasma proteins.
F = (B) Probenecid.
F = (C) Induction of hepatic microsomal enzymes.
T = (D) Old age.
F = (E) Alkalinization of urine.

(33) Dopamine
F = (A) Produces renal & mesenteric vasoconstriction.
T = (B) Is administered by continuous intravenous infusion.
T = (C) Is useful in cardiogenic shock.
F = (D) Produces no inotropic actions on heart.
T = (E) Adverse effects are usually rapidly reversed on stopping administration.

(34) Pain of peptic ulcer is relieved by
T = (A) Substances which neutralize acid.
T = (B) Taking normal food in small quantity more frequently.
F = (C) Drugs which stimulates vagus.
F = (D) Drugs which interfere with the action of cholinesterase.
F = (E) Oral administration of beta blockers.

(35) Xanthine
T = (A) Oxidase inhibitor allopurinol is used in gout to block uric acid production.
F = (B) Is oxidized to form purines.
T = (C) Is a substrate as well as a product of the enzyme xanthine oxidase.
F = (D) Is an intermediate product during catabolism of pyrimidines.
T = (E) Is the precursor of uric acid.

(36) Pharmacological actions resulting from known drug-receptor interactions include
T = (A) Miosis by pilocarpine.
F = (B) Diuresis by mannitol.
F = (C) Decreased gastric acidity by aluminium hydroxide.
T = (D) Vasoconstriction by adrenaline.
T = (E) Bronchodilation by albuterol.

(37) Following have vasoconstrictor effects when applied locally
T = (A) Ephedrine.
F = (B) Procaine.
F = (C) Timolol.
F = (D) Cocaine.
T = (E) Phenylephedrine.

(38) Drugs which need daily dose reduction in case of renal failure include
T = (A) Chloramphenicol.
T = (B) Gentamicin.
F = (C) Erythromycin.
F = (D) Doxycycline.
F = (E) Rifampicin.

(39) Bioavailability of a drug depends on
T = (A) Route of administration.
F = (B) Route of excretion.
T = (C) Extend of first pass metabolism.
F = (D) Extent of plasma protein binding.
T = (E) Dosage form.

(40) Drug interactions of pharmacokinetic type include
T = (A) Prolongation of procaine local anesthesia by adrenaline.
F = (B) Reversal of morphine induced respiratory depression by naloxone.
F = (C) Reversal of hydralazine induced tachycardia by propranolol.
T = (D) Increased toxicity of methotrexate by aspirin.
T = (E) Decreased peripheral adverse effects of levodopa by carbidopa.

(41) Muscarinic effects of acetylcholine are produced at
F = (A) Skeletal muscle.
T = (B) Cardiac muscle.
T = (C) Gastrointestinal smooth muscle.
T = (D) Sweat glands.
F = (E) Autonomic ganglions.

(42) Recognized side effects of the propranolol include
T = (A) Bronchospasm.
T = (B) Heart failure.
F = (C) Retinal degeneration.
F = (D) Tachycardia.
T = (E) Hypoglycemia.

(43) Gallamine causes paralysis of muscles by
F = (A) Blocking the synthesis of acetylcholine in motor nerve endings.
F = (B) Blocking release of activator Ca^{2+} in the sarcoplasm.
T = (C) Competing with acetylcholine at motor endplate.
F = (D) Depolarizing motor endplate.

F = (E) Blocking interneurones in spinal cord.

(44) For the treatment of Parkinsonism carbidopa is used in combination with levodopa because it

F = (A) Facilitates dopamine entry into brain.
F = (B) Inhibits dopamine inactivation in brain.
T = (C) Inhibits the peripheral conversion of levodopa into dopamine.
F = (D) Acts as a dopamine receptor agonist.
T = (E) Significantly decreases the peripheral adverse effects of levodopa.

(45) Use of propranolol is better avoided in patients having

T = (A) Bronchial asthma.
F = (B) Hypertension.
T = (C) Congestive heart failure.
T = (D) Heart block.
F = (E) Angina of effort.

(46) The main actions of digoxin when used in congestive cardiac failure include

T = (A) Positive inotropic effects.
F = (B) Positive chronotropic effects.
F = (C) Decrease in AV nodal conduction time.
F = (D) Increase in atrial effective refractory period.
T = (E) Inhibition of Na-K-ATPase.

(47) Thiazide diuretics are capable of producing

F = (A) Hypolipidemia.
T = (B) Hypokalemia.
F = (C) Hypoglycemia.
F = (D) Hypouricemia.
T = (E) Hyponatremia.

(48) Antiboitics which are bactericidal in usual therapeutic dosage include

T = (A) Ampicillin.
F = (B) Chloramphenicol.
F = (C) Oxytetracycline.
T = (D) Streptomycin.
T = (E) Cephalexin.

(49) The benefits of dopamine therapy in cardiogenic shock include

T = (A) Rise in diastolic blood pressure.
T = (B) Arteriolar constriction.
F = (C) Bradycardia.
T = (D) Increased force of cardiac contraction.
T = (E) Vasodilatation in kidneys.

(50) Regarding oxytetracycline

T = (A) Antacids inhibit its absorption.
F = (B) Is bactericidal.
T = (C) Causes yellow discoloration of teeth.
T = (D) May cause superinfections.
T = (E) Show cross sensitivity to other tetracyclines.

(51) When following two drugs are used in combined form, the first drug tends to increase the adverse effects of second

F = (A) Methotrexate & aspirin.
T = (B) Allupurinol & mercaptopurine.
T = (C) Verapamil & digitalis.
F = (D) Halothane & nitrous oxide.
F = (E) Phenobarbital & oral anti-coagulants.

(52) Regarding non-steroidal anti inflammatory drugs (NSAIDs)

T = (A) Aspirin has short half life.
T = (B) Phenylbutazone has long half life.
F = (C) None of the NSAIDs interact with methotrexate.
F = (D) All NSAIDs except sulindac interact with antihypertensive & diuretic agents.
T = (E) Non-steroidal anti inflammatory drugs do not cause bronchospasm & pulmonary edema.

(53) Atropine given intravenously in therapeutic doses

T = (A) Increases the resting heart rate.
T = (B) Produces vasodilation of the skin.
T = (C) Reduces the flow of saliva.
F = (D) Produces over activity of the small intestine.
T = (E) Reduces gastric secretion.

(54) Halothane

F = (A) Causes good muscle relaxation.
T = (B) Causes hypotension.
T = (C) Causes bronchodilation.
F = (D) Is a good analgesic.
T = (E) Increases the risk of hepatitis.

(55) Following drugs act as an coagulant by acting against warfarin

F = (A) Aspirin.
T = (B) Phenobarbital.
T = (C) Vit. K.
F = (D) Phenylbutazone.
F = (E) Amiodarone.

(56) When injected subcutaneously noradrenaline causes

F = (A) Decreased diastolic blood pressure.
T = (B) Increased systolic blood pressure.
T = (C) Increased peripheral resistance.
F = (D) Relaxation of bronchial smooth muscles.
F = (E) Relaxation of smooth muscles of blood vessels.

(57) Following are nephrotoxic drugs

T = (A) Gentamycin.
F = (B) Cephalothin.
T = (C) Cephaloridine.
T = (D) Rifampin.
F = (E) Amoxycillin.

(58) Prolonged use of corticosteroids causes

T = (A) Osteoporosis.
F = (B) Hypotension.
F = (C) Weight loss.

F = (D) Increased ACTH.
T = (E) Worsening of clinical diabetes.

(59) Tubocurarine
T = (A) Is a non-depolarizing blocker.
T = (B) Is antagonized by neostigmine.
T = (C) Causes bronchospasm.
T = (D) Causes hypotension.
T = (E) Used frequently in electroconvulsive therapy.

(60) Cimetidine
F = (A) Decreases salivary secretion.
F = (B) Decreases gastric motility.
T = (C) Inhibit hepatic enzymes.
F = (D) Is a proton pump inhibitor.
T = (E) Decreases gastric acid secretion.

(61) Following intravenous administration, rapid redistribution of the drug is responsible for the short duration of
T = (A) General anaesthesia by thiopentone.
F = (B) Cardiovascular effects of dopamine.
F = (C) Hypotensive effects of trimethaphan.
T = (D) Anticonvulsant effect of diazepam.
F = (E) Skeletal muscle relaxation by succinylcholine (suxamethonium).

(62) Durgs known to be associated with fetal abnormalities when used during pregnancy include
T = (A) Phenytoin.
F = (B) Ampicillin.
T = (C) Captopril.
T = (D) Valproic acid.
F = (E) Chloroquin.

(63) Chlorpromazine
T = (A) Effectively controls nausea & vomiting in motion sickness.
T = (B) Acts mainly by blocking D_2 dopamine receptors.
T = (C) Can cause cholestatic jaundice.
T = (D) Effectively controls hicoughs.
F = (E) Can cause hypertensive episodes.

(64) Succinylcholine (suxamethonium)
T = (A) Is a depolarizing type of neuromuscular blocker.
T = (B) Rate of metabolism markedly differs in different persons.
T = (C) Muscle paralysis is preceded by muscle fasiculations.
T = (D) Overdose effects are reversed by neostigmine in phase II.
T = (E) Use with halothane may sometimes cause malignant hyperthermia.

(65) If the blood gas partition coefficient of an inhalation general anaesthetic is high, it will result in
T = (A) Slow induction.
F = (B) Good analgesia.
T = (C) High blood solubility.
F = (D) Quick recovery.
F = (E) Good skeletal muscular relaxation.

(66) Recognized side effects of phenytoin include
T = (A) Gingival hyperplasia.
T = (B) Ataxia.
T = (C) Hirsutism.
F = (D) Epileptic seizures.
T = (E) Folate depletion.

(67) Loop diuretics
F = (A) Inhibits reabsorption of chlorides in distal tubule.
T = (B) Act independent of changes in acid base balance.
F = (C) Inhibit carbonic anhydrase.
T = (D) Produce metabolic alkalosis.
T = (E) Produce hyperuricemia.

(68) Nitrous oxide inhalations may lead to
F = (A) Pulmonary edema.
F = (B) Bronchogenic carcinomas.
F = (C) Mesothelioma.
F = (D) Asthma.
F = (E) Respiratory distress syndrome.

(69) Regarding antithyroid drugs
T = (A) Carbimazole interfere with synthesis of thyroid hormone.
F = (B) Propylthiouracil is not suitable during pregnancy.
T = (C) Propylthiouracil crosses the placenta.
T = (D) Carbimazole does not causes fetal scalp defects.
F = (E) Propylthiouracil is not transferred to breast milk.

(70) Drugs having a half life exceeding 12 hours include
T = (A) Chlorpropamide.
F = (B) Atropine.
T = (C) Amitriptyline.
F = (D) Chlordiazopoxide.
T = (E) Lithium carbonate.

(71) Drugs which are known to have teratogenic effects & should be avoided in pregnancy include
F = (A) Cephalexin.
T = (B) Captopril.
T = (C) Lithium carbonate.
T = (D) Valproic acid.
F = (E) Methyldopa.

(72) Regarding acetylcholine in the nervous system
T = (A) It is the chemical transmiter of the parasympathetic nervous system.
F = (B) It is absent from the brain.
T = (C) Some receptors are blocked by atropine.
T = (D) Some receptors are blocked by curare.
T = (E) It stimulates b receptors in the sympathetic nervous system.

(73) Regarding the biosynthesis of noradrenaline from tyrosine
F = (A) Dopamine beta-hydroxylase is required.

F = (B) Phenylalanine is an intermediary.
F = (C) Dopamine is formed by the addition of a hydroxyl group to DOPA.
F = (D) Tryptophan is an intermediary.
F = (E) Noradrenaline is formed by the action of N-methyl transferase on adrenalin.

(74) Concerning the rate of uptake of drugs from the blood into the brain
F = (A) Dopamine is taken up more rapidly than levodopa.
T = (B) Serotonin is taken up more rapidly than tryptophan.
T = (C) Thiopentone is taken up more rapidly than other barbiturate.
T = (D) Physostigmine is taken up more rapidly than neostigmine.
T = (E) Lithium ions are takes up more rapidly than dopamine.

(75) Nalorphine
T = (A) Causes dilation of the pupils in narcotic addicts.
F = (B) Is used in the treatment of thiamine deficiency.
F = (C) Causes constriction of the pupils in non-norcotic subjects.
F = (D) Prevents withdrawal symptoms in morphine addicts.
F = (E) Is effective when taken by mouth.

(76) The adverse effects of the first drug usually increase when it is used concurrently with the second drug
T = (A) Aminophylline with tricyclic antidepressants.
T = (B) Methotrexate with aspirin.
F = (C) Halothane with nitrous oxide.
T = (D) Verapamil with propranolol.
F = (E) Sulphamethoxazole with trimotheprim.

(77) The characteristics of general anesthesia produced by intravenous thiopentone sodium include
T = (A) Quick induction.
F = (B) Good analgesia.
F = (C) Good skeletal muscular relaxation.
T = (D) Short lived anesthesia.
T = (E) Quick recovery.

(78) Pharmacological actions of cimetidine include inhibition of
F = (A) Gastric motility.
T = (B) Gastric acid secretion.
F = (C) H^+ - K^+ ATPase (proton pump).
F = (D) Salivary secretion.
T = (E) Hepatic microsomal drug metabolizing enzymes.

(79) Long term use of estrogen increases the risk of
T = (A) Gallstone formation.
T = (B) Breast cancer.
T = (C) Deep vein thrombosis.
F = (D) Osteoporosis.
F = (E) Ovarian cancer.

(80) Plasma half life of a drug depends on
F = (A) Dose administered.
T = (B) Renal plasma flow.
T = (C) Rate of drug metabolizm.
T = (D) Rate of elimination.
T = (E) Addition of a 2nd drug.

(81) Drugs which are capable of enhancing the anti-coagulant effects of warfarin include
F = (A) Oxytetracycline.
T = (B) Aspirin.
F = (C) Phenobarbitone.
F = (D) Vitamin K.
T = (E) Phenylbutazone.

30 ONE BEST TYPE MCQs

SEE ANSWERS AT THE END OF CHAPTER

(1) A patient is having herpes simplex ophthalmitis; this disease can be treated with
(A) Trifluridine
(B) Sulfacetamide
(C) Chloramphenicol
(D) Ganciclovir
(E) Zidovudine

(2) Curare act to
(A) Prevent depolarization in neuromuscular junction
(B) Inhibit transmission of impulses in the nerve fibers
(C) Compete with acetylcholine for nicotinic receptor sites
(D) Produce hypertension
(E) Produce hyperkalemia

(3) The anesthetic used along with the halothane to give excellent analgesia & rapid induction is
(A) Nitrous oxide
(B) Thiopental
(C) Desflurane
(D) Propofol
(E) Chloroform

(4) A 42-years-old asthamatic is on salbutamol, prednisolone and theophylline. He also uses diazepam for depression and also takes aspirin. He develops bone fracture; the drug most likely to cause this effect is
(A) Salbutamol
(B) Prednisolone
(C) Theophylline
(D) Diazepam
(E) Aspirin

(5) Mechanism of action of local anesthetic is
(A) Blockage of Na^+ current
(B) Increase Na^+ current
(C) Increase Ca^{++} influx
(D) Increase of K^+ outflow
(E) None of the above

(6) A 20-years-old male has severe chest pain, due to rib fracture; which of the following long acting local anesthetic should be given
(A) Lignocaine
(B) Procaine
(C) Bupivacaine
(D) Prilocaine
(E) Mepivacaine

(7) A known patient of myasthenia gravis comes to you, with his disease previously well control on atropine & neostigmine; but now he feels weakness & the disease is not under control. He is given injection stigma & his condition improved; the next step is to
(A) Reduce the dose of neostigmine
(B) Withdraw atropine
(C) Increase the dose of atropine
(D) Increase the dose of neostigmine
(E) Corticosteroid treatment

(8) Effect of curare on acetylcholine is to
(A) Block competitively the transmitter action of acetylcholine
(B) Increase the action of acetylcholine
(C) Decrease the action of acetylcholine
(D) Block Na^+ pump
(E) Increase Ca^{++} influx

(9) A patient already receiving digitalis, when given the hydrochlorothiazide will result in
(A) Hypokalemia
(B) Hypercalcemia
(C) Its decreased renal excretion
(D) Its increased GIT absorption
(E) Hyperglycemia

(10) A drug is at blood level of 16 mg/dl, has a ½ life of 8 hrs. If clinical effects appear at 4 mg/dl, for how many hrs will its action last following stopping of its constant infusion
(A) 8 hours
(B) 16 hours
(C) 32 hours
(D) 24 hours
(E) 64 hours

(11) Dopamine exerts its effect when it reached a steady state. If its ½ life is 2 min., after how many minutes it will show its effect
(A) 2 min
(B) 4 min
(C) 9 min
(D) 15 min
(E) More than 20 min

(12) The antiepileptic drug which result in nystagmus, ataxia, & gum hypertrophy is
(A) Phenytoin
(B) Phenobarbitone
(C) Carbamazepine
(D) Ethosuximide
(E) Valproic acid

(13) The insulin used in case of a patient suffering from diabetic ketoacidosis is
(A) Lente insulin
(B) Ultralente insulin
(C) NPH
(D) Regular insulin
(E) NPH iletin I

(14) A 35-years-old male after having checked up by an ophthalmologist, feels blurring of vision. This is most likely due to
(A) Homatropine
(B) Pilocarpine
(C) Xylocaine
(D) Edrophonium
(E) Phenylephrine

(15) A 12-years-old boy has tonsillitis, caused by beta hemolytic streptococci; which drug is most suitable
(A) Ampicillin
(B) Benzyl penicillin
(C) Benzathine penicillin
(D) Gentamicin
(E) Chloramphenicol

(16) A cancer patient is on cyclophosphamide. A second drug is added to his regimen and the patient experiences a sharper decline in pulmonary and renal function. The added drug most likely is
(A) dactinomycin
(B) methotrexate
(C) prednisone
(D) vinblastine
(E) vincristine

(17) A patient with a catheter advanced into a forearm artery is infused with an alpha blocker at a rate that produces a local effect, but not a systemic effect. Assume that the patient is resting quietly during the procedure. Which of the following changes would most likely occur in the forearm?

	Cap/ Pres	Blood Flow	Limb wt	AV/O2/Diff.
(A)	dec.	dec.	dec.	dec.
(B)	inc.	inc.	dec.	dec.
(C)	inc.	inc.	dec.	inc.
(D)	inc.	inc.	inc.	dec.
(E)	inc.	inc.	inc.	inc.

(18) A patient is taking the oral contraceptives, & now she is also taking the anti-tuberculous drugs. She has gone pregnant. Which of the following drug is responsible for her pregnancy
(A) Rifampin
(B) Isoniazid
(C) Ethambutol
(D) Streptomycin
(E) Pyrazinamide

(19) A 54-year-old woman suffers from hypertension due to excessive sympathetic activity. In particular, she complains of frightening palpitations and pain in the extremities due to poor blood supply. Labetalol was tried successfully and the physician decides to prescribe a similar agent with a longer duration of action. Which of the following medications would be the most appropriate in this case?
(A) Acebutolol
(B) Atenolol
(C) Carteolol
(D) Carvedilol
(E) Pindolol

(20) Injection of penicillin is given to a patient; after 2 to 3 hours, the patient become unconscious & his BP becomes low. Which drug should be given
(A) Dopamine
(B) Dobutamine
(C) Norepinephrine
(D) Adrenaline
(E) Aminophylline

(21) The drug of choice for the tape worm infestation is
(A) Niclosamide
(B) Albendazole
(C) Mebendazole
(D) Dichlorophen
(E) Oxamniquine

(22) A patient is suffering from streptococcal pharyngitis; one injection of the following will treat the patient
(A) Benzyl penicillin
(B) Benzathin penicillin
(C) Amoxycillin
(D) Procaine penicillin
(E) Methicillin

(23) A 54-year-old obese white male with a history of hypertension is managed by captopril and a diuretic. Which of the following clinical situations is most clearly a contraindication for the use of captopril?
(A) Congestive heart failure
(B) Essential hypertension
(C) High LDL levels
(D) Post-myocardial infarction
(E) Renovascular hypertension

(24) The component of a local anesthetic agent that is directly responsible for neuronal conduction block is the
(A) free base inside the neuron
(B) free base outside the neuron
(C) ionized base inside the neuron
(D) ionized base outside the neuron

(25) Tumor cells from a person with cancer are being analyzed to determine which oncogene is involved in the transformation. After partial sequencing of the gene, the predicted gene product is identified as a tyrosine kinase. Which of the following proteins would most likely be encoded by this gene?
(A) Alpha-1 adrenergic receptor
(B) Corticosteroid receptor
(C) Epidermal growth factor receptor
(D) Nicotinic cholinergic receptor
(E) N-menthyl-D-aspartate (NMDA) receptor

(26) An old patient with compromised renal function develops gram-positive infection. The best drug that does not require renal adjustment is
(A) Vancomycin
(B) Penicillin-G
(C) Cloxacillin
(D) Erythromycin
(E) Clarithromycin

(27) Cimetidine & warfarin are given to a patient, & the bleeding time is prolonged. What is the cause
(A) Inhibition of drug metabolism
(B) Impairment of platelet aggregation
(C) Increased half life
(D) Impaired absorption
(E) Promote platelet aggregation

(28) Which of the following drugs is associated with cumulative cardiotoxicity?
(A) Digoxin
(B) Doxorubicin
(C) Etoposide
(D) Ifosfamide
(E) Procarbazine

(29) A Parkinson's patient presents to you complaining of a purplish-red mottling of the skin of the lower leg. The patient denies any associated itching or pain and reports that the color intensifies upon standing or with cold temperatures. Physical exam reveals slight pitting edema of the ankles. Therapy with which drug would most likely account for these observations?
(A) Amantadine
(B) Benztropine
(C) Bromocriptine
(D) Levodopa
(E) Selegiline

(30) A 47-years-old male with CHF develops symptoms & signs of digoxin toxicity, while he is also on other CHF drugs. Digoxin levels found to be in normal range. The reason for this is
(A) Decreased renal function
(B) Wrong time to take digoxin level
(C) Hypokalemia by diuretics
(D) Decreased protein bounding of digoxin due to competition
(E) Abnormal LFTs

(31) Mountain sickness can be corrected with the use of
(A) Acetazolamide
(B) Metoclopramide
(C) Furosemide
(D) Promethazine
(E) Cyclizine

(32) A women which is on phenytoin, wants to conceive. What advice you can give to her about the drug
(A) Increase the dose of phenytoin
(B) Change to valproic acid
(C) Addition of valproic acid
(D) Change to phenobarbitone.
(E) Decrease the dose of phenytoin

(33) A 49-year-old frequent business traveler presents to his physician requesting medication to help him with nausea and dizziness that he gets during turbulent flights. A scopolamine patch is prescribed for his motion sickness. Which of the following is the most likely side effect from this patch?
(A) Bradycardia
(B) Diaphoresis
(C) Diarrhea
(D) Salivation
(E) Urinary retention

(34) A 56-year-old male presents with fatigue, a malar rash on his cheek, and arthralgia/myalgia. He reports that even with sunscreens, he "burns easily". Laboratory tests are positive for antinuclear antibodies (ANA). He has been treated for essential hypertension for the past 3 years. Antihypertensive therapy with which of the following drugs would be most consistent with this patient's presentation?
(A) Captopril
(B) Hydralazine
(C) Hydrochlorothiazide
(D) Procainamide
(E) Propranolol

(35) A 45-year-old female with metastatic breast cancer is placed on a combination of antineoplastics, including an anthracycline antibiotic. Which of the following drugs can act as a cytoprotective agent that will minimize the cumulative cardiotoxicity from the antineoplastic agents?
(A) Amifostine
(B) Dexrazoxane
(C) Leucovorin
(D) Mesna
(E) Ondansetron

(36) A 45-year-old man came in emergency department with pin-point pupil, unconsciousness & history of taken morphine. Which will be the antidote
(A) Naloxone
(B) Nalorphine
(C) Flumazenil
(D) Benztropine
(E) Neostigmine

(37) A 48-year-old hypertensive male is diagnosed with benign prostatic hyperplasia (BPH). He is currently taking hydrochlorothiazide, but his blood pressure is still not adequately controlled. Addition of which of the following drugs would constitute rational treatment of both of the patient's disorders?
(A) Captopril
(B) Clonidine
(C) Finasteride
(D) Nifedipine
(E) Terazosin

(38) A women $G_3P_2A_0$ at 28 weeks of pregnancy, gone in preterm labor pains. Tocolytics was given; which is the most common side effect.
(A) Palpitation
(B) Pallor
(C) Tachycardia
(D) Hypotension.
(E) Cough

(39) A 33-year-old female with a history of IV drug use and AIDS is being treated for Pneumocystis carinii pneumonia with IV pentamidine after having developed severe hematological side effects to co-trimoxazole. Her last CD4+ cell count was below 100 cell/mm3 and she is moderately hypocalcemic and hyponatremic. She complains of difficulty reading and says she "sees spots". Which of the following drugs would be most appropriate for the treatment of her visual problems?
(A) Acyclovir
(B) Foscarnet
(C) Ganciclovir
(D) Zalcitabine
(E) Zidovudine

(40) A 65-year-old man with an 18-year history of non-insulin dependent diabetes mellitus (NIDDM) presents to clinic. Despite oral hypoglycemic medications, his HbA1c levels are 15%, indicating persistent, sustained hyperglycemia. Which of the following drugs could be added to this man's regimen in order to blunt the postprandial increase in plasma glucose?
(A) Acarbose
(B) Chlorpropamide
(C) Metformin
(D) Regular insulin
(E) Troglitazone

(41) A 31-year-old female is diagnosed as schizophrenic, disorganized type. Her symptoms include blunt affect, motor retardation, mutism, and apathy. In the past, she has had severe extrapyramidal side effects and has an extreme fear of developing tardive dyskinesia. Which of the following drugs would be most appropriate for this patient?
(A) Amantadine
(B) Clozapine
(C) Fluphenazine
(D) Phenelzine
(E) Triazolam

(42) Indomethacin is an useful drug to be given in neonates for the closure of
(A) Foramen ovale
(B) Ductus arteriosus
(C) VSD
(D) Ductus venosus
(E) Septum primum

(43) A 46-year-old woman with debilitating rheumatoid arthritis is being treated with a non-steroidal ant-inflammatory (NSAID) drug. After 3 months, she develops renal tubular acidosis. Which of the following drugs is she most likely taking?
(A) Aspirin

(B) Ibuprofen
(C) Indomethacin
(D) Misoprostol
(E) Naproxen

(44) A 39-year-old female is seen in the emergency room because of acute diarrhea of 3 days duration and a fever of 103.5 degrees F. Her blood pressure is 96/60, her heart rate is 130/min. and her respiratory rate is 321/min. No bowel sounds are heard, and the patient is unable to produce a specimen for urinalysis. She is confused and disoriented. Which of the following drugs would initially increase her renal blood flow and cardiac output, but would increase peripheral resistance at higher doses?
(A) Dobutamine
(B) Dopamine
(C) Isoproterenol
(D) Prazosin
(E) Terbutaline

(45) The drug of choice for HSV kerato-conjunctivitis is
(A) Chloramphenicol
(B) Tetracycline
(C) Neomycin
(D) Aciclovir
(E) Gentacin

(46) Thiopentone sodium was used as an anesthetic agent, but the patient awake just after 15 minutes. What is the cause of this short duration of action
(A) Redistribution of drug
(B) Excretion thru kidneys
(C) Excretion thru lungs or in air
(D) Metabolism in liver
(E) B & D

(47) Acetylcholine is given to the patient, after which the patient remained unconscious for very long time. What is the cause?
(A) Deficiency of acetylcholinesterase
(B) Deficiency of pseudo-acetylcholinesterase
(C) Reuptake of acetylcholine.
(D) Decreased excretion by liver
(E) Decreased excretion by kidney

(48) A patient is on aspirin, which has antiplatelet action. He needs surgery, & the surgeon advises him to stop aspirin; he can be operated after
(A) 1-3 days
(B) 3-4 days
(C) 15 days
(D) 7 days
(E) 20 days

(49) A 5-year-old child presents to his pediatrician with abdominal pain, irritability, loss appetite, and slurred speech. On physical exam, he is pale and ataxic. Upon questioning, his mother says that she is in the process of remodeling her home, and states that her child may have ingested paint chips. Which of the following drugs could be given orally to treat the child's condition?
(A) CaNa2EDTA
(B) Deferoxamine
(C) Dimercaprol
(D) Sodium thiosulfate
(E) Succimer

(50) In a child with tapeworm infestation drug of choice is
(A) Albendazole
(B) Mebendazole
(C) Pyrantal pamoate
(D) Niclosamide
(E) Piperazine

(51) A 50-year-old, 175 lb female with a 10-year history of high blood pressure controlled with propranolol and furosemide returns to clinic because of high LDL levels. She is evaluated, and treatment is initiated for her high cholesterol levels. Initially, she experiences gastrointestinal disturbances, but over the next two weeks, her blood pressure gradually increases. Which of the following drugs is most likely to have interacted with her previous antihypertensive treatment?
(A) Cholestyramine
(B) Gemfibrozil
(C) Lovastatin
(D) Niacin

(52) Metronidazole can be given in all of the followings, except
(A) Amebiasis
(B) Candidiasis
(C) Giardiasis
(D) Trichomoniasis
(E) Balantidiasis

(53) A 65-year-old man presents to his physician complaining of his need to make frequent trips to the bathroom during the day and the night. He also admits to occasional urinary incontinence. Which of the following drugs would most likely be helpful to this patient?
(A) Bethanechol
(B) Glycopyrrolate
(C) Neostigmine
(D) Phenoxybenzamine
(E) Phentolamine

(54) A 4-year-old girl is sent home from daycare after complaining of abdominal pain. The mother takes her daughter to the pediatrician and states that she has been continually scratching around her anus. On examination, the pediatrician notes red excoriations in the perianal area. He places a strip of clear cellulose acetate tape on her perianal region and subsequently removes it. The pediatrician views the tape under the microscope and notes diagnostic structures. Which of the following drugs would be most efficacious in eradicating this infection.
(A) Mebendazole
(B) Metronidazole
(C) Praziquantel
(D) Pyrimethamine-sulfonamides
(E) Stibogluconate

(55) Which of the following conditions is the most appropriate indication for buspirone?
(A) Bipolar disorder
(B) Generalized anxiety disorder
(C) Obsessive compulsive disorder
(D) Psychosis
(E) Stage fright

(56) A patient who did not disclose frequent use of aspirin to the physician is placed on warfarin and develops severe bleeding episodes. These episodes are best explained by
(A) decreased efficacy of antithrombin III
(B) decreased production of vitamin K dependent clotting factors
(C) drug action on platelets
(D) potentiation of PGI2 production

(57) Which drug is given in the form of injection when 40 weeks uterus is contracting
(A) FSH
(B) LH
(C) ACTH
(D) Prolactin
(E) Oxytocin

(58) If a patient has renal compromise, which drug should be avoided
(A) Gentamicin
(B) Chloramphenicol
(C) Furosemide
(D) Digoxin
(E) Phenytoin

(59) A patient on a particular medication complains of severe dizziness. His blood pressure in a supine position is 115/80 mm Hg; on standing it drops to 82/50 mm Hg. Which of the following drugs is most likely responsible for these symptoms?
(A) Carabamazepine
(B) Chlorpromazine
(C) Chlordiazepoxide
(D) Cortisone
(E) Ibuprofen

(60) Epinephrine will cause all of the following except
(A) Increase diastolic BP
(B) Increase systolic BP
(C) Increase peripheral resistance
(D) Increase pulse rate
(E) Increase coronary resistance

(61) A 67-year-old male with severe refractory congestive heart failure is being treated by afterload reduction. An intravenous infusion of nitroprusside is begun. Which of the following signaling molecules would most likely be elevated in this patient's vascular smooth muscle during this treatment?
(A) cAMP
(B) cGMP
(C) Potassium
(D) Thromboxane A2
(E) Tyrosine kinase

(62) On routine checkup a physician prescribe acetazolamide, to a team of mountaineer, to be taken from 5 days prior; this is to prevent
(A) Respiratory acidosis
(B) Respiratory alkalosis
(C) Loss of HCO_3^-
(D) Gain of H^+
(E) Decrease pH

(63) A 20-year-old female being treated for acute lymphocytic leukemia (ALL) complains of pain and weakness in her knees. Neurological examination reveals severe bilateral foot drop, loss of deep tendon reflexes, and decreased vibratory sensation. Which of the following agents is most likely to be involved in the etiology of her current problem?
(A) Bleomycin
(B) Daunorubicin
(C) L-Asparaginase
(D) Prednisone
(E) Vincristine

(64) Which of the following antibiotics directly affects bacterial nucleic acid synthesis?
(A) Ciprofloxacin
(B) Doxycycline
(C) Gentamicin
(D) Pyrimethamine
(E) Sulfadiazine

(65) A patient presents to the emergency room complaining of tremors, insomnia, sweating, and generalized anxiety. While waiting to be seen, he becomes delirious, disoriented, and eventually goes into shock. The patient is most likely suffering from withdrawal from
(A) amphetamines
(B) barbiturates
(C) hashish
(D) heroin
(E) inhalants

(66) A 30-year-old woman being treated for hypertension has the sudden onset of fever and malaise. Temperature is 38.3 C (101 F) orally and blood pressure is normal. She has a malar rash, swelling and tenderness of the wrists and knees, and a friction rub at the left lower sternal border. Which of the following drugs is the most likely cause of these findings?
(A) Captopril
(B) Hydralazine
(C) Minoxidil
(D) Nitroprusside
(E) Propranolol

(67) A subject who is given one dose of a drug intravenously 16 hours ago still retains 16 mg of the drug in his body. Assuming that the half-life of the drug is 8 hours, how much drug was originally given to the subject?
(A) 4 mg
(B) 32 mg
(C) 64 mg
(D) 108 mg
(E) 256 mg

(68) Various anesthetics are used for different purposes. The drug that is used for rapid anesthesia and has got good analgesia is
(A) Nitrous oxide
(B) Halothane
(C) Diazepam
(D) Thiopental
(E) Propofol

(69) Consultant gynecologist wants to induce ovulation in premenopausal women; most likely she gets benefit from
(A) Clomiphene citrate
(B) LH
(C) GnRH
(D) FSH
(E) Octreotide

(70) A 60-years-old male is brought to ER. He is comatose and his pupils are constricted. Physician suspects opium overdose. What is best to administer
(A) Flumazanil
(B) Calcium gluconate
(C) Naltraxone
(D) Naloxone
(E) Atropine

(71) A 16-years-old boy is a know patient of epilepsy. Following several years of a drug therapy, he is observed to have gingival hyperplasia. The common drug causing this side effect is
(A) Alprazolam
(B) Carbamazepine
(C) Valproic acid
(D) Ethosuximide
(E) Phenytoin

(72) A 60-years-old lady is put on oral anticoagulant therapy. To monitor the optimum performance of drug, it is most wise to observe her
(A) PT
(B) APTT
(C) Bleeding time
(D) Platelet count
(E) Fibrinogen time

(73) A 38-year-old man presents to the emergency room complaining of a painful right eye and blurred vision. Ophthalmological examination reveals injection of the conjunctiva, corneal edema, and increased intraocular pressure. The patient states that he had just returned from a boat ride for which he used a scopolamine patch to prevent sea sickness. Which of the following drugs would be most appropriate to treat this patient's condition?
(A) Amiloride
(B) Chenodiol
(C) Hydrochlorothiazide
(D) Mannitol
(E) Triamterene

(74) A 74-year-old man with urinary frequency & urgency has benign prostatic hypertrophy. He refuses operative intervention but agrees to a trial of finasteride therapy. During the trial, synthesis of which of the following substances is most likely to be inhibited?
(A) Androstenedione
(B) Dihydrotestosterone
(C) Estradiol
(D) Estrone
(E) Testosterone

(75) Escherichia coli strains X and Y are both resistant to ampicillin. Ampicillin resistance is stable in strain X when it is grown for multiple generations in the absence of the antibiotic. However, strain Y loses ampicillin resistance when it is grown in media without the antibiotic. Which of the following best explains the acquisition of ampicillin susceptibility in strain Y?
(A) Downregulation of the resistance gene
(B) Insertion of a transposon into the resistance gene
(C) Loss of a plasmid carrying the resistance gene
(D) Point mutations in the resistance gene
(E) Recombination with a defective copy of the resistance gene

(76) Following will be given for staphylococcus aureus infection
(A) Ceftazidime
(B) Aminoglycoside
(C) Tetracycline
(D) Cloxacillin
(E) Ciprofloxacin

(77) Most earliest effect of warfarin is seen on which of the following clotting factor
(A) Fibrinogen
(B) Prothrombin
(C) von Wille brand
(D) Thromboplastin
(E) Antihemophilic

(78) A 32-year-old man is brought to the emergency department because of confusion, wheezing, vomiting, and diarrhea for the past 6 hours. He is sweating and salivating profusely. There is generalized muscle weakness. Which of the following substances is the most likely cause of these findings?
(A) Glutethimide
(B) Heroin
(C) Jimson weed (belladonna alkaloids)
(D) Parathion
(E) Phencylidine (PCP)

(79) Tamoxifen, an anti estrogen, affects the following
(A) Breast
(B) Reproductive system
(C) Cardiovascular system
(D) Gastrointestinal system
(E) Urinary system

(80) The most important complication for discontinuation of oral contraceptive pills is
(A) Migraine
(B) Heavy menstrual period
(C) Vaginal discharge
(D) Acne
(E) Dysmenorrhea

(81) A 56-year-old man has progressive shortness of breath, a cough, & a low-grade fever. He began taking a drug for recurrent ventricular arrhythmias 5 months ago. Erythrocyte sedimentation rate is increased. Pulmonary function tests show decreased diffusing capacity. X-ray film of the chest shows diffuse interstitial pneumonia. Which of the following drugs is the most likely cause of these findings?
(A) Amiodarone
(B) Angiotensin-converting enzyme (ACE) inhibitor
(C) Atenolol
(D) Furosemide
(E) Metronidazole

(82) A patient is brought to emergency room in subconscious state, who has taken some drug at home. Bicarbonate is given as a treatment; which is the drug that patient has taken
(A) Tricyclic antidepressant
(B) Pethidine
(C) Phenobarbitone
(D) Benzodiazepine
(E) Aspirin

(83) Which of the following drugs applied topically produces mydriasis without producing cycloplegia?
(A) Atropine
(B) Neostigmine
(C) Phentolamine
(D) Phenylephrine
(E) Pilocarpine

(84) A 35-years-old male otherwise healthy, given a drug for his nausea during his mountain climbing. He also started having excess urine. The most likely prescribed drug is
(A) Scopolamine
(B) Metochlopramide
(C) Domperidone
(D) Acetozolamide
(E) Cyclizine

(85) The most important benefit of Tamoxifen is to the following structure
(A) Breast
(B) Liver
(C) Kidney
(D) Stomach
(E) Ovary

(86) The most important complication, optic neuritis is caused by which of the following anti-tuberculous drug
(A) INH
(B) Ethambutol
(C) Rifampicin
(D) Pyrazinamide
(E) Streptomycin

(87) A patient with 10 weeks pregnancy develop hyperthyroidism; which treatment should be given
(A) Beta-blockers
(B) Thyroidectomy
(C) Propylthiouracil
(D) Wait till end of pregnancy
(E) Iodinized salt

(88) A mountaineer climbing rapidly to a height of 3000 feet develops general body weakness, headache, nausea & malaise. These symptoms can be relieved by
(A) Paracetamol
(B) Acetazolamide
(C) Aspirin
(D) Caffeine
(E) Amphetamine

(89) A patient with rheumatoid arthritis is on disease modifying drug. His Hb is 8.1 gm/dl & MCV is 115. This can be due to
(A) Azathioprine
(B) Gold salts
(C) Methotrexate
(D) Hydrocortisone
(E) Chloroquine

(90) During pregnancy the diabetes is managed by
(A) Sulfonylureas
(B) Insulin
(C) Insulin + sulfonylureas
(D) Biguanide
(E) Acarbose

(91) Regarding mechanism of action of different diuretics, the mannitol acts on
(A) Proximal convoluted tubule
(B) Distal convoluted tubule (late)
(C) Early distal convoluted tubule
(D) Ascending limb of loop of Henle
(E) Collecting duct

(92) A 10-year-old girl is brought to emergency department; her chest is full of wheezes, & she is cyanosed & dyspneic. The best treatment will be
(A) Salbutamol
(B) Steroid inhaler
(C) Oxygen
(D) Aminophylline
(E) Systemic steroid + salbutamol

(93) Amongst the mechanism of action of antiulcer drugs, the way that cimetidine act is
(A) Decrease in acid production due to achlorhydria and gastrin
(B) Decrease in acid production due to gastrin, but not achlorhydria
(C) Decrease in cAMP
(D) Increase in H^+ in parietal cells
(E) Increase in Ca^{++} concentration in parietal cells

(94) A patient given succinylcholine for skeletal muscle relaxation during operation, is not recovering for the last 1 hour; this may be due to congenital deficiency of
(A) N-acetyl transferase
(B) Cholinesterase
(C) G-6-P dehydrogenase
(D) Uridly transferase
(E) Phospho-fructo kinase

(95) A 59-year-old man develops excessive sweating and salivation, diarrhea, and bradycardia while being treated with neostigmine for myasthenia gravis. Which of the following is the most appropriate therapy for these symptoms and signs?
(A) Atropine
(B) Carbachol
(C) Edrophonium
(D) Epinephrine
(E) Pralidoxime

(96) A patient is on digoxin for congestive heart failure. He develops digoxin toxicity. His plasma level of digoxin is 4 nano gm/dl. Plasma half life of digoxin is 36 hours. For how much time digoxin is withheld so that its plasma level drops to a safe level (1 nano gm/dl)
(A) 36 hours
(B) 52 hours
(C) 72 hours
(D) 92 hours
(E) 112 hours

(97) A patient is taking digoxin & hydrochlorothiazide. He develops digoxin toxicity, but the plasma level of digoxin is within safe range. Digoxin toxicity in this case is due to
(A) Hyponatremia
(B) Hyperlipidemia
(C) Hypokalemia
(D) Hyperuricemia
(E) Hyperglycemia

(98) Warfarin is administered to a 56-year-old man following placement of a prosthetic cardiac valve. The warfarin dosage is adjusted to maintain a prothrombin time of 18 sec. Subsequently, trimethoprim-sulfamethoxazole therapy is begun for recurring urinary tract infection. In addition to monitoring prothrombin time, what action should the physician take to maintain adequate anticoagulation?
(A) Begin therapy with vitamin K
(B) Increase the dosage of warfarin
(C) Make no alterations in the dosage of warfarin
(D) Reduce the dosage of warfarin
(E) Stop the warfarin and change to low-dose aspirin

(99) A patient on anti-tuberculous therapy develops eye symptoms; which drug is responsible
(A) INH
(B) Rifampin
(C) Ethambutol
(D) Streptomycin
(E) Pyrazinamide

(100) Compared with normal persons, the dosage regimen of a drug for a patient known to be a "rapid metabolizer" is modified most rationally by which of the following loading and maintenance doses?

	Loading	Maintenance
(A)	Increased	increased
(B)	Increased	normal
(C)	Decreased	normal
(D)	Normal	decreased
(E)	Normal	increased

(101) A 22-year-old woman, gravida 1, para 1, comes to the physician because of vaginal discharge and vulvar pruritus for 7 days. She is allergic to penicillin. Her last menstrual period was 1 week ago. There is a thin, bubbly, pale green discharge. A wet mount preparation shows a mobile, pear-shaped, flagellated organism. Select the most appropriate pharmacotherapy.
(A) Acyclovir
(B) Cefazolin
(C) Ceftriaxone
(D) Erythromycin
(E) Metronidazole

(102) A 25-year-old woman, gravida 2, para 2, comes to the physician because of vaginal discharge and vulvar pruritus and burning, and dyspareunia for 3 days. She has no drug allergies. The vagina is tender and erythematous. A KOH wet mount preparation shows spores and hyphae. Select the most appropriate pharmacotherapy.
(A) Acyclovir
(B) Miconazole
(C) Ceftriaxone
(D) Griseofulvin
(E) Gentamicin

(103) A 20-year-woman is brought to the emergency department because of fever, severe myalgias, diarrhea, and a diffuse scarlatiniform rash for 4 hours. She recovered from a similar illness 6 months ago. She is menstruating and using a tampon. She appears very ill. Her temperature is 40 C (104 F), blood pressure is 75/30 mm Hg, and pulse is 130/min. Which of the following is the most appropriate pharmacotherapy?
(A) Ampicillin
(B) Chloramphenicol
(C) Doxycycline
(D) Gentamicin
(E) Nafcillin

(104) A 42-years-old patient with known case of tuberculosis developed visual disturbance. Which drug he used for T.B. is responsible for causing this disturbance
(A) INH
(B) Ethambutol
(C) Rifampicin
(D) Pyrazinamide
(E) Pholcodine

(105) A 14-year-old girl is brought to the physician because of severe dysmenorrhea over the past year. The dysmenorrhea is accompanied by nausea and vomiting the first 2 days of her menstrual period and causes her to miss 2 days of school each month; aspirin does not relieve the pain. Menarche was at 11 years of age. Pelvic examination shows no abnormalities. Serum studies show luteinizing hormone level of 7 mIU/mL, follicle-stimulating hormone level of 7 mIU/mL, and thyroid-stimulating hormone level of 4.0 mU/mL. A pregnancy test is negative. Which of the following is the most appropriate next step in mangement?
(A) Doxycycline therapy for 10 days
(B) Acetaminophen therapy prior to expected menses
(C) Ibuprofen therapy prior to expected menses
(D) Codeine therapy during menses
(E) Danazol therapy daily

(106) Poisoning the Na+ - K+ pump with digitalis causes which of the following changes in large axons?
(A) decreased intracellular Cl-concentration
(B) decreased intracellular K+ concentration
(C) decreased intracellular Na+ concentration
(D) Immediate block in propagation of action potentials
(E) Slow heperpolarization of membrane potentials

(107) A 30-year-old, over-weight, male is diagnosed as diabetic with blood glucose 20 mmol/L; what treatment should you advised with diet & exercise
(A) Sulfonylurea
(B) Biguanides
(C) Insulin
(D) Insulin with sulfonylurea
(E) Insulin & low energy diet

(108) An otherwise healthy 55-year-old man is given isoniazid and vitamin B6 (pyridoxine) after conversion of his PPD skin test. An x-ray film of the chest shows no abnormalities. Four weeks later he develops abdominal pain & jaundice. Which of the following is the most likely explanation?
(A) Hepatic tuberculosis
(B) Hepatitis B
(C) Isoniazed-induced hepatitis

(D) Pyridoxine-induced cholecystitis
(E) Tuberculous pancreatitis

(109) An 24-year-old newly married nulligravid woman comes to the physician because of temperatures to 39 C (102.2 F), malaise, and multiple painful blisters on her vulva for 2 days; she has been unable to void for 12 hours. She has bilateral inguinal adenopathy. There are shallow-based ulcers on the vulva, vaginal mucosa, and ectocervix. The most appropriate treatment is administration of which of the following?
(A) Acyclovir
(B) Ganciclovir
(C) Immune globulin
(D) Interferon
(E) Zidovudine (AZT)

(110) A 78-year-old man comes to the physician because of swelling of both ankles for 4 days. He has been taking indomethacin for low back pain for 2 weeks with partial relief of symptoms. Examination confirms the pedal edema but is otherwise unremarkable; the bladder is not distended. His serum urea nitrogen (BUN) level is 56 mg/dL and creatinine level is 2.9 mg/dL; these values were previously within normal limits. Which of the following is the most appropriate next step?
(A) Discontinuation of indomethacin
(B) Prescription of a thiazide diuretic
(C) Evaluation for multiple myeloma
(D) Measurement of urine sodium and creatinine levels
(E) Renal ultrasonography

(111) A patient with acute inferior wall myocardial infarction is having rhonchi (upto mid-chest), dyspnea, sweating, pulse 120 bpm, BP 130/90 mmHg. What treatment should you give to relieve both the pain & dyspnea
(A) Furosemide
(B) Sublingual GTN
(C) Morphine
(D) Aspirin
(E) Anticoagulants

(112) The labs of a patient shows MCV 120, & Hb 9 g/dl; patient is on what drug
(A) Azathioprine
(B) Methotrexate
(C) Cisplatin
(D) Chloroquin
(E) Cyclophosphamide

(113) Which of the following characteristics of amphetamines is most likely to be responsible for increasing blood pressure?
(A) Indirect release of endogenous catecholamines
(B) Inhibition of catecholamine metabolism
(C) Metabolism to false neurochemical transmitters
(D) Potent alpha1-adrenergic agonism
(E) Potent B2-adrenergic agonism

(114) A mother brings her 2-year-old daughter to the emergency dept after finding her bottle of iron pills spilled on the floor & noticing that her daughter's mouth was discolored. The child's plasma iron conc. is 400 mg/dL. Which of the following agents is most appropriate for chelation therapy?
(A) Acetylcysteine
(B) Calcium disodium edetate (EDTA)
(C) Deferoxamine
(D) Dimercaprol
(E) Penicillamine

(115) A patient is on digoxin & diuretics; digoxin level is within normal limits but its toxicity appears. The likely reason is
(A) Decreased K+
(B) Decreased PO_4^-
(C) Decreased Cl^-
(D) Decreased Na^+
(E) Decreased HCO_3^-

(116) A 45-year-old woman who is being treated for hypertension and hypercholesterolemia develops diffuse muscle pain and weakness. Serum creatine kinase activity is increased. Which of the following drugs is most likely to have caused this clinical picture?
(A) Captopril
(B) Hyrdochlorothiazide
(C) Lovastatin
(D) Nicotinic acid
(E) Propranolol

(117) A 58-year-old man with chronic congestive heart failure requires ongoing hydrochlorothiazide therapy. His monthly serum chemistry profile shows persistent hypokalemia. The most appropriate next step is to add which of the following diuretics to the regimen?
(A) Acetazolamide
(B) Amiloride
(C) Furosemide
(D) Mannitol
(E) Metolazone

(118) H2-receptor blocker will
(A) Inhibit gastrin induced H^+ release
(B) Inhibit vagally induced H^+ release
(C) Inhibit vagally + gastrin induced H^+ release
(D) Doesn't inhibit gastrin induced H^+ release
(E) Doesn't inhibit insulin induced H^+ release

(119) A pregnant woman taking phenytoin for epilepsy. The least likely teratogenic effects of phenytoin is
(A) Nail hypoplasia
(B) Cleft lip
(C) Spina bifida
(D) IUGR
(E) Cardiac defects

(120) A 52-year-old man with chronic obstructive pulmonary disease who has been taking theophylline for 14 weeks now requires treatment for hypertension, peptic ulcer, and tuberculosis. After 2 weeks of therapy, he has a toxic plasma theophylline concentration. The drug most likely to have caused the theophylline toxicity is
(A) Cimetidine
(B) 'hydrochlorothiazide
(C) prazonsin
(D) rifampin

(121) An 18-year-old primigravid woman at term has been in spontaneous labor with ruptured membranes for 14 hours. Her cervix is 7 cm dilated. Fetal heart rate monitoring shows a baseline of 180/min with decreased variability. Her temperature is 38.5 C (101.3 F), and her uterus is tender to palpation. Gram's stain of the amniotic fluid shows multiple organisms. Which of the following is the most appropriate pharmacotherapy?
(A) Ampicillin and gentamicin
(B) Ciprofloxacin and clindoamycin
(C) Erythromycin
(D) Metronidazole
(E) Penicillin

(122) Antidote of morphine is
(A) Naloxone
(B) Naltrixone
(C) Amphetamine
(D) Fluconazole
(E) Meperidine

(123) Fluconazole, an antifungal drug, act by inhibiting synthesis of
(A) DNA
(B) RNA
(C) Fungal membrane ergosterol
(D) Protein
(E) Folic acid

(124) Halothane is a weak analgesic & is co-administrated with
(A) Thiopental
(B) Nitrous oxide
(C) Oxygen
(D) Ketamine
(E) Enflurane

(125) Release of neurotransmitter is blocked by
(A) Hemicholinium
(B) Acetylcholinesterase
(C) Botulinum toxin & spider venom
(D) Choline
(E) Ca^{++}

(126) Drug which act on cell wall synthesis of bacteria is
(A) Quinolones
(B) Macrolides
(C) Tetracycline
(D) Penicillin
(E) Co-trimoxazole

(127) A patient with myocardial infarction is having rhonchi, dyspnea, & sweating. What treatment should be given to relieve pain & dyspnea
(A) Aspirin orally
(B) Morphine
(C) Nitroglycerine
(D) Anticoagulant
(E) Diuretics

(128) An asthmatic patient, on multiple drugs for his asthma treatment & also uses diazepam for depression, develops bone fracture; this is likely to be from
(A) Diazepam
(B) Theophylline
(C) Salbutamol
(D) Prednisolone
(E) Aspirin

(129) An old epileptic patient on phenytoin is having an attack now. What you give to this patient in emergency
(A) Phenytoin
(B) Carbamazepine
(C) Diazepam
(D) Valproic acid
(E) Primidone

(130) A patient suffering from congestive heart failure, has difficulty is swallowing. Barium studies shows esophageal constriction; this is likely to be due to the following drug
(A) Aspirin
(B) Captopril
(C) Atenolol
(D) Fosinopril
(E) Estrialol

(131) Nitrous oxide can not be given in an old man undergoing laparotomy because
(A) It causes analgesia
(B) It causes intestinal dilatation
(C) It causes bronchoconstriction
(D) It supports combustion
(E) It lowers blood pressure

(132) In a patient, who is under general anaesthesia with spontaneous ventilation, Halothane with 66% N_2O & 33% O_2 can cause
(A) Bronchoconstriction
(B) Increase in airway resistance
(C) Increase in alveolar ventilation
(D) Increase in tidal volume
(E) Decrease in $PaCO_2$

(133) Sevoflurane is preferred over isoflurane for induction because
(A) It has got pleasant smell
(B) It has low blood gas solubility coefficient
(C) Metabolites are less active
(D) Don't sensitize myocardium to exogenous catecholamines
(E) Causes bronchodilatation

(134) Hypotensive effects of propofol are mainly due to
(A) Peripheral vasodilation
(B) Splanchnic vasodilation
(C) Cerebral vasodilation
(D) Alpha 1 & alpha2 blockage
(E) Beta 1 & beta 2 blockage

(135) Ketamine is use in repeated burn dressings because of its
(A) Analgesic effects
(B) Antihypotensive effects
(C) Less cardiac depression
(D) Less respiratory depression
(E) Early recovery

(136) A young boy with burns is brought to emergency ward. There is history of death of one of his family members due to succinylcholine induction. So we will avoid succinylcholine because it
(A) Causes hyperkalemia
(B) Causes hepatotoxicity
(C) Causes muscle pains
(D) Can trigger malignant hyperthermia
(E) Can cause spasm of masseter muscle

(137) Which of the following benzodiazepines have not active metabolites
(A) Chlordiazepoxide
(B) Diazepam
(C) Clonazepam
(D) Midazolam
(E) Oxazepam

(138) Midazolam is given before induction because
(A) It causes retrograde amnesia
(B) It decreases post operative sedation
(C) It decreases MAC value
(D) It is a short acting
(E) Side effect can easily be reversed with flumazenil

(139) Diazepam
(A) 50% bound with proteins
(B) Has no toxic metabolites
(C) Not easily absorbed on intramuscular injection
(D) Cannot cross placenta readily
(E) Twice more potent than midazolam

(140) Morphine causes
(A) Decrease in gastroesophageal reflux
(B) Decrease in tone of sphincters
(C) Increase in peristalsis
(D) Increase in acid production
(E) Increase in gastric emptying time

(141) Fentanyl is used because
(A) It has minimal cardiac effects
(B) Metabolites are inactive
(C) On high doses it cause anaesthesia
(D) Its half life (t 1/2) is 30-40 minutes
(E) It is lipid soluble

(142) Following a dose of local anaesthetic which of the fibres will be affected first
(A) A alpha
(B) A beta
(C) A gamma
(D) B
(E) C

(143) A 50 kg person is schedule to stitch a 10 cm long wound on the scalp, which recommended dosage of lidocaine will you choose
(A) 150 mg plain
(B) 250 mg 1% with adrenaline
(C) 250 mg 2% with adrenaline
(D) 250 mg 3% with adrenaline
(E) 350 mg 3% with adrenaline

(144) Roivacain is preferred over bupivacaine for epidural in labor because
(A) It is less toxic to baby
(B) It is less cardiotoxic
(C) Dose is equipotent
(D) Toxicity can easily be reversed
(E) Produces a block of longer duration

(145) Glycopyrrolate is preferred over atropine because
(A) It is quaternary compound
(B) Can cross blood brain barrier
(C) Increases sympathetic activity
(D) Cardiac acceleration is less
(E) Causes amnesia

(146) Ketorolac can be given safely for postoperative analgesia in
(A) A patient undergone thoracic surgery without any systemic disease
(B) A patient undergone laparotomy with asthmatic history
(C) Hip replacement of a patient with IHD

(D) Patient with increased creatinine
(E) In a patient of known peptic ulcer

(147) A drug which is used against enemies in war. Its mechanism of action can be
(A) Inhibition of acetylcholine
(B) Inhibition of alpha & beta receptors
(C) Inhibition of acetyl transferase
(D) Inhibition of cholinesterase
(E) Inhibition of dopamine

(148) Which of the following antibiotic can block neuromuscular transmission
(A) Ceftriaxone
(B) Crentamycine
(C) Penicillin
(D) Metronidazole
(E) Chloramphenicol

(149) Atropine is given before reversal with neostigmine because it
(A) Decreases secretions
(B) Increases sympathetic activity
(C) Increases heart rate
(D) Causes bronchodilatation
(E) Causes mydriasis

(150) A patient was given 450 mg of thiopentone sodium but after 15 minutes the patient awoke, what had happened to the drug
(A) Inactivated by liver
(B) Excreted by kidneys
(C) Redistribution
(D) Settled in brain
(E) Drug bound to plasma proteins

(151) A patient with history of injury & has broken ribs 6 & 7 on right side which local anaesthetic will you give for prolonged pain relief
(A) Bupivacaine
(B) Ropivacain
(C) Lidocaine
(D) Cinchocaine
(E) Phenoles

(152) Bupivacaine
(A) Can be made hyperbaric with 8% glucose
(B) Is aminoester
(C) 0.5% contain 50 mg/ml
(D) Short duration of action
(E) Can cause allergic reactions

(153) Lignocaine on local anaesthesia
(A) Cause vasodilatation
(B) Increase Cl^- transfer
(C) Block Na^+ channel
(D) Block K^+ channel
(E) Decreases pH of tissue

(154) Isoflurane
(A) Blood gas solubility coefficient is 1.4
(B) Maintains peripheral vascular resistance
(C) Increases end tidal CO_2 when use spontaneously
(D) Very pleasant to smell
(E) Can cause seizures

(155) Suxamethonium is avoided is burn patients because it causes
(A) Bradycardia
(B) Hyperkalemia
(C) Muscle pain
(D) Increased intracranial pressure
(E) Increased intraocular pressure

(156) Morphine
(A) Causes diarrhea
(B) Causes mydriasis
(C) Prevents Nausea & vomiting
(D) Prevents histamine release
(E) Acts on all receptors

(157) Which of the following in imidazole derivative
(A) Thiopentone sodium
(B) Methohexitone
(C) Propofol
(D) Etomidate
(E) Ketamine

(158) Dopamine increases urine production in a shocked patient because it
(A) Increase cardiac output
(B) Decreases aldosterone release
(C) Decreases ADH release
(D) Causes peripheral vasodilatation
(E) Causes renal arterial vasodilatation

(159) A patient is on antiarrhythmic therapy. During the period of treatment CNS toxicity appears with adverse cardiac effects. Which is the drug responsible for these effects
(A) Phenytoin
(B) Lidocaine
(C) Bretylium
(D) Verapamil
(E) Propranolol

(160) A patient of congestive cardiac failure is taking digoxin. Which of the following change will occur in his ECG
(A) Increase in PR interval
(B) Increase in QT interval
(C) A tall T wave
(D) A tall P wave
(E) QRS complex more than 0.2 sec

(161) What is the drug of choice in prinzmeatal angina
(A) Lignocaine
(B) Verapamil
(C) Nitroglycerine

(D) Nifedipine
(E) Diltiazem

(162) Loop diuretics & thiazide diuretics act synergistically at which site of nephron
(A) Proximal convoluted tubule
(B) Descending limb of loop of Henle
(C) Ascending limb of loop of Henle
(D) Distal convoluted tubule
(E) Collecting ducts

(163) Paracetamol
(A) Has poor antiinflammatory effects
(B) Inhibit platelet aggregation
(C) Causes renal function worsening
(D) Does not bind to plasma proteins
(E) Plasma half life is 30 minutes

(164) A patient with IHD undergoing anaesthesia suddenly have increased blood pressure. Which one of the following drug will you prefer to give
(A) I/V nitroglycerine
(B) I/V nifedipine
(C) I/V hydralazine
(D) I/V sodium nitroprusside
(E) I/V esmolol

(165) In a patient of IHD intravenous fentanyl is preferred to analgesia because
(A) It has minimal cardiac effects
(B) At high doses it causes anaesthesia
(C) Can be reversed with naloxone
(D) Its duration is 30-40 minutes
(E) It is lipid soluble

(166) Labetalol is
(A) Alpha 1 blocker
(B) Alpha 2 blocker
(C) Beta 1 blocker
(D) Beta 2 blocker
(E) Both alpha & beta blocker

(167) Dopamine increases systolic & diastolic blood pressure by acting primarily on
(A) Beta 1 receptors
(B) Beta 2 receptors
(C) On both Beta 1 & beta 2 receptors
(D) Alpha 1 receptors
(E) Alpha 2 receptors

(168) In hyperkalemia which of the following drug should be avoided
(A) Frusemide
(B) Ethacrynic acid
(C) Bumetanide
(D) Spironolactone
(E) Chlorthiazide

(169) Cytochrome P-450 induces which one of the following
(A) Acetylation of disulfiram
(B) Hydroxylation of phenytoin
(C) Glucoronidation of chloramphenicol
(D) Conjugation of isoniazid
(E) Oxidation of cimetidine

(170) A drug is injected intravenously. After half hour its plasma concentration following first order kinetics was 400 mg/ml & after 12 hrs its plasma concentration was 50 mg/ml. What is the half life of drug
(A) 2 hrs
(B) 4 hrs
(C) 6 hrs
(D) 8 hrs
(E) 10 hrs

(171) Cimetidine is given preoperatively because
(A) It reduces gastric motility
(B) It blocks H2 receptors
(C) It decreases acidity
(D) It increases bioavailability of some drugs
(E) It decreases release of histamine

(172) Cimetidine is not given with warfarin because it causes
(A) Increased destruction of warfarin
(B) Decreased protein binding of warfarin
(C) Inhibit excretion of warfarin thru kidney
(D) Inhibit excretion of warfarin thru feces
(E) Inhibit its metabolism thru liver

(173) An asthmatic patient comes in emergency ward with severe shortness of breath. Which of the drug will you give to relieve his symptoms
(A) Salbutamol
(B) Terbutaline
(C) Corticosteroids
(D) Theophylline
(E) Ipratropium

(174) A patient of IHD undergoing anaesthesia suddenly develops bronchospasm. Which drug will you choose to relieve his bronchospasm
(A) Salbutamol
(B) Terbutaline
(C) Corticosteroids
(D) Theophylline
(E) Ipratropium

(175) A patient comes to you with bacterial infection. His serum creatinine is 150 mmol/liter, urea 40 mmol/liter & TLC is 8 x 10^{12} / liter. Which of the following drug will you avoid to give
(A) Quinolones
(B) Ceftriaxone
(C) Gentamicin
(D) Ampicillin
(E) Chloramphenicol

(176) In the treatment of nausea & vomiting
(A) Metoclopromide has no role
(B) Metoclopromide has less effects as compared to ondansetron following cytotoxic drug therapy induced nausea & vomiting
(C) Glucocorticoids are contraindicated
(D) Phenothiazines have no role
(E) Ipecac is very effective

(177) Following combination is used effectively
(A) Halothane & adrenaline
(B) Sevoflurane & phenytoin
(C) Isoflurane & verapamil
(D) Monoamine oxidase inhibitors & pethidine
(E) Ephedrine & amphetamine

(178) Monoamine oxidase inhibitors can be used safely with
(A) Fentanyl
(B) Ephedrine
(C) Pethidine
(D) Morphine
(E) Nalbuphine

(179) In atrial fibrillation which drug can be given
(A) Propranolol
(B) Digoxin
(C) Verapamil
(D) Nifedipine
(E) Lidocaine

(180) A patient on digoxin therapy has to undergo a surgery & you are on a pre operative round. Which toxicity would you suspect
(A) Hyperkalemia
(B) Ventricular arrhythmias
(C) Pain abdomen
(D) Third degree heart block
(E) Renal failure

(181) In a patient of severe asthmatic attack which of the following drug will you give intravenously
(A) Propranolol
(B) Phentolamine
(C) Isoprenaline
(D) Theophylline
(E) Esmolol

(182) The mechanism of action of theophylline is
(A) Antagonism of adenosine
(B) Alpha blocker
(C) Beta blocker
(D) Phosphodiesterase inhibitor
(E) Ganglion blocker

(183) Ondansetron is
(A) Alpha blocker
(B) Beta blocker
(C) Ca^{++} channel blocker
(D) 5-HT3 blocker
(E) Ganglion blocker

(184) Which one of the following is cardioselective Beta-blocker
(A) Esmolol
(B) Pindolol
(C) Practolol
(D) Propranolol
(E) Labetalol

(185) Which one of the following is a calcium channel blocker
(A) Propranolol
(B) Captopril
(C) Hydralazine
(D) Nifedipine
(E) Glyceryl trinitrate

(186) Hydralazine acts by
(A) Blocking alpha receptors
(B) Blocking beta receptors
(C) Directly acting on vascular smooth muscular
(D) Ganglion blocking
(E) Blocking renin-angiotensin system

(187) Low molecular weight heparin
(A) Antagonize anti thrombine III
(B) Inhibit factor V
(C) Inhibit factor VIII
(D) Inhibit factor X
(E) Decrease platelet aggregation

(188) Which one of the following drug lowers blood glucose level
(A) Adrenaline
(B) Chlorpromazine
(C) Chlorpropamide
(D) Propranolol
(E) Hydrocortisone

(189) Ephedrine
(A) Has actions on both alpha & beta receptors
(B) Has actions on nicotinic receptors
(C) Has actions on muscarinic receptors
(D) Actions can be blocked by adrenaline
(E) It causes mydriasis

(190) Adrenaline causes
(A) Mydriasis
(B) Cutaneous vasoconstriction
(C) Renal vasodilation
(D) Muscle spasm
(E) Glycogenesis

(191) A patient is admitted in ICU with TCA poisoning. Which is the most likely presentation
(A) Acute urine retention
(B) Convulsions
(C) Coma
(D) Tinnitus

(E) Hypertension

(192) What is the drug of choice in supraventricular arrhythmias

(A) Verapamil
(B) Propranolol
(C) Lidocaine
(D) Quinidine
(E) Procainamide

Answers of One Best Type MCQs

1.	A	2.	C	3.	B	4.	B	5.	A	6.	C	7.	D	8.	A
9.	A	10.	B	11.	C	12.	A	13.	D	14.	A	15.	C	16.	B
17.	D	18.	B	19.	D	20.	D	21.	A	22.	A	23.	E	24.	C
25.	C	26.	A	27.	A	28.	B	29.	A	30.	C	31.	A	32.	E
33.	E	34.	B	35.	B	36.	A	37.	E	38.	C	39.	C	40.	A
41.	B	42.	B	43.	C	44.	B	45.	D	46.	A	47.	A	48.	D
49.	E	50.	D	51.	A	52.	B	53.	B	54.	D	55.	B	56.	B
57.	E	58.	B	59.	B	60.	E	61.	B	62.	B	63.	E	64.	A
65.	B	66.	B	67.	C	68.	A	69.	A	70.	D	71.	E	72.	A
73.	D	74.	B	75.	D	76.	D	77.	B	78.	D	79.	A	80.	A
81.	A	82.	A	83.	D	84.	D	85.	A	86.	B	87.	C	88.	B
89.	C	90.	B	91.	A	92.	E	93.	C	94.	B	95.	A	96.	C
97.	C	98.	D	99.	C	100.	E	101.	E	102.	B	103.	E	104.	B
105.	C	106.	B	107.	E	108.	C	109.	A	110.	A	111.	C	112.	B
113.	A	114.	C	115.	A	116.	C	117.	B	118.	C	119.	A	120.	A
121.	A	122.	A	123.	C	124.	B	125.	C	126.	D	127.	B	128.	D
129.	D	130.	A	131.	B	132.	C	133.	B	134.	A	135.	A	136.	D
137.	D	138.	B	139.	C	140.	E	141.	A	142.	E	143.	C	144.	D
145.	D	146.	A	147.	D	148.	B	149.	C	150.	C	151.	E	152.	A
153.	C	154.	A	155.	B	156.	E	157.	D	158.	E	159.	B	160.	A
161.	C	162.	C	163.	A	164.	E	165.	A	166.	E	167.	A	168.	D
169.	B	170.	B	171.	C	172.	E	173.	A	174.	B	175.	C	176.	B
177.	E	178.	B	179.	B	180.	B	181.	D	182.	A	183.	D	184.	A
185.	D	186.	C	187.	D	188.	C	189.	A	190.	B	191.	A	192.	A

31 GET THRU PHARMA VIVA

INTRODUCTION

Clinico-Basic PHARMACOLOGY is quite different from other publications available in market in that it contains:
(1) Complete, comprehensive, & update classification.
(2) Details of almost all drugs, including dosage.
This will help in comprehensive preparation of MCQ exam., but for viva you need not to "memorize" a comprehensive classification & detail of "all drugs". This section will therefore reduce your burden by pointing out toward important aspects of each chapter.

✓ CHAPTER 1: GENERAL PHARMACOLOGY

(1) Pharmacology, Pharmacokinetics, Pharmacodynamics.
(2) Drug, pharmacopoeia.
(3) Formulae for children's dose.
(4) Routes of administration of drugs.
(5) Oral & parenteral routes: Advantages & disadvantages.
(6) 1st order & zero order kinetics.
(7) Bioavailability (def).
(8) Vol. of distribution (def).
(9) Enzyme induction & inhibition.
(10) First - pass effect.
(11) Enterohepatic circulation.
(12) Clearance of drug (def).
(13) Half - life.
(14) Receptor & its regulation.
(15) Affinity & Intrinsic activity.
(16) Agonist, Partial agonist & Antagonist.
(17) Potentiation, Potency & Efficacy.
(18) Therapeutic index.
(19) Idiosyncrasy & Hypersensitivity.
(20) Tolerance & Tachyphylaxis.

✓ CHAPTER 2: SYMPATHETIC NERVOUS SYSTEM DRUGS

(1) Effects produced by adrenoceptor stimulation.
(2) Classification of sympathomimetics according to receptor selectivity.
(3) Mechanism of action of sympathomimetics.
(4) Pharmacological effects of sympathomimetics (complete).
(5) Epinephrine (Clinical uses, Adverse effects, Contraindications, Dosage).
(6) Classification of sympatholytics.
(7) Phenoxybenzamine (complete).
(8) Propranolol (complete).

✓ CHAPTER 3: PARASYMPATHETIC NERVOUS SYSTEM DRUGS

(1) Effects produced by cholinoceptor stimulation.
(2) Classification of parasympathomimetics (complete).
(3) Direct & indirect acting parasympathomimetics (mechanism of action & pharmacological effects).
(4) Clinical uses of direct & indirect acting parasympathomimetics (Methacholine, Bethanechol, Neostigmine, Ecothiofate).
(5) Adverse effects of direct & indirect acting parasympathomimetics (complete).
(6) Contraindications of direct-acting parasympathomimetics.
(7) Classification of parasympatholytics (complete).
(8) Atropine & scopolamine (mechanism of action, pharmacological effects, clinical uses, adverse effects, contraindications).

CHAPTER 4: OPHTHALMOLOGICAL DRUGS

(1) Miotics (complete).
(2) Mydriatics (complete).
(3) Anti-glaucoma drugs (complete).
(4) Sulfonamides used in eye infections (systemically & locally).

✓ CHAPTER 5: CENTRAL NERVOUS SYSTEM DRUGS

(1) Classification of sedative-hypnotics (complete).
(2) Benzodiazepines (complete).
(3) Barbiturates (clinical use & adverse effects).
(4) Alcohol (chronic alcoholism).
(5) Classification of anti-epileptics (complete).
(6) Phenytoin & Ethosuximide (mechanism of action & adverse effects).
(7) Classification of anti-Parkinsonism drugs (complete).
(8) Levodopa, Bromocriptine & Amantadine (mechanism of action & adverse effects).
(9) Classification of anti-psychotic drugs (complete).
(10) Anti-psychotic drugs (mechanism of action, clinical uses & adverse effects).
(11) Drugs for bipolar affective disorder (complete).
(12) Lithium (complete).

(13) Classification of anti-depressants.
(14) Tricyclic anti-depressants & MAO inhibitors (mechanism of action, adverse effects & contraindications).
(15) Classification of CNS stimulants.
(16) Amphetamine (mechanism of action, clinical uses & adverse effects).
(17) Classification of antimigrain drugs (complete).
(18) Ergotamine tartarate (complete).

✓ CHAPTER 6: ANESTHETICS

(1) Classification of general anesthetics (complete).
(2) Mechanism of action of general anesthetics.
(3) Halothane (complete).
(4) Chloroform & Diethyl ether (disadvantages).
(5) Classification of local anesthetics (complete).
(6) Local anesthetics (mechanism of action, pharmacological effects, clinical uses, & adverse effects).

CHAPTER 7: SKELETAL MUSCLE RELAXANTS

(1) Classification (complete).
(2) Neuromuscular blockers (complete).

✓ CHAPTER 8: OPIOID ANALGESICS & ANTAGONISTS

(1) Classification (complete).
(2) Opioid agonists (complete).
(3) Opioid antagonists (clinical uses).

✓ CHAPTER 9: NSAIDS, NONOPIOID ANALGESICS & ANTI-GOUT DRUGS

(1) Classification of NSAIDs (complete).
(2) Aspirin (complete).
(3) Classification of Nonopioid analgesics (complete).
(4) Acetaminophen (complete).
(5) Classification of anti-gout drugs (complete).
(6) Colchicine & allopurinol (complete).

CHAPTER 10: DRUGS AFFECTING BLOOD

(1) Classification of anti-anemic drugs (complete).
(2) Iron (adverse effects, toxicity, contraindications).
(3) Vit. B_{12} & folic acid (clinical uses).
(4) Classification of anticoagulants (complete).
(5) Warfarin & heparin (complete).
(6) Classification of coagulants (complete).
(7) Vit. K (complete).
(8) Classification of antihyperlipidemic agents (complete).
(9) Anaphylaxis (complete).

✓ CHAPTER 11: CARDIOVASCULAR SYSTEM DRUGS

(1) Classification of antihypertensive drugs (complete).
(2) Methyldopa & Reserpine (complete).
(3) Diazoxide (complete).
(4) Saralasin, Captopril & Enalapril (complete).
(5) Classification of anti-anginal drugs (complete).
(6) Nitrates & nitrites, Beta-blockers & Ca channel blockers (complete).
(7) Classification of anti-congestive cardiac failure drugs (complete).
(8) Digitalis (complete).
(9) Classification of anti-arrhythmic drugs (complete).
(10) Quinidine, Amiodarone (complete).

✓ CHAPTER 12: RENAL DRUGS

(1) Classification of diuretics.
(2) Osmotic, High-ceiling (loop), Thiazide, & K^+ - sparing diuretics (complete).

CHAPTER 13: DRUGS AFFECTING RESPIRATORY SYSTEM

✓ (1) Classification of anti-asthmatic drugs (complete).
(2) Methylxanthine drugs (complete).
(3) Beta 2 selective sympathomimetics (complete).
(4) Cromolyn sodium (clinical uses).
(5) Classification of analeptic (complete).
(6) Nikethamide (complete).
(7) Classification of anti - tussives (complete).
(8) Expectorants.

CHAPTER 14: GASTROINTESTINAL DRUGS

✓ (1) Classification of anti - peptic ulcer drugs (complete).
(2) Antacids (Na bicarbonate, Mg trisilicate, Ca carbonate).
✓ (3) H_2 - receptor antagonists (complete).
(4) Emetics (classification, indication & contra-indications).
(5) Anti-emetics (classification).
(6) Purgatives (classification, indications & contraindications).
(7) Anti-diarrheals (classification).
(8) Appetite stimulants & suppressants (classification).

CHAPTER 15: HEPATO-PANCREATICO-BILIARY DRUGS

(1) Classification of anti - hepatitis drugs.
(2) Drugs used to dissolve gall stones.

CHAPTER 16: AUTACOIDS & ITS ANTAGONISTS

(1) Clinical uses of histamine.
(2) Drugs that cause histamine release.
✓ (3) H_1 - receptor antagonists (classification, clinical uses & adverse effects).
(4) Biosynthesis of kinins.
(5) Clinical uses of prostaglandins.

CHAPTER 17: ENDOCRINOLOGY

✓ (1) Adrenal corticosteroids (classification, clinical uses, adverse effects & contraindications).

(2) Estrogen, Progestins & Testosterone (clinical uses & adverse effects).
✓ (3) Oral contraceptive (classification, clinical uses, adverse effects, & contraindications).
✓ (4) Classification of anti-diabetic drugs (complete).
(5) Insulin preparations (clinical uses, & adverse effects).
(6) Sulfonylureas & Biguanides (mechanism of action, clinical uses & adverse effects).
✓ (7) Classification of anti-thyroid drugs (complete).
(8) Thioamides, Iodides, Radioactive iodine (mechanism of action & adverse effects).

✓ CHAPTER 18: CHEMOTHERAPY OF BACTERIAL INFECTIONS

(1) Penicillins (complete).
(2) Cephalosporins (complete).
(3) Chloramphenicol (complete).
(4) Tetracyclines (complete).
(5) Aminoglycosides (complete).
(6) Sulfonamides (complete).
(7) Trimethoprim (complete).
(8) Cotrimoxazole (complete).
(9) Erythromycin (complete).
(10) Fluoroquinolones (complete).
(11) Classification of anti-tuberculous drugs (complete).
(12) Isoniazid, Rifampin, & Ethambutol (mechanism of action & adverse effects).
(13) Classification of anti-leprosy drugs (complete).
(14) Sulfones (mechanism of action & adverse effects).
(15) Classification of drugs used in urinary tract infections.
(16) Nitrofurantoin & Nalidixic acid (mechanism of action, clinical uses & adverse effects).

CHAPTER 19: CHEMOTHERAPY OF FUNGAL INFECTIONS

(1) Classification of anti-fungal agents (complete).
(2) Amphotericin B, Nystatin, Griseofulvin (mechanism of action, clinical uses & adverse effects).

CHAPTER 20: CHEMOTHERAPY OF VIRAL INFECTIONS

(1) Classification of anti-viral drugs (complete).
(2) Amantadine (complete).

CHAPTER 21: CHEMOTHERAPY OF PROTOZOAL INFECTIONS

(1) Classification of anti - malarial drugs.
(2) 4-Aminoquinolines, Quinine, Primaquine & Pyrimethamine & Fansidar (mechanism of action, & adverse effects).
(3) Metronidazole, (mechanism of action, clinical uses & adverse effects).
(4) Classification of anti-leishmaniasis drugs.
(5) Pentavalent antimonials (mechanism of action).
(6) Classification of anti-trypanosomiasis.
(7) Suramin (mechanism of action & adverse effects).

CHAPTER 22: CHEMOTHERAPY OF HELMINTIC INFECTIONS

(1) Classification of anti-schistosomiasis drugs.
(2) Praziquantal (mechanism of action, clinical uses & adverse effects).
(3) Classification of drugs used in tape worm infections.
(4) Niclosamide (mechanism of action & adverse effects).
(5) Classification of drugs used in round worm infections.
(6) Pyrantal pamoate (mechanism of action & adverse effects).

CHAPTER 23: CANCER CHEMOTHERAPY

(1) Classification of anti-cancer drugs.
(2) Methotrexate (mechanism of action, clinical uses & adverse effects).

CHAPTER 24: VITAMINS & MINERALS

(1) Vit. A, Vit. B_1, Nicotinamide, Vit. B6, Vit. C, Vit. D_3, Vit. E (only clinical uses & adverse effects).
(2) Calcium (clinical uses, adverse effects & contraindications).

CHAPTER 25: DRUG INTERACTIONS

Not important to get thru.

✓ CHAPTER 26: ANTIDOTES

All are important.

CHAPTER 27: COMPARATIVE PHARMACOLOGY

Following are important;
(1) Physostigmine & Neostigmine.
(2) Atropine & Hyoscine.
(3) Epinephrine & Norepinephrine.
(4) Cocaine & Procaine.
(5) Halothane & Ether.
(6) Tubocurarine & Suxamethonium.
(7) Morphine & Pethidine.
(8) Morphine & Codeine.
(9) Heparin & Warfarin.
(10) Digoxin & Digitoxin.

CHAPTER 28: PRACTICAL PHARMACOLOGY

Do completely.

32 ANSWERS OF SELF ASSESSMENT QUESTIONS

	A	B	C	D	E
(1)	T	F	T	T	T
(2)	T	F	T	F	T
(3)	F	F	T	F	F
(4)	T	T	F	F	T
(5)	T	T	F	T	F
(6)	T	T	T	F	F
(7)	T	F	T	F	F
(8)	T	F	F	F	F
(9)	F	T	F	T	F
(10)	F	F	T	F	F
(11)	F	T	F	T	T
(12)	T	T	T	T	F
(13)	T	T	T	T	F
(14)	T	F	T	T	T
(15)	F	F	F	T	F
(16)	F	T	F	F	F
(17)	T	F	F	F	T
(18)	F	T	T	F	F
(19)	F	F	F	T	F
(20)	T	T	T	F	F
(21)	T	F	T	F	T
(22)	T	F	T	F	T
(23)	F	T	T	F	F
(24)	T	T	T	F	F
(25)	F	F	T	F	T
(26)	T	T	F	T	T
(27)	T	F	T	F	T
(28)	F	T	T	T	F
(29)	T	T	T	T	F
(30)	T	F	T	T	F
(31)	F	F	F	F	T
(32)	T	F	T	F	F
(33)	T	T	T	T	F
(34)	T	F	T	F	T
(35)	T	F	F	T	T
(36)	F	F	T	T	T
(37)	T	T	T	F	T
(38)	T	F	F	F	F
(39)	T	T	F	T	F
(40)	F	F	T	F	F
(41)	F	T	F	T	F
(42)	T	T	T	F	T
(43)	T	F	T	T	T
(44)	T	F	T	T	T

	A	B	C	D	E
(45)	T	F	F	T	T
(46)	T	T	F	F	T
(47)	T	T	F	F	T
(48)	F	F	F	T	F
(49)	T	F	T	T	T
(50)	T	T	F	F	T
(51)	T	T	T	T	F
(52)	F	T	F	T	T
(53)	T	F	F	F	F
(54)	T	T	F	T	F
(55)	T	T	T	T	F
(56)	T	T	F	T	F
(57)	T	F	F	T	F
(58)	F	T	T	T	F
(59)	T	T	F	T	F
(60)	T	T	F	T	T
(61)	T	F	T	T	F
(62)	T	T	T	T	F
(63)	F	T	T	T	F
(64)	T	F	F	T	F
(65)	T	T	T	F	T
(66)	F	F	T	T	F
(67)	T	F	T	F	T
(68)	F	T	F	T	T
(69)	F	F	T	T	T
(70)	T	F	T	T	F
(71)	F	T	T	T	F
(72)	T	F	F	T	T
(73)	T	F	T	T	F
(74)	F	T	T	F	T
(75)	T	T	F	T	T
(76)	T	F	F	T	T
(77)	T	F	F	F	T
(78)	T	T	T	F	T
(79)	T	T	T	F	F
(80)	T	T	T	F	T
(81)	F	T	T	T	T
(82)	F	F	T	T	T
(83)	T	T	T	T	F
(84)	F	T	F	T	T
(85)	F	F	F	T	F
(86)	F	T	T	T	T
(87)	F	T	T	T	T

	A	B	C	D	E
(88)	T	T	T	F	T
(89)	T	T	F	T	F
(90)	T	T	F	T	F
(91)	F	T	T	F	T
(92)	F	T	T	T	T
(93)	T	F	T	T	T
(94)	T	T	T	T	F
(95)	T	T	F	F	T
(96)	T	T	F	T	T
(97)	T	T	F	T	T
(98)	F	F	F	T	F
(99)	T	T	F	T	T
(100)	T	T	T	T	F
(101)	F	T	T	T	T
(102)	T	T	T	T	F
(103)	T	T	F	F	T
(104)	T	F	T	T	T
(105)	F	T	F	T	F
(106)	T	F	T	F	T
(107)	F	T	F	F	T
(108)	T	T	T	T	T
(109)	T	T	T	F	T
(110)	F	T	F	T	T
(111)	F	F	F	T	F
(112)	T	F	F	T	T
(113)	T	F	T	F	F
(114)	T	T	F	T	T
(115)	F	T	F	F	F
(116)	T	F	F	F	F
(117)	F	F	F	T	T
(118)	F	F	T	T	T
(119)	F	T	T	F	F
(120)	T	T	T	T	T
(121)	T	T	F	T	T
(122)	T	T	T	F	F
(123)	T	T	F	F	T
(124)	T	T	T	T	F
(125)	F	T	T	T	T
(126)	F	F	T	F	F
(127)	T	T	T	F	T
(128)	T	T	F	T	T
(129)	T	F	F	F	F
(130)	T	T	T	T	F

	A	B	C	D	E
(131)	T	T	T	F	T
(132)	F	T	F	F	F
(133)	T	T	F	T	T
(134)	T	T	F	F	T
(135)	F	F	T	F	F
(136)	F	T	T	T	T
(137)	F	T	T	T	F
(138)	T	T	T	F	F
(139)	T	T	F	F	F
(140)	T	T	T	F	T
(141)	T	F	T	T	T
(142)	F	F	T	F	F
(143)	T	T	F	T	T
(144)	T	T	F	T	T
(145)	F	T	T	T	F
(146)	F	T	T	T	F
(147)	T	T	T	F	T
(148)	T	T	F	T	F
(149)	T	T	T	F	T
(150)	T	T	T	T	T
(151)	F	F	F	T	F
(152)	T	F	T	T	T
(153)	T	F	T	T	F
(154)	T	F	T	F	T
(155)	T	T	T	F	T
(156)	T	T	T	F	F
(157)	T	T	T	F	T
(158)	T	F	T	F	T
(159)	T	T	F	T	T
(160)	T	T	F	F	F
(161)	T	T	T	T	F
(162)	T	T	T	F	T
(163)	T	T	T	F	F
(164)	F	T	T	T	T
(165)	F	T	F	T	F
(166)	T	F	F	T	F
(167)	T	F	T	T	F
(168)	T	T	T	F	T
(169)	T	T	T	F	F
(170)	T	T	F	T	T
(171)	T	T	T	T	F

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