CHAPTER-1

INTRODUCTION TO PHARMACOLOGY

This chapter focuses on the fundamental principles of pharmacology. It discusses basic information, such as how drugs are named and how they're created. It also discusses the different routes by which drugs can be administered.

- **Introduction to pharmacology, scope of pharmacology.**
- **Routes of administration of drugs, their advantages and disadvantages.**
- **Various processes of absorption of drugs and the factors affecting them.**
- **Metabolism, distribution and excretion of drugs.**
- **General mechanism of drugs action and their factors which modify drugs action.**

INTRODUCTION TO PHARMACOLOGY

Pharmacology is the branch of science which deals with study of drugs. It deals with pharmacokinetics, pharmacodynamics and pharmacotherapeutics.

Pharmacodynamics means what the drug does to the body. Examples: Drug Actions, Therapeutic Effects, Adverse drug effects.

Pharmacokinetics means what the body does to the drug. Examples: Absorption, Distribution, Metabolism, Excretion.

Pharmacotherapeutics means use of drugs to prevent and treat diseases.

According to WHO, **Drug** is any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient.
Prevention: BCG vaccine, Anti-malarial drugs for malarial prophylaxis.
Diagnosis: Barium meal for Peptic ulcer diagnosis.
Treatment: Antibiotics, Anti-TB drugs.

Medicines are chemical substances or mixtures of one or more substances used in suitable convenient form for treatment of diseases.All medicines are drugs but all drugs are not medicine. Drugs in aseptic formulation are medicines.

Essential drugs/ essential medicines are those medicines, which satisfy the priority health care needs of the population.

Orphan drugs are used for diagnosis, prevention or treatment of life-threatening or very serious diseases or very rare disorders/diseases. These are named "orphan" because pharmaceutical industry has little/no interest in developing and marketing these drugs, which are meant for only a small number of patients.
Examples: Arsenic Trioxide, Thalidomide, Nitric Oxide, L-Glutamine, Apomorphine Hydrochloride.

Prodrug is an inactive drug which is metabolized in the body to become an active drug. Examples include:

- Cortisone ---- Hydrocortisone
- Prednisone---- Prednisolone
- Dipivefrine ---- Epinephrine
- Minoxidil ---- Minoxidil sulphate
- Vanciclovir ---- Aciclovir

Some Branches of Pharmacology

Toxicology: It is the study of poisonous effect of drugs and other chemicals. It includes detection, prevention and treatment of poisonings. Drug toxicity may be reversible or irreversible, depending upon the organs affected. Example of reversible toxicity includes liver toxicity due to paracetamol overdose/prolonged use, whereas example

of irreversible toxicity includes permanent hearing loss (due to 8th cranial nerve damage) because of excessive use of streptomycin.

Pharmacovigilance: It is the science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects which occurs due to use of pharmaceutical products, biological products, blood products, vaccines and herbal formulations.

Chemotherapy: Chemotherapy is the treatment of cancer) with specific drugs/chemical agents which have selective toxicity for the cancer cell with no/minimal effects on the host cells. **Examples:** Methotrexate, Cyclophosphamide, Carmustine, Lomustine.

Clinical pharmacology: Clinical Pharmacology is the scientific discipline that involves all aspects of the relationship between drugs and humans. Its breadth includes the discovery and development of new drugs, the application of drugs as therapeutic agents, the use of drugs, the beneficial and harmful effects of drugs in individuals and society, and the deliberate misuse of drugs.

SCOPE OF PHARMACOLOGY

- To screen the drug for getting desired active drug
- To find out the mechanism of action of drugs.
- For quantification of drug activities
- To provide preclinical data that is essential for human study.

- To perform bioassay.
- For research and development of new molecules as well as old drugs.

DIFFERENT NOMENCLATURES OF DRUGS

There are generally 4 categories of drug names.

- Chemical name/ scientific name
- Non-proprietary name/ Generic name
- Official name
- Proprietary (Brand/ trade) name

Chemical name/ scientific name of drugs: It describes the exact chemical makeup of the drug and placing of atoms and molecular structures of drug. **Example:** N-(4-hydroxyphenyl) acetamide

Non-proprietary name/ Generic name of drugs: It is the name accepted by a competent scientific body/authority. It is the name provided to a drug before it becomes official. **Example**: Diazepam

Official name of drugs: It is the name that listed in USP-NF. It is similar to generic name. **Example**: Diazepam

Proprietary (Brand/ trade) name of drugs: It is the name assigned by the manufacturer and is his property or trade mark. One drug may have multiple proprietary/brand/trade names depending on the number of manufacturers. **Example:** Crocin

DIFFERENT SOURCES OF DRUGS

- **Plants:** Morphine, digoxin, atropine, castor oil, etc.
- **Animals:** Insulin, thyroid extract, heparin and antitoxin sera, etc.

- **Minerals:** Liquid paraffin, magnesium sulfate, magnesium trisilicate, kaolin.
- **Synthetic source:** Aspirin, sulphonamides, paracetamol, acyclovir, etc.
- **Microorganisms:** Penicillin, streptomycin and cephalosporin etc.
- **Genetic engineering:** Human insulin, human growth hormone etc.

VARIOUS ROUTES OF DRUG ADMINISTRATION:

Various routes of drug administration are mainly categorized into two types.

a) Systemic Routes
- Enteral Route: Oral, Rectal
- Parenteral Route: Intravenous, Intramuscular, Subcutaneous, Sublingual, Transdermal, Nasal, Inhalational, Intradermal etc.

b) Local Routes: Topical, Intra-articular etc.

ORAL ROUTE: In this route drugs are swallowed through buccal cavity.

Advantages of oral route are:

- Most commonly used method (safe, convenient & painless procedure).
- Economical as sterilization of drug products is not required.
- There is no need of any assistant.

Disadvantages of oral route are:

- Onset of drug action is slower than parenteral routes.
- Polar drugs (like streptomycin) cannot be absorbed in g.i.t.
- Drugs like Penicillin-G, Insulin, and Oxytocin are destroyed by the gastric HCl, so cannot be used orally.
- First pass metabolism of drugs occurs in this route, so bioavailability becomes lower.
- Bad test, bad smell and irritant drugs are nonacceptable by many patients mainly by paediatric populations.
- Drugs cannot be given to unconscious patents in this route.
- Drugs cannot be administered to uncooperative patients like Schizophrenics.
- Drugs cannot be given during emesis/vomiting.

INTRAVENOUS ROUTE: Drugs are injected into the lumen of veins.

Advantages of this route are:

- Drugs can directly enter into the systemic circulation.
- No first pass effects are observed.
- Quicker onset of action of drug is produced as compared to oral.
- Few quantities of drugs are needed to get better effects.
- This route is valuable in emergency conditions like Acute MI, angina pectoris, epilepsy etc.
- Can be administered to unconscious, uncooperative patients.

- Gastric irritants can be infused by this route.
- Large volume of liquid drugs can be infused.
- Amount of the drug can be controlled without variation.

Disadvantages of IV route are

- Strict aseptic conditions are required for administration.
- Patient needs assistance of healthcare professionals.
- It is a painful method of administration of drugs as needle is used.
- Risky because once drug is injected, it cannot be recalled.
- Air/particulate matter entry may produce embolism.
- Drugs in suspensions / emulsions cannot be administered.
- Oily drugs cannot be injected.
- Depot injections cannot be given.
- Chances of venous thrombosis, necrosis and thrombophlebitis at/around the site of injection.

INTRAMUSCULAR ROUTE: Drugs are injected into muscles. These injections can be given to deltoid or gluteal muscle.

Advantages of intramuscular route are

- Absorption is predictable.
- Rapid onset of action compared to oral route.
- Depot injections can be given in this route.

Disadvantages of intramuscular route are

- Strict aseptic conditions are required.
- There may be chances of abscess formation at injection site.

- Nerve damage of muscle can occur.
- Large volume of drugs cannot be administered.

RECTAL ROUTE: Drugs are inserted into rectum. E.g. rectal suppositories, bisacodyl laxatives.

Advantages of rectal route are:

- This route is useful in patients having nausea and vomiting.
- Drugs cannot undergo first pass effects
- This route is useful for gastric irritant drug administration.

Disadvantages of rectal route are:

- Rectal damage may occur.
- Drug bioavailability is irregular.
- Inconvenient method.
- Embarrassing to the patient.
- Not suitable in emergency condition.

SUBLINGUAL ROUTE: Drug is placed below tongue or crushed inside buccal cavity.

Advantages of sublingual route are:

- Fast onset of action due to rapid absorption in larger surface area.
- Drugs bypass the portal circulation, so no first pass effect of drugs.
- Drugs can be spitted out at any time when side effects are seen.

Disadvantages of sublingual route are:

- Distasteful, irritant drugs cannot be taken in this route.

- Drugs like Insulin cannot be absorbed due to high molecular weight.
- Examples of drugs used in this route are: Nifedipine, glyceryl trinitrate, Isosorbide dinitrate, Isoprenaline sulphate.

Other Routes are:

- **Intrathecal route**: Drugs are injected into subarachnoid space of spinal cord e.g. spinalanaesthetics.

- **Inhalation route:** Inhalation means inspiration of drug through nose or mouth. The drugs administered by this route include salbutamol, ipratropium bromide, montelukast, and nitrous oxide.

- **Intraperitonial route**: Drugs are injected into the abdominal cavity e.g. infant saline,glucose etc.

- **Intra-articular route**: Drugs are injected directly into a joint space e.g.hydrocortisone.

- **Intradermal**: Drug is given into the layers of the skin e.g. B.C.G.vaccine.

- **Subcutaneous**: Non-irritant drug substances are given into subcutaneoustissue e.g. insulin.

- **Transdermal patches:** In these adhesive patches, the drug is incorporated into a polymer which in turn is bonded to an adhesive plaster. The drugs can be delivered for a period ranging from 1-3 days from the site of their application. Different site of application include chest, abdomen, upper arm or mastoid region. **Examples**: Transdermal Patches of nitroglycerine, scopolamine, clonidine.

- **Conjunctival:** Drugs (Sulfacetamide) are instilled/ applied into the conjunctiva.

- **Vaginal and Urethral:** Different pessaries are used for fungal infections.

- **Inunction (Rubbing):** Rubbing onto the skin. Example: creams, ointments etc.

ABSORPTION OF DRUGS

- The process of movement of drug from its site of administration to the systemic circulation is called as absorption.

- **Bioavailability:** It is the rate and amount of drug that is absorbed from a given dosage form and reaches the systemic circulation

following non-vascular administration. When the drug is given IV, the bioavailability is 100%.

- **Bioequivalence:** Many pharmaceutical companies can manufacture same drug (with same dose and dosage form). For example, Phenytoin is available as tablet Dilantin and tablet Eptoin by two different companies. If the difference in the bioavailability of these two drug preparations is less than 20%, they are known to be bioequivalent.

MECHANISMS OF DRUG ABSORPTION

- **Passive diffusion:** The rate of diffusion is directly proportional to the concentration gradient across the membrane; that means the drug molecules diffuse from a region of higher concentration to lower concentration until equilibrium is maintained. It is also called as down-hill transport mechanism. Majority of drugs are transported through this mechanism.

- **Active transport:** It is also called as up-hill transport mechanism; that means the movement of drug molecules across a membrane from a region of their lower concentration to a region of their higher concentration in the direction against the concentration gradient. Examples: 5FU by intestine, digitalis by liver etc.

- **Facilitated diffusion:** Facilitated diffusion is the process of spontaneous passive diffusion of drugs across a biological membrane through specific proteins. It is also called as downhill transport mechanism. Examples: Aminoacid transport in brain, antiviral drugs, riboflavin, thiamine etc.

- **Pinocytosis:** It is one type of endocytosis method, in which cells engulf liquid drug substances, gathering them into special membrane-bound vesicles. The transport of liquid drugs takes place into a cell by means of local infoldings by the cell membrane. Examples: Insulin is transported through BBB by pinocytosis.

- **Phagocytosis:** Phagocytosis means engulfing of larger, solid drug particles into membrane-bound vesicles called phagosomes. Examples: Poisoning by botulinum toxin.

- **Filtration:** It is important in absorption of low molecular weight (<100D), low molecular size e.g: urea, sugar. This phenomenon important in renal excretion, removal of drug from CSF and entry of drugs into the liver. Examples: Urea, alcohol, glucose.

FACTORS AFFECTING ABSORPTION/BIOAVAILABILITY

Physico-chemical properties of drug:

- **Physical state:** Liquids are absorbed better than solids.
- **Lipid or water solubility:** Drugs in aqueous solution mix more readily than oily solution. But at cell membrane, lipid soluble

drugs enter into the cell more rapidly than the water soluble drugs.

- **Ionization:** Unionized drugs are lipid soluble, so they are absorbed rapidly. Ionized drugs are water soluble, so they are absorbed poorly.
- **Particle size:** Small particle size drug is better absorbed than larger one.
- **Formulation:** Fillers like lactose, sucrose, starch and calcium phosphate in tablet formulations may affect the absorption and stability of the drugs.
- **Disintegration time and dissolution rate:** So decreasing disintegration time and increasing dissolution rate causes faster absorption of drugs.

Physiological factors

- **Gastrointestinal transit time:** Fast absorption of drug occurs when it is given on empty stomach. But some drugs like griseofulvin, propranolol and riboflavin are better absorbed in the presence of food.
- **Presence of other agents:** Presence of some agents affects bioavailability of drugs. Vitamin C enhances the absorption of iron from the G.I.T. Milk can reduce absorption of tetracycline as it forms insoluble complexes.Calcium present antacid also reduces tetracycline absorption.
- **Area of the absorbing surface and local circulation:** Drugs are absorbed better from the small intestine than from the stomach

because of the larger surface area. Increased capillary supply can increase the absorption of drugs.

- **First pass effect:** Rapid degradation of a drug by the liver during the first pass metabolism affects the bioavailability. Thus better absorbed drug after oral administration may not be effective because of its extensive first pass metabolism.
- **Pharmacogenetic factors:** Individual variations occur due to the genetically mediated reason in drug absorption and response.
- **Disease conditions:** Absorption and first pass metabolism may be affected in disease states like malabsorption, thyrotoxicosis, achlorhydria and liver cirrhosis.

DISTRIBUTION OF DRUGS

Drug distribution refers to the movement of a drug to and from the blood and various tissues of the body (for example, fat, muscle, and brain tissue). In other words, distribution means the pattern of scattering of drugs to different body tissues. Drugs are generally distributed through various body fluid compartments such as (a) plasma (b) interstitial fluid compartment (c) transcellular compartment.

FACTORS THOSE AFFECT DISTRIBUTION OF DRUGS

- **Protein binding of drug:** Plasma protein binding refers to binding of drugs to plasma proteins **(human serum albumin, lipoprotein, glycoprotein,** and **α, β, and γ globulins)** those are present in the blood circulation. A drug's efficiency is affected by the degree to

which it binds to plasma proteins. A variable portion of absorbed drug is reversibly bound to plasma proteins. The less bound drug can more efficiently cross cell membranes or diffuse. High protein binding drugs are long acting, because bound drug fraction is not available for metabolism or excretion. Acidic drugs generally bind to plasma albumin and basic drugs to α_1 acid glycoprotein. High protein bound drug like phenylbutazone is long acting. Low protein bound drug like thiopental sodium is short acting.

- **Physiological barriers to distribution**: There are some specialized physiological (not anatomical) barriers in the body due to which the drug will not be distributed uniformly in all the tissues. These barriers are: Blood brain barrier (BBB)through which thiopental sodium is easily crossed but dopamine cannot cross, placental barrier which allows non-ionized drugs with high lipid soluble drugs like morphine and alcohol by a process of simple diffusion to the foetus.
- **Tissue binding:** The concentration of a drug in certain tissues after a single dose may persist even when its plasma concentration is reduced to low. On chronic use, their concentration reaches a very high level. Example: Iodine is stored in the thyroid tissue.
- **Clearance:** It is defined as volume of plasma cleared off the drug by metabolism and excretion per unit time. Protein binding reduces the amount of drug available for filtration at the kidneys and hence delays the excretion, thus the protein binding reduces the clearance.

DRUG BIOTRANSFORMATION/METABOLISM

Biotransformation of drug means chemical alterations/changes of drugs in the body by enzymes.

Consequences of drug biotransformation/metabolism:

A) Active drugs are converted to inactive metabolites: Most drugs and their active metabolites are rendered inactive or less active, e.g. cocaine

Cocaine (active) -- benzoylecgonine (inactive)

B) Active drugs are converted to Active metabolites:

Morphine -- Morphine-6-glucuronide

Digitoxin -- Digoxin

Chloral hydrate -- Trichloroethanol

Imipramine -- Desipramine

C) Inactive drugs (Prodrugs) are converted to active metabolites:

Few drugs are inactive as such and need conversion in the body to one or more active metabolites. Such a drug is called a prodrug.

Microsomal enzymes and Non-microsomal enzymes are responsible for drug metabolism.

DRUG BIOTRANSFORMATION REACTIONS

Drug biotransformation reactions involve two phases of reactions.

- **Phase I reactions:** Oxidation, reduction and hydrolysis.
- **Phase II reactions:** Glucuronidation, Acetylation, Sulfate conjugation

PHASE I REACTIONS: These reactions are degradative in nature. The drug molecules are metabolized to smaller polar and non-polar compounds by introduction of new functional groups. The metabolites (end products) may be active or inactive.

A) Oxidation reactions: Oxidation reactions involve the introduction of oxygen and/or the removal of hydrogen atom or hydroxylation, dealkylation or demethylation of drug molecule. Examples of drugs undergoing oxidation reactions include:

- Phenobarbitone---- p-hydroxyphenobarbitone
- Pentobarbitone---- hydroxypentobarbitone
- Mephobarbitone---- phenobarbitone
- Morphine---- Normorphine
- Amitriptyline---- Nortriptyline
- Phenacetin----Paracetamol
- Parathion---- Paraoxon
- Alcohol ---- Acetaldehyde---- Acetic acid

B) Reduction reactions: The reduction reactions will take place in the presence of enzyme reductase, which catalyze the reduction of azo and nitro compounds. Examples of drugs undergoing reduction reactions include:

- Cortisone ---- Hydrocortisone
- Chloral hydrate----trichloroethanol
- Prontosil ---- Sulfanilamide

C) Hydrolysis: Examples of drugs undergoing hydrolysis include:

- Procaine----PABA
- Atropine---- Tropic acid

PHASE II REACTIONS: These reactions are synthetic in nature. The metabolites are mainly water soluble and are inactive. These reactions are also called as conjugation reactions.

A) Glucuronide conjugation: This reaction is carried out by a group of UDP-glucuronosyl transferases (UGTs). Examples of drugs undergoing glucuronide conjugation reactions are: diazepam, chloramphenicol, paracetamol, lorazepam, metronidazole, and aspirin.

B) Sulfate conjugation: Sulfotransferases carry out these reactions. Examples of drugs undergoing sulphate conjugation include: chloramphenicol, methyldopa etc.

C) Methylation: Methyl transferases carry out these reactions. Examples of drugs undergoing methylation include: adrenaline, histamine, methyldopa, and captopril.

DIFFERENT CLASSES OF PRODRUGS

These can be classified into 2 types:

Type I: These are converted intracellularly. Example: statins

Type II: These are converted extracellularly. Example: etoposide phosphate

FACTORS THESE AFFECT DRUG METABOLISM

The factors affecting drug metabolism are:

- **Chemical factors:** enzyme induction, enzyme inhibition, chemicals present in environment
- **Biological factors:** Age, sex, diet, species, strain, altered physiological factor etc.
- **Physicochemical factors**

Chemical factors:

a) Enzyme induction: It is defined as increase in metabolizing ability of enzymes.

Mechanisms of enzyme induction: Enzyme induction takes place due to following factors:

- Increase in size of liver
- Increase in blood flow to liver

Consequences of enzyme induction include:

- Decreased pharmacological activity of drugs
- Increased activity of drugs when active metabolites are formed

b) Enzyme inhibition: A decrease in the drug metabolizing ability of an enzyme is called as enzyme inhibition. The process of inhibition may be direct or indirect.

Enzyme inhibition is more important clinically than enzyme induction especially for drugs with narrow therapeutic index.

Examples of enzyme inhibitors: ketoconazole, itraconazole, sulphonamides, chloramphenicol, metronidazole.

c) **Chemicals/heavy metals present in environment:** Several environmental chemicals influence the drug metabolizing ability of enzymes. For example: DDT has enzyme induction effect. Organophosphates and heavy metals inhibit drug metabolizing ability of enzymes.

Biological Factors

- **Age:** In neonates and in infants the microsomal enzyme system is under-developed. So, most drugs are metabolized slowly. For example: caffeine has a half-life of 4 days in neonates where as in adults it is 4 hours. Children metabolize many drugs much more rapidly than adults as the rate of metabolism increases in this age group. In elderly, the microsomal enzyme activity is decreased due to decreased liver size. So decreased metabolism of drugs takes place at this age.
- **Diet:** Diet can alter the enzyme content and activity. Low protein diet decreases the drug metabolizing activity and high protein diet increases the drug metabolizing ability.
- **Sex difference:** In humans, women metabolize benzodiazepines slowly than men.

Physicochemical factors: Factors like molecular size and shape of drug influence drug metabolism.

FIRST PASS METABOLISM/FIRST PASS EFFECT

The first pass effect is a phenomenon of drug metabolism whereby the concentration of a drug is reduced before it reaches the blood circulation. In other words, some quantity of drugs gets metabolized before entering into the systemic circulation. Routes other than Enteral and topical routes avoid first pass metabolism. Examples: Sublingual, Transdermal patches Intravenous, Intramuscular, Subcutaneous etc.
The drugs which undergo extensive first pass metabolism are:

CVS drugs: Aspirin, Nitrates, Metoprolol, propranolol, verapamil

Respiratory drugs: Salbutamol

CNS drugs: levodopa, carbidopa

DRUG EXCRETION

Drug excretion means the removal of unaltered/altered form of drug out of the body. The major routes are renal, hepatobiliary and pulmonary. The minor routes of excretion are saliva, sweat, tears, breast milk, vaginal fluid, nails and hair. The rate of drug excretion affects its duration of action. The drug that is excreted slowly has longer duration of action.

DIFFERENT ROUTES OF DRUG EXCRETION

- **Renal excretion:** The excretion of drugs by the kidney involves:
    - Glomerular filtration
    - Active tubular secretion
    - Passive tubular reabsorption.

The primary function of glomerular filtration and active tubular secretion is to remove drug out of the body, while tubular reabsorption tends to retain the drug.

Glomerular filtration: Only free form of drugs (not bound to plasma proteins) can pass through glomerulus. High molecular weight drugs (above 20000) cannot excrete in this route. Low molecular weight drugs also can filtered through glomerulus e.g. digoxin, ethambutol, etc. This process depends on

- the concentration of drug in the plasma
- molecular size, shape and charge of drug
- Glomerular filtration rate.

Active tubular secretion: This process is energy dependent carrier mediated active transport. The cells of the proximal convoluted tubule in nephron actively transport drugs like acetazolamide, dopamine, and thiazides from the plasma into the lumen of the tubule.

Tubular reabsorption: Tubular reabsorption process helps to retain the drug. The reabsorption of drug from the lumen of the distal convoluted tubules into plasma occurs either by simple diffusion or by

active transport. When the urine is acidic, the degree of ionization of basic drug increase and their reabsorption decreases. When the urine is more alkaline, the degree of ionization of acidic drug increases and the reabsorption decreases. So the amount of drug excreted is the sum of drugs filtered and secreted minus the amount of drugs reabsorbed.

Amount of Drugs excreted = Filtered drugs + secreted drugs - reabsorbed drugs.

- **Hepatobiliary excretion:** Polar drugs and drugs having molecular weight more than 300 daltons are excreted in the bile. After drug excretion through bile into intestine, some amount of drug is reabsorbed into portal vein leading to an enterohepatic cycling which can prolong the action of drug. Examples of such drugs are chloramphenicol and oral estrogen. They are secreted into bile and largely reabsorbed and have long duration of action.
- **Excretion through faecal route:** When a drug is administered orally, some part of the drug is not absorbed, so these are excreted in the faeces. The drugs which do not undergo enterohepatic cycle after excretion into the bile are ultimately passed with stool e.g. aluminium hydroxide changes the stool into white colour, ferrous sulfate changes the stool into black and rifampicin into orange red.
- **Pulmonary excretion:** Drugs like inhalation anaesthetics and alcohols are excreted through lungs. The rate of drug excretion through lung depends on the volume of air exchange, depth of respiration, rate of pulmonary blood flow and the drug concentration

gradient.

- **Sweat**: A number of drugs are excreted into the sweat. e.g. rifampicin, arsenic etc.
- **Mammary excretion:** Many drugs mostly weak basic drugs can be accumulated into the milk. So lactating mothers should be cautious about the intake of these drugs because they may enter into baby through breast milk and produce harmful effects in the baby e.g. ampicillin, aspirin, chlordiazepoxide, diazepam, furosemide, morphine, streptomycin etc.

PLASMA HALF-LIFE/BIOLOGICAL HALF-LIFE/TERMINAL HALF-LIFE /t ½

Plasma half-life/biological half-life of a drug is the time required for the body to eliminate 50% of the drug. A drug's biological or terminal half-life is how long it takes for half of the dose to be eliminated from the bloodstream. For example if a blood level of drug A is 8.6 mg/ml at 10 minutes and 4.3 mg/ml at 60 minutes, so the half – life of that drug is 50 minutes. T1/2 determination of a drug is important because it helps to determine how much and when doses of drugs need to be administered in order to produce therapeutic effects. Drugs having short half-lives require frequent dosing whereas drugs with long half-lives required less frequent dosing.

PHARMACODYNAMICS

It deals with drug actions and drug effects

PRINCIPLES OF DRUG ACTION

- **Stimulation:** Adrenaline increases heart rate by stimulating heart, Pilocarpine secrets saliva by stimulating salivary glands.
- **Depression:** Barbiturates produces sedation by depressing CNS, quinidine depresses heart in cardiac arrythmia.
- **Irritation:** Bitters increase salivary and gastric secretion by irritating salivary gland and gastric glands.
- **Replacement:** Application of natural metabolites, hormones in deficiency states. E.g. levodopa in Parkinsonism, insulin in diabetes mellitus, iron in anaemia.
- **Cytotoxic action:** Selective cytotoxic action on malignant cells without affecting host cells. **Examples:** Cyclophosphamide (anticancer drug).

SOME TERMINOLOGIES IN PHARMACODYNAMICS

AGONISTS

Agonists are drugs which activate receptors to produce effects similar to that of the physiological signal molecules like acetylcholine, adrenaline, dopamine, serotonine. These are the drugs which have both high affinity as well as high intrinsic activity.

ANTAGONISTS:

Antagonists are drugs which prevent the action of agonists on specific receptor or the subsequent response, but do not have any effect of their

own. These are the drugs which have only the affinity but no intrinsic activity.

PARTIAL AGONIST

It is a drug which activates the receptor submaximally. E.g. Pindolol has partial agonistic activity at β1 receptors. But in the presence of agonist like adrenaline, it produces antagonistic effects.

INVERSE AGONIST

Inverse agonist is a drug that binds with the same receptor as an agonist, but produces pharmacological actions opposite to that of agonist. E.g. β carboline is an inverse agonist at $GABA_A$ receptor producing anxiogenic effect and convulsive effect. [Full Agonist for $GABA_A$ Receptor: Benzodiazepine, which produces sedative effect].

THERAPEUTIC WINDOW

Therapeutic window or safety window is a range of doses of drugs, which lies between efficacy of drugs and their toxicity.

Therapeutic window provides best therapeutic effects without side effects or toxicity.

Within therapeutic window, a drug can treat disease effectively.

THERAPEUTIC INDEX

The therapeutic index (therapeutic ratio) is a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes toxicity. It is a measure of the safety of a drug. It is calculated as LD_{50}/ED_{50}.

Drugs having high T.I. are safer whereas those having low T.I. are more likely to be toxic.

Drugs with high T.I.: Penicillin and majority antimicrobials [except Aminoglycosides].

Drugs with Low T.I.: Digoxin, Insulin, Warfarin.

SYNERGISM

Combination of two or more drugs, which produces an effect greater than the sum of their individual effects, is called as synergism. It is also called as synergetic effect or synergistic effect. Synergism is opposite of antagonism.

ADDITIVE EFFECT

Additive effect means the effect of two drugs is equal to the sum of the effect of the two drugs taken separately. This is usually occurs due to the two drugs acting on the body through same mechanism. **Examples:** tranquilizer and painkiller.

DRUG POTENTIATION

When a drug lacks effects of its own, but increases the effect of a second active drug, it is called as drug potentiation.
Examples: Levodopa and Carbidopa.

DRUG ANTAGONISM: Any time when the combined effect of two drugs is less than the sum of the effects of the individual drugs, this concept is known as Antagonism.

CHEMICAL ANTAGONISM: When two drugs show chemically opposite actions with each other it is called chemical antagonism. E.g. Heparin is antagonized by protamine.

PHYSIOLOGICAL ANTAGONISM: When two agonists, acting at different sites, counterbalance each other by showing opposite effects on a same physiological system, it is called as physiological antagonism. E.g. CNS stimulants antagonize CNS depressants.

BIOLOGICAL ANTAGONISM: When one drug affects the absorption, metabolism or excretion of the other drugs and reduces the concentration of the active drug at its site of action, it is called as biological antagonism. E.g. Sodium Bicarbonate and Sodium dihydrogen citrate increase the excretion of acidic drugs.

PHARMACOLOGICAL ANTAGONISM: It is pharmacodynamic antagonism between two drugs action on the same receptor.

Reversible (or competitive or equilibrium type) Antagonism: Agonist and the antagonist bind to the same receptor and compete for binding. By increasing the concentration of agonist, response of antagonist can be overcome. E.g., atropine is a competitive antagonist of acetylcholine.

Irreversible (non-equilibrium type) Antagonism: In this type,the removal of antagonist from the receptor is less when agonist concentration is increased. There is no change in the response of antagonist as agonist is unable to replace antagonist. E.g. Phenoxybenzamine is an irreversible alpha adrenergic receptor blocker; Methysergide is an irreversible 5-HT receptor blocker.

Non-Competitive Antagonism: In this type, the antagonist produces its action through another receptor or through other mechanisms. There is no competition between the agonist and the antagonist at receptor site as antagonist is not chemically similar with the agonist. There is change in the response of agonist in presence of antagonist. E.g., Diazepam and Bucuculline

Negative Antagonism (Inverse agonism): These antagonists stabilize the receptor from undergoing conformational change and produce responses that are opposite to those of agonist. E.g., β-carbolines are negative antagonist at benzodiazepine receptors.

GRADED DOSE RESPONSE: A response to a drug such that as the dose of drug increases the intensity of the response increases.

QUANTAL DOSE RESPONSE: A quantal dose response is all-or-none. That means, there either is or is not a response. E.g. antiemetic drug stops the vomiting or not.

A LOADING DOSE is an initial higher dose of a drug that is administered at the beginning of a course of treatment before dropping down to a lower maintenance dose.

A MAINTENANCE DOSE is a small and fixed dose. Maintenance dose usually takes long time to reach the minimum effective concentration, as the drug plasma concentration slowly increases and then exceeds the minimum effective concentration. **Example:** Anti-platelet drug **Clopidogrel.** First Intravenous clopidogrel is given as a loading dose to prevent clotting and then oral maintenance doses.

DOSE: It is carefully measured and administered quantity of a drug that is prescribed by a physician for a patient at any one time. It is the right amount of a drug needed to produce a certain degree of response in a given patient.

MECHANISMS OF DRUG ACTIONS

Generally two types of drug actions are observed. They are

- Non receptor mediated drug action
- Receptor Mediated drug action

NON-RECEPTOR MEDIATED DRUG ACTION

The drugs produce/show their actions without binding with receptors. Examples include:

- Ispaghula (Bulk laxatives): It increases physical mass.
- Paraamino benzoic acid: It produces effect by absorbing UV rays.
- Activated charcoal: Used in the treatment of poisoning for its adsorptive property.
- Mannitol, magnesium sulfate: Produces osmotic activity.
- Radioisotopes: Produces radioactivity.
- Antacids: They neutralize gastric acid (HCl) in stomach and relieves from acidity.
- Potassium permanganate: Shows oxidizing property by inducing oxidation.
- Chelating agents (EDTA, dimercaprol): Cause chelation of heavy metals like Arsenic, Cadmium, and mercury.

RECEPTOR MEDIATED DRUG ACTION

Receptor is defined as a macromolecular binding site present on the surface or inside the effector cell that recognizes the drug and produces the response to it, but itself has no other function.

- **Type I:** Agonist mediated ion channel receptor
- **Type II:** G-protein coupled receptor
- **Type III:** Enzymatic receptor
- **Type IV:** Steroidal receptor

Agonist mediated ion channel receptors:

These receptors are present on cell surfaces and are coupled to ion channels directly. These channels open after binding to an agonist. After opening, ions move through these channels causing depolarization/hyperpolarization and produces response.Examples: Nicotinic receptors, GABA receptor, glutamate receptor, Glycine receptor.

G-protein coupled receptor (Metabotropic receptors): These are cell membrane receptors which are bound to the enzyme/ ion channel/carrier protein through one or more GTP activated proteins (G-proteins) for producing effects. These receptors have seven transmembrane spanning segments in their structure. Drugs bind to the receptor and activate the inactive G protein (GTP activated protein). Activation of G protein produces one of the 3 actions:

- Activation or inhibition of adenyl cyclase: Examples: β-receptors increase cAMP, and somatostatin decreases cAMP.
- Activation of phospholipase C: This enzyme converts PIP2 to IP3 and DAG. Final result is increased intracellular calcium and response production. E.g. vasopressin V1 receptors.
- Stimulation or inhibition of ion channels: E.g. M_2 receptors of ACh.

Enzymatic receptor (Kinase- linked receptors):

It is also called enzyme-linked receptor, enzymatic receptor, and catalytic receptor. It is a transmembrane receptor, which means it is

present inside and outside of cell membrane. Binding of drug to this receptor, produces enzymatic activity on the intracellular side. Example of drugs acting on this receptor is Insulin.

Steroidal receptor (intracellular receptors/ cytosolic receptors)

Ligands bind to their receptor in cytoplasm and the complex then migrates to the nucleus and binds to specific DNA sites, producing alterations in gene transcription and altered protein synthesis. Such effects occur over a time-course of minutes to hours.

Functions of Receptors

- They determine the quantitative relations between concentration of drug & effects.
- Receptors are responsible for selectivity of drug action.
- Receptors mediate the actions of both agonists as well as antagonists.

SECOND MESSENGER is a substance, whose release within a cell is promoted by a hormone to produce response by the cell.

- **Examples**: cAMP, cGMP, inositol trisphosphate (IP_3), diacylglycerol (DAG), and calcium.

FACTORS THOSE MODIFY DRUG ACTIONS

There are a number of factors which can modify drug response.

- **Pharmacokinetic Factors:** In neonates, the chances of drug toxicity are increased due to inefficient renal filtration, relative enzyme deficiencies etc. Geriatrics are highly susceptible to nephrotoxic drugs as drug metabolism capacity by the liver are reduced.
- **Pharmacodynamics Factors:** Tolerance leads to decreased drug response.
- **Genetic Factors:** Individual susceptibility to increased toxicity with particular drugs can occur due to genetic variations.
- **Pregnancy:** It affects pharmacokinetics of drugs by decreased gastrointestinal activity, enhanced blood volume, decreased plasma albumin, increased body fat and increased renal blood flow.
- **Life Style:** Drug responses can be decreased by factors like alcohol intake, cigarette smoking etc.
- **Drug Interaction:** One drug can modify the effects to another drug.
- **Psychological Factors:** Psychological factors can affect patient's response to a drug. Example, analgesics are more effective if the patient thinks drugs are effective.

DIFFERENT ADVERSE DRUG EFFECTS/ ADVERSE DRUG REACTIONS

- Side effects
- Secondary effects
- Toxic effects
- Intolerance
- Idiosyncrasy
- Drug allergy
- Photosensitivity

- Drug dependence
- Drug withdrawal reactions
- Teratogenicity
- Mutagenicity
- Carcinogenicity
- Drug induced diseases

- **Adverse drug reaction:** A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function. This definition excludes overdose, drug abuse, and treatment failure and drug administration errors.

- **Adverse drug event:** An adverse drug event is "an injury resulting from the use of a drug. Under this definition, the term ADE includes harm caused by the drug (adverse drug reactions and overdoses) and harm from the use of the drug (including dose reductions and discontinuations of drug therapy)." Adverse Drug Events may results from medication errors but most do not.

- **Side effects:** These are unwanted but often unavoidable pharmacodynamic effects which occur at therapeutic doses of drugs. E.g. promethazine causes sedation which is unrelated to its antiallergic action.

- **Secondary effects:** These are the indirect consequences of a primary action of the drug. E.g. suppression of bacterial flora by tetracyclines causes superinfections.

- **Toxic effects:** These are the result of excessive pharmacological action of the drug due to over dosage or prolonged use. E.g. Morphine causes respiratory failure in over dosage, Paracetamol causes liver toxicity, and Aminoglycosides cause ototoxicity.

- **Intolerance:** It is the appearance of characteristic adverse effects of a drug in an individual at therapeutic doses. **Examples:** one tablet of chloroquine may cause vomiting and abdominal pain in some individuals.

- **Idiosyncrasy:** It is genetically determined abnormal reactivity to a chemical. The drug produces the uncharacteristic reaction after administration. E.g. Barbiturates cause excitement and mental confusion in some individuals, Quinine causes cramps, diarrhoea, purpura, asthma and vascular collapse in some patients, Chloramphenicol produces nondose-related serious aplastic anaemia in rare individuals.

- **Drug allergy:** It is an immunologically mediated reaction producing symptoms which are unrelated to the pharmacodynamic profile of the drug. It generally occurs even with much smaller doses. These reactions are also called **drug hypersensitivity.**

- **Photosensitivity:** It is a cutaneous reaction resulting from drug induced sensitization of the skin to UV radiation. The reactions are of two types:
  (a) **Phototoxic:** In photo toxic reactions, drugs or their metabolites accumulate in the skin, absorb light and undergo photochemical reactions and photo-biological reactions like erythema, edema, blistering by damaging local tissues. **Examples:** tetracyclines.
  (b) **Photoallergic:** Drugs or their metabolites produces cell mediated immune responses, which on exposure to light of longer wave lengths (320–400nm, UV-A) produces eczematous contact dermatitis like reactions. **Examples:** Drugs which can induce photoallergic reactions are sulfonamides, griseofulvin, chloroquine, carbamazepine etc.

- **Drug dependence:** Drug dependence is a psychological or sometimes physical state resulting from the interaction between a living organism and a drug, characterised by behavioural and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychological/ physical effects and sometimes to avoid the discomfort of its absence.
  Drug dependence is a state in which use of drugs for personal satisfaction is accorded a higher priority than other basic needs. E.g. nalorphine produces physical dependence.

- **Drug withdrawal reactions:** These reactions appear after sudden stoppage of drugs during a course of therapy**.** E.g.severe hypertension, restlessness may occur shortly after discontinuing clonidine, Worsening of angina pectoris may result from stoppage of β blockers.

- **Teratogenicity:** It is the capacity of a drug to cause foetal abnormalities when given to the pregnant mother.

  Thalidomide: It can cause phocomelia, multiple defects of internal organs.

  Anticancer drugs: Drugs like methotrexate can cause cleft palate, hydrocephalus, multiple defects, and foetal death.

  Androgens: They can produce limb defects, and cardiac defects to newborns.

  Progestins: They can produce virilization of female foetus.

- **Mutagenicity:** It is the capacity of a drug to cause genetic defects.

- **Carcinogenicity:** It is the ability of a drug to cause cancer.

- **Drug induced diseases:** These are also called **iatrogenic (physician induced)** diseases. Example: Peptic ulcer is caused by salicylates and corticosteroids.

- **Drug tolerance:** Tolerance is defined as 'unusual resistance to a drug causing either a total loss or a decreased response to a drug'.

- **Pseudo-tolerance:** is defined as 'resistance to drug response on oral route of administration only, if a drug is taken for a long time in small amounts'.

- **True-tolerance:** is defined as 'resistance to drug response on both oral/parenteral route of administration'. It could be:
    - Natural (species or racial).
    - Acquired (functional or dispositional).

- **Cross-tolerance:** means 'if tolerance develops in an individual to one member of a group of drugs, then tolerance will also be seen with other members of that group'. Example: Opioids: If an individual show tolerance to morphine, then he will also show tolerance to pethidine.

- **Drug addiction** is defined as chronic, relapsing brain disease characterized by compulsive drug seeking and use, regardless harmful consequences.

- **Drug habituation** is a condition resulting from the repeated consumption of a drug.

- **Drug abuse** is use of drug for nonmedical purpose, for altering consciousness or for body building. Example: Cocaine, Heroin, Marijuana.

- **Anaphylaxis:** A rapidly developing immunological reaction occurring within minutes after the combination of an antigen with an antibody bound to mast cells or basophils in individuals or animals previously sensitised to the antigen.

DRUG DEVELOPMENT PROCESSES

Drug development process is broadly divided into 3 phases:

- **Drug discovery phase**
- **Preclinical studies**
- **Clinicial trials**

➢ **Drug Discovery Phase:** Most new drugs are discovered through random screening, compound oriented approach, and target oriented approach or rational drug designing.

➢ **Pre-clinical studies (Animal study):** The lead compounds are tested on animals to know their whole pharmacological profile. Experiments are first conducted on small animals like mice, rat, guinea pig and then on large animals like cat, dog, monkey etc.

➢ **Clinical trials (human study):** Before a new drug comes to the market, it is largely tested in animals and in vitro studies (in laboratory) for safety and efficacy. If the drug is found to be promising in these studies, an application called **IND (Investigational New Drug)** is fled with the United States Food and

Drug Administration. If the permission is granted, then drug is tested in humans. This testing is called **clinical trials.**

CHAPTER -2

DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM

- General anaesthetics- adjunction to anaesthesia, intravenous anaesthetics.
- Analgesic antipyretics and non-steroidal Anti-inflammatory drugs- Narcotic analgesics.
- Antirheumatic and anti-gout remedies.
- Sedatives & Hypnotics, psychopharmacological agents, anticonvulsants, analeptics.
- Centrally acting muscle relaxants and anti parkinsonism agents.
- Local anesthetics.

1. GENERAL ANAESTHETICS

Anaesthesia is the reversible loss of response to a noxious stimuli. It may be **general anaesthesia** (if associated with loss of consciousness)

or **local anaesthesia** (consciousness is maintained). Four main features of balanced anaesthesia are

- Unconsciousness
- Muscle relaxation
- Analgesia
- Abolition of compensatory reflex response

CLASSIFICATION OF GENERAL ANAESTHESIA

Inhalational Agents: These agents are stored in cylinders and are delivered to the patient through Boyle's machine. Two important properties of an inhalational agent is its minimum alveolar concentration (MAC) and blood gas partition coefficient.

Minimum Alveolar Concentration (MAC): It is the minimum concentration of an inhalational agent required in the alveoli to produce unresponsiveness to the skin incision in 50% of the patients. It is the **measure of potency** of an agent. *Greater is the MAC, lesser is the potency*. **Nitrous oxide** is a gas with **maximum MAC** and thus **least potency**. Its MAC is 104% i.e. even with pure (100%) nitric oxide alone, we cannot get complete anaesthesia. This is thus, not a complete anaesthetic agent. **Methoxyflurane** is the **most potent** agent (having least MAC).

• **Blood gas partition coefficient:** It is determined by solubility of an agent in the blood. It **determines the speed of onset and recovery** of an anaesthetic drug. Greater is blood gas partition coefficient, lesser is the speed of onset and recovery and vice versa. **Desflurane** is the **fastest acting** agent as it has minimum blood gas partition coefficient.

Methoxyflurane is the **slowest acting** agent (maximum blood gas partition coefficient). **Ether** also has a very high value of this coefficient; therefore it is also a **slow acting** agent.

PHARMACOLOGY OF INDIVIDUAL DRUGS

NITROUS OXIDE

• It is also called 'laughing gas'.

• It is colourless, non-irritating and non-inflammable.

• Colour of N2O cylinder is blue.

• It is a very good analgesic but *weak* anaesthetic agent.

• It is a poor muscle relaxant.

• It shows faster induction & recovery of anaesthesia (low blood gas partition coefficient).

• It is used in a concentration of 50 to 65% with 33% oxygen.

• Entonox is a *mixture of 50% N2O +50% O2*.

HALOTHANE

• It is a colourless, volatile liquid.

• It is a non-irritant, non-explosive and pleasant smelling agent.

• It is stored in amber coloured bottles and contains thymol (0.01%) as preservative.

• It is a good anaesthetic but very poor analgesic agent.

• It can cause hepatitis on repeated use.

• It can also result in malignant hyperthermia, which can be treated with dantrolene.

• It can result in post-anaesthetic chills and shivering. Pethidine is used for treatment of this condition.

ETHER

• It is a pungent smelling and irritant liquid (can result in excessive secretions).
• It is a highly inflammable and explosive agent. Cautery should not be used with ether anaesthesia.
• It is a very good analgesic and muscle relaxant.
• It is very slow in induction of anaesthesia. Guedel's four stages of anaesthesia are based on ether.
• It does not affect the ciliary action and is also a good bronchodilator. Therefore it is safe in asthmatic patients.
• It is very economical and can be used as a sole agent for anaesthesia.
• It is the safest agent in unskilled hands.
• It can result in hyperglycemia, therefore is contra-indicated in diabetic patients.

ENFLURANE

• It is a halogenated ether.
• It is inflammable at high concentrations (> 5%)
• It is contra-indicated in epilepsy as it can raise intracranial tension and produce tonic clonic seizures.
• Like other newer agents, it is also not a good analgesic.

ISOFLURANE

• It is an isomer of enflurane.

• It is not a good analgesic agent.

• Cardiac output is maintained with isoflurane. Therefore, it is the inhalational agent of choice for cardiac surgery.

• It produces least increase in intra-cranial tension, therefore is the agent of choice for neurosurgery.

• It produces maximum decrease in blood pressure, therefore is inhalational agent of choice for producing controlled hypotension.

• It can be used in day care surgery.

• It is safe in pheochromocytoma (does not sensitize the heart to catecholamines).

• It can cause coronary steal phenomenon.

DESFLURANE

• It has minimum blood gas partition coefficient and therefore is the fastest inducing agent.

• It has very high vapour pressure. Its boiling point is 23°C; therefore it boils at room temperature. It requires special vaporizers due to this property.

• It produces cardiovascular effects similar to isoflurane except coronary steal phenomenon.

• Induction with desflurane is unpleasant as it can lead to coughing, breath holding and laryngospasm.

• It can also be used in day care surgery.

SEVOFLURANE

• It is the inhalational agent of choice for induction in children.

• It is a very good muscle relaxant but poor analgesic agent.

• It should not be used in closed circuit because it can produce a nephrotoxic metabolite, Compound A.

METHOXYFLURANE

• It is the most potent inhalational agent (least MAC).

• It has the slowest induction and recovery (highest B/G partition coefficient).

• It can lead to high output renal failure (highest amount of fluoride content).

• It should not be used in closed circuit (reacts with rubber tubing of the closed circuit).

TRIELENE (TRICHLORETHYLENE)

• It is the most potent analgesic agent.

• It should not be used in closed circuit because reaction with soda lime can result in the production of phosgene gas (responsible for Acute Respiratory Distress Syndrome), and dichloroacetylene (neurotoxic to Vth and VIIth cranial nerves).

• It can be used for analgesia in labour.

CYCLOPROPANE

• It is highly inflammable and explosive agent.

• Colour of its cylinder is orange.

• It is the inhalational agent of choice in hemorrhagic shock (increases BP by increasing sympathetic tone).

• It should be stopped slowly because sudden discontinuation may result in hypotension (cyclopropane shock).

CHLOROFORM

• It is a cardiotoxic agent and can result in ventricular fibrillation.

• It is also a hepatotoxic drug.

• It can cause profound hyperglycemia.

CARBON DIOXIDE

• 5% concentration is used for creating pneumoperitoneum in laparoscopy.

• Colour of its cylinder is grey.

HELIUM

• It is lighter than air.

• Mixture of 80% helium and 20% oxygen is used in cases of tracheal obstruction.

XENON

Xenon is Greek for stranger. It was discovered in 1898 and found to be the only noble gas to be anaesthetic under normobaric conditions. Xenon is extremely scarce with an average room containing only 4ml. It is very close to the 'ideal agent'.

It is a colourless and odourless gas with no irritation to the respiratory tract. Well tolerated with gas induction.

• It has lowest blood/gas partition co-efficient (0.115) allowing rapid induction and reversal of anaesthesia.

• It produces unconsciousness with analgesia and a degree of muscle relaxation

• It has a MAC of 60-70% that allows a reasonable inspired oxygen concentration

• It does cause respiratory depression, to the point of apnoea.

• It is has no effect on cardiovascular function.

• It is not metabolised in the body and is eliminated rapidly and completely via the lungs.

• It is non toxic and is not associated with allergic reactions

• It is stable in storage, has no interaction with anaesthesia circuits or soda lime.

• It is non-inflammable.

• Major problem with xenon is that is highly expensive and routine usage will only be possible with a closed circuit delivery system that recycles xenon.

INTRAVENOUS AGENTS

These may be fast acting (used for induction) or may be slow acting.

1. INDUCING AGENTS

THIOPENTONE

• It is an ultra short acting barbiturate and is the most commonly used intravenous inducing agent. It is used as a 2.5% solution.

• Sulphur is added to pentobarbitone to increase the lipid solubility.

• Due to high lipid solubility, it is very fast acting drug.

• Action of this drug terminates very quickly due to redistribution (although half life is longer).

• It also possesses anticonvulsant action (another barbiturate methohexitone increases the risk of convulsions, therefore used for electroconvulsive therapy).

• It is the agent of choice for cerebral protection (decreases cerebral oxygen consumption, decreases intra-cranial tension and decreases cerebral metabolic rate).

• It causes peripheral vasodilatation and also depresses cardiovascular system, therefore can cause hypotension.

• Instead of producing analgesic effect, it can produce hyperalgesia at subanaesthetic doses.

• Respiratory depression and transient apnea are other problems seen with this agent.

• On accidental injection of thiopentone in the arteries, it can lead to thrombosis and vasoconstriction that may progress to ischemia and gangrene. It is accompanied by very severe pain. This condition is treated by leaving the needle in situ (needle should not be withdrawn), dilution of injected thiopentone with saline, immediate heparinization and papaverine injection to relieve spasm.

METHOHEXITONE

• It is also an ultra short acting barbiturate.

• It is 3 times more potent than thiopentone.

• It induces seizures; therefore, it is the agent of choice for electroconvulsive therapy.

KETAMINE

• It is a phencyclidine (hallucinogenic) derivative that is administered in a dose of 2 mg/kg.

• Its onset of action is 30-60s whereas action terminates in 15-20 min. due to redistribution.

• It acts by blocking NMDA receptors of glutamate.

• It is a very strong analgesic agent but lacks muscle relaxant property.

• It is used for producing dissociative anaesthesia (state of profound analgesia, amnesia with light sleep, immobility, feeling of dissociation from one's own body and the surroundings).

• It does not depress pharyngeal and laryngeal reflexes; therefore is the agent of choice for emergency anaesthesia with full stomach (because vomiting will prevent aspiration).

• It increases all pressures (blood pressure, intracranial tension, intraocular pressure) in the body. It is therefore intravenous anaesthetic of choice for shock (increases blood pressure). Further it is contraindicated in glaucoma (increases IOP) and head injuries (increases ICT).

• It is a powerful bronchodilator agent and is therefore intravenous anaesthetic of choice in bronchial asthma (halothane is the inhalational anaesthetic agent of choice for bronchial asthma).

• It is the intravenous anaesthetic agent of choice for induction in children (Sevoflurane is inhalational agent of choice in children).

• On discontinuation of ketamine anaesthesia, several adverse effects may be seen (known as emergence reaction). Hallucinations are the most common side effect. Other effects include vivid dreams, illusions and excitement.

PROPOFOL

• It is a milky white powder that is preservative free. Therefore, it must be used within 6 hours.

• It is an oil based preparation, therefore injection is painful.

• Its onset of action is within 15 seconds and last for 5-10 min. (due to redistribution)

• It possesses very strong antiemetic and antipruritic action.

• It decreases blood pressure and impairs baroreceptor reflexes.

• It produces more severe and prolonged respiratory depression than thiopentone.

• It has no muscle relaxant property.

• It has cerebroprotective activity but does not possess anticonvulsant activity. Rather, myoclonic jerking and muscle twitching can be seen with the use of propofol.

• It is the intravenous anaesthetic of choice for day care surgery.

• It is also the intravenous anaesthetic of choice for sedation in ICU.

• Propofol is the intravenous anaesthetic of choice in the patients with malignant hyperthermia.

• This agent is intravenous anaesthetic of choice, and is used with alfentanil for total intravenous anaesthesia (TIVA).

ETOMIDATE

• It does not interfere with cardiovascular functions; therefore is the agent of choice for aneurysm surgeries and cardiac disease.

• It causes minimal respiratory depression.

• Maximum incidence of nausea and vomiting is seen with the use of this agent.

• It can also produce myoclonus.

• Injection of etomidate is painful and may result in thrombophlebitis.

• It can lead to adrenocortical suppression.

• Vitamin C deficiency can also develop with the use of etomidate.

2. SLOW ACTING AGENTS

BENZODIAZEPINES

• Important benzodiazepines are diazepam, lorazepam and midazolam.

• These are not analgesic agents.

• However, these possess muscle relaxing and anticonvulsant property.

• Lorazepam is the most commonly used benzodiazepine in pre-anaesthetic medication.

• Midazolam is used for day care surgery.

• These agents may cause sedation and anterograde amnesia.

OPIOIDS

• Fentanyl, alfentanil, sufentanil and remifentanil are the opioids used in anaesthesia.

• These are 100 times more potent than morphine. Sufentanil is the most potent opioid.

• These drugs possess very strong analgesic activity.

• Fentanyl is used along with droperidol for neurolept analgesia.

• If nitrous oxide is also added, the combination can be used as neurolept anaesthesia (N2O + fentanyl + droperidol).

• These agents can lead to post operative muscle rigidity (SCh causes post operative muscle pain and fasciculations).

• Alfentanil is used for day care surgery and for total intravenous anaesthesia.

• Remifentanil is the shortest acting opioid (due to its metabolism by esterases).

NEUROLEPTIC AGENT

• Droperidol is a D2 receptor blocker.

• It is used along with fentanyl to produce neurolept analgesia and neurolept anaesthesia.

• It can produce extrapyramidal symptoms.

2. ANALGESIC, ANTIPYRETICS AND NSAIDs

NSAIDs act by inhibiting COX enzyme and thus prostaglandin synthesis. These drugs act as antipyretic, analgesic and anti-inflammatory agents. Prostaglandins play a protective role in the stomach and non-selective COX inhibitors can cause GI toxicity (peptic ulcer) on long term use.

CLASSIFICATION

- **Nonselective Cox inhibitors**: Aspirin, Indomethacin, Sulindac, Ibuprofen, Naproxen, Ketoprofen, Mephenamic acid, Diclofenac sodium,Piroxicam, Tenoxicam,Ketorolac
- **Preferential cox-2 inhibitor:** Nimesulide, Meloxicam.
- **Selective cox- 2 inhibitors**: Celecoxib, Rofecoxib,Valdecoxib
- **Analgesics**- **Antipyretics:** Paracetamol, Metamizol, Nefopam (non opiod analgesic which donot inhibit PG synthesis)

MECHANISM OF ACTIONS

- All of the non-steroidal anti-inflammatory drugs (NSAIDs) appear to possess at least one common mechanism, inhibition of cyclooxygenase (COX) enzyme(s) which leads to a decrease in the synthesis of various prostaglandins and thromboxanes.
- They reduce biosynthesis of Prostanoids by inhibiting both isoforms of the Cyclooxygenase (COX) enzyme (COX-1& COX-2).

INDIVIDUAL DRUGS

ASPIRIN

Aspirin is acetylsalicylic acid. It is rapidly converted in the body to salicylic acid which is responsible for most of the actions. Other actions are the result of acetylation of certain macromolecules including COX.

MOA: Aspirin inhibits the cyclooxygenase and thus inhibits the prostaglandin synthesis. The drug has analgesic, anti-inflammatory and antipyretic effects. It inhibits the formation of a highly effective platelet (thrombocyte) aggregator and a vasoconstrictor (thromboxane A2).

Use: Aspirin is used to reduce fever and relieve mild to moderate pain from conditions such as muscle aches, toothaches, common cold, dysmenorhoea, post operative pain and headaches. It may also be used to reduce pain and swelling in conditions such as arthritis. Aspirin is used prophylactically for primary & secondary prevention of transient ischemic attacks & stroke, unstable angina, coronary artery thrombosis & myocardial infarction.

Side effects include Upset stomach and heartburn. Hepatotoxicity, asthma, rashes, GI bleeding, and renal toxicity rarely occur at antithrombotic doses.

PARACETAMOL

It does not possess anti-inflammatory activity because it is ineffective in the presence of peroxides generated at the site of inflammation. Other explanation offered is selective COX 3 inhibition in the brain. It produces very little GI toxicity and can be administered in patients intolerant to other NSAIDs. It is metabolized to N-acetyl paraaminobenzo quinoneimine (NAPQ) by microsomal enzymes. This metabolite has high affinity for sulfhydryl groups and can combine with the enzymes and other biomolecules resulting in hepatotoxicity.

Paracetamol Poisoning: Acetaminophen toxicity can be decreased by providing sulfhydryl donors like N-acetylcysteine (antidote of choice). Acetaminophen overdose constitutes medical emergency and 90% of patients will develop severe liver damage, if plasma concentration is

greater than 300 μg/ml at 4 hours or 45 μg/ml at 15 hours after ingestion. Gastric lavage (with activated charcoal) should be done to prevent further absorption but it is ineffective after 4 hours of ingestion.

DICLOFENAC

- Diclofenac is a potent cyclooxygenase inhibitor with antiinflammatory, analgesic, and antipyretic properties.
- The drug is rapidly absorbed following oral administration and has a half-life of 1-2 hours.
- It accumulates in the synovial fluid.
- The potency of diclofenac as a cyclooxygenase inhibitor is greater than that of naproxen.
- The drug is recommended for chronic inflammatory conditions such as rheumatoid arthritis and osteoarthritis and for the treatment of acute musculoskeletal pain.

Adverse effects include gastrointestinal distress, occult gastrointestinal bleeding, and gastric ulceration.

SULINDAC

- Sulindac is a prodrug. Its active metabolite is, like diclofenac, an acetic acid derivative. The drug is effective only after it is converted by liver enz ymes to a sulfide, which is excreted in bile and then reabsorbed from the intestine.

- The enterohepatic cycling prolongs the duration of action to 12-16 hours. The indications and adverse reactions are similar to those of other NSAIDs.
- Among the more severe reactions, Stevens-Johnson epidermal necrolysis syndrome, thrombocytopenia, agranulocytosis, and nephrotic syndrome have all been observed.
- Like diclofenac, sulindac may have some propensity to cause elevation of serum aminotransferase; it is also sometimes associated with cholestatic liver damage.

IBUPROFEN

Ibuprofen is extensively metabolized in the liver, and little is excreted unchanged.

Gastrointestinal irritation and bleeding occur, though less frequently than with aspirin. In addition to the gastrointestinal symptoms, rash, pruritus, tinnitus, dizziness, headache, and fluid retention have been reported. Rare hematologic effects include agranulocytosis and aplastic anemia. Effects on the kidney include acute renal failure, interstitial nephritis, and nephrotic syndrome, occurring very rarely.

INDOMETHACIN

Indomethacin is slightly more toxic but in certain circumstances more effective than aspirin. Indomethacin is well absorbed after oral

administration and highly bound to plasma proteins. Metabolism occurs in the liver and unchanged drug and inactive metabolites are excreted in bile and urine.

Clinical Uses: treatment of patent ductus arteriosus, acute gouty arthritis and ankylosing spondylitis, pericarditis and pleurisy.

Adverse Effects: The gastrointestinal effects may include abdominal pain, diarrhea, gastrointestinal hemorrhage, and pancreatitis. CNS effects include be associated with dizziness, confusion, and depression. Serious hematologic reactions' including thrombocytopenia and aplastic anemia has been reported.

OTHERS

Naproxen and oxaprozin are long acting drugs that also inhibit leucocyte migration.

• **Mefenamic acid** also possesses PG receptor antagonistic and PLPA2 inhibitory activity. It is very useful in dysmenorrhoea.

• **Phenacetin** (prodrug of paracetamol) is implicated in causing analgesic nephropathy

• **Ketorolac** is the only NSAID that can be used i.v. It is also available as eye drops. Course longer than 5 days is not recommended.

• **Piroxicam and tenoxicam** are longest acting NSAIDs due to enterohepatic cycling. **Oxaprozin** is another very long acting NSAID.

• **Apazone** possess potent uricosuric activity. It is indicated in conditions, in which other NSAIDs have failed.

3. ANTIRHEUMATIC AND ANTIGOUT DRUGS

ANTI-GOUT DRUGS

Gout is a type of arthritis that causes inflammation, usually in one joint, that begins suddenly. Gouty arthritis is caused by the deposition of crystals of uric acid in a joint.

Gout can cause symptoms and signs such as

- nodules under the skin called tophi,
- joint redness,
- swollen joints,
- joint pain, and
- warmth of the joint.

Classification

- **Nonsteroidal anti-inflammatory drugs (NSAIDs).**
  - ibuprofen
  - naproxen sodium
  - indomethacin
  - celecoxib
- **Colchicine.**a type of pain reliever that effectively reduces gout pain.
- **Corticosteroids.** Corticosteroid medications, such as the drug prednisone, may control gout inflammation and pain. Corticosteroids may be administered in pill form, or they can be injected into your joint.

- **Medications that block uric acid production.**
  - allopurinol
  - febuxostat ,

  This may lower your blood's uric acid level and reduce your risk of gout.

ANTIRHEUMATIC DRUGS

Rheumatoid arthritis (RA) is an autoimmune multisystem disease. NSAIDs are used to provide symptomatic relief but exert no effect on the progression of the disease. Disease modifying anti-rheumatoid drugs (DMARDs) slow the progression of disease but act slowly (takes 6 weeks to 6 months).

Classification of Drugs

1. **NSAIDs:** NSAIDs are used as the initial therapy for RA and as an adjunct to DMARDs to provide symptomatic relief for pain and inflammation. They do not prevent the degenerative changes and tissue damage responsible for the deformity.
2. **Glucocorticoids:** Glucocorticoids are not only anti-inflammatory but are also immunosuppressants. They relieve the symptoms and control the degenerative process of RA. Glucocorticoids are still used in lower doses for symptomatic relief while waiting for a response to a slow acting DMARD, persistent synovitis despite adequate trials of NSAIDs and DMARDs and for severe constitutional symptoms (fever and weight loss) or extra-articular disease (vasculitis, episcleritis, or pleurisy). **Prednisone (orally) and methylprednisolone (IV)** are generally preferred, because of cost

and half-life considerations. Adverse effects are dose related and duration of the treatment and except for **cataract and osteopenia,** can be minimized by alternate day administration, once the disease is controlled.

3. **Disease Modifying Antirheumatic Drugs (Dmards):** DMARDs are **immunomodulatory** and **immunosuppressive drugs** and include a large number of pharmacologically diverse agents that exert anti-inflammatory as well as immunosuppressive effects and retard the progression of bony erosions and cartilage loss. **The main drugs in this class are:** Hydroxychloroquine, Sulfasalazine, Methotrexate, Biologic DMARDs, and Other DMARDs.

a. **Hydroxychloroquine:** Hydroxychloroquine, an antimalarial drug, appears to be of some benefit in treating the morning stiffness and joint pain of rheumatoid arthritis and also in the skin lesions of lupus erythematosus. It probably acts by blocking the production of inflammatory mediator and by interfering with the actions of leucocytes. It also inhibits the proliferation of lymphocytes. Side effects with prolonged treatment may result in corneal opacities and more seriously, retinal damage. It is contraindicated in pregnancy.

b. **Sulfasalazine:** Sulfasalazine, another DMARD, is used as the initial choice in very mild RA. It takes about 3 months to produce its full therapeutic effect. **Side effects** include hematologic and liver toxicity and necessitate regular blood counts and liver function tests.

c. **Methotrexate:** Methotrexate, **a folic acid antagonist cytotoxic**, is the initial choice for moderate to severe RA. It acts more rapidly, and

if given in relative low doses is better tolerated, provided renal functions are normal. Concomitant use of folic acid may reduce methotrexate toxicity without impeding its efficacy. The main adverse effects are GI disorders, bone marrow suppression, liver cirrhosis and pulmonary fibrosis. Methotrexate is teratogenic and is contraindicated in pregnancy. It should be avoided in patients with significant hepatic or renal impairment.

d. Biologic DMARDs: The term biologic is used for genetically engineered proteins that interact with protein of the body that mediate disease producing reactions. Biologic DMARDs neutralize one of the cytokines-tumour necrosis factor α (TNF-α) or interleukin-1α (IL-1), that are the prime activator of the inflammatory response. Cytokines are non- antibody proteins released by specific cells which on contact with specific antigen act as intracellular modulators in the generation of an immune response. Tumour necrosis factor (TNF) inhibitors comprise **etanercept and infliximab**. Etanercept is a protein that resembles the cellular receptor to which TNF-α normally binds to exert its effects. Etanercept binds to TNF-α, blocking its interaction with cell surface receptors, thus inhibiting the inflammatory and immune-regulatory properties of TNF. **Infliximab** is an antibody raised against TNF-α and when injected it binds to it and renders it inactive.

Inhibitors of interleukin -1 (IL-1): Anakinra is a recombinant form of the naturally occurring IL-1 receptor antagonist that is used for RA. It blocks binding of IL-1 to its receptor, thus inhibiting the pro-

inflammatory and immuno-modulatory actions of IL-1. These drugs are used in patients with moderate to severe RA who do not respond to one or more DMARDs listed above. They have similar efficacy and toxicity profile. They are given by injection. These drugs act faster and slow degenerative changes better than other DMARDs, but their use is associated with serious side effects. The most serious side effect is infection and sepsis, which may be fatal. These drugs are contraindicated in patients with acute or chronic infections or with a history of recurrent infection.

e. **Other Dmards: Azathioprine, cyclophosphamide or cyclosporines** are at times combined with methotrxate for treatment of severe RA. Combination therapy may lead to synergistic or unexpected toxicities and require proper precautions.

4. SEDATIVES AND HYPNOTICS

- **Sedative**: A drug that subdues excitement and calms the subject without inducing sleep, though drowsiness may be produced. Sedation refers to decreased responsiveness to any level of stimulation; is associated with some decrease in motor activity and ideation.
- **Hypnotic**: A drug that induces and/or maintains sleep, similar to normal arousable sleep. They are more or less CNS depressants with somewhat differing time-action and dose-action relationships. A hypnotic at lower dose may act as sedative.

CLASSIFICATION

Barbiturates

- **Long acting:** Phenobarbitone
- **Short acting:** Butobarbitone, Pentobarbitone
- **Ultra-short acting:** Thiopentone, Methohexitone

Benzodiazepines

- **Hypnotic:** Diazepam, Flurazepam, Nitrazepam, Alprazolam
- **Antianxiety:** Diazepam, Chlordiazepoxide, Oxazepam, Lorazepam, Alprazolam
- **Anticonvulsant:** Diazepam, Clonazepam, Lorazepam, Clobazam

Newer nonbenzodiazepine hypnotics: Zopiclone, Zolpidem, Zaleplon

INDIVIDUAL DRUG GROUPS

BARBITURATES

Mechanism of action: Barbiturates appear to act primarily at the GABA: BZD receptor–Cl^- channel complex and potentiate GABAergic inhibition by increasing the lifetime of Cl^- channel opening induced by GABA.

Uses: Except for **phenobarbitone** in epilepsy and **thiopentone** in anaesthesia no other barbiturate is used now.

Barbiturate Poisoning

Signs and symptoms:

- CNS depression
- Patient is flabby and comatose with shallow and failing respiration,

- Fall in BP and cardiovascular collapse,
- Renal shut down, pulmonary complications, Bullous eruptions.

Lethal dose depends on lipid solubility. It is 2–3 g for the more lipid-soluble agents (short-acting barbiturates) and 5–10 g for less lipid-soluble phenobarbitone.

Treatment

- **Gastric lavage** by activated charcoal in the stomach to prevent absorption of the drug from intestines.
- Supportive measures like patent airway, assisted respiration, oxygen, maintenance of blood volume by fluid infusion and use of dopamine is generally preferred for renal vasodilating action.
- **Alkaline diuresis** with sodium bicarbonate 1 mEq/kg i.v. with or without mannitol is helpful only in the case of longacting barbiturates which are eliminated primarily by renal excretion.
- **Haemodialysis and haemoperfusion** is highly effective in removing long-acting as well as short-acting barbiturates. There is no specific antidote for barbiturates.

BENZODIAZEPINES

MOA: BZDs act by enhancing presynaptic/postsynaptic inhibition through a specific BZD receptor which is an integral part of the $GABA_A$ receptor–Cl^- channel complex.

Adverse effects: Benzodiazepines are relatively safe drugs. Side effects of hypnotic doses are dizziness, vertigo, ataxia, disorientation, amnesia,

prolongation of reaction time: impairment of psychomotor skills (that means patient should not drive).

ANTIEPILEPTIC DRUGS

Classification

- **Narrow spectrum:** Gabapentin, vigabatrin, Phenobarbital, carbamazepine.
- **Broad-spectrum**: Valproic acid, lamotrigine, topiramate, zonisamide.

Mechanism of Action

- **Inhibition of Use-Dependent Na+ channel**

  e.g., phenytoin, carbamazepine, valproate, lamotrigine

- **Enhancement of GABAergic action**

  e.g., Phenobarbital & benzodiazepines activates $GABA_A$ receptors to facilitate GABA-mediated opening of Cl^- channels.

  Benzodiazepines increase the frequency of opening of Cl^- channel.

  Phenobarbital increases the duration of opening of Cl^- channel.

- **Blockade of NMDA receptors/ AMPA**
  - Felbamate: They are not available for clinical use
  - Barbiturates, Topiramate: Inhibit AMPA

- **Inhibition of T-type Ca^{+2} channels:** Ethosuximide, Valproate, Zonisamide, Trimethadione.

INDIVIDUAL DRUGS

PHENYTOIN

- Phenytoin acts mainly by **use-dependent block of sodium channels**.
- It also inhibits calcium influx across the cells and inhibits the secretory release of hormones.
- At high doses it inhibits release of NE and 5HT. It also inhibits MAO activity.
- It is mainly used in treatment of generalized tonoc-clonic seizure (grand mal), simple partial and complex partial seizures, trigeminal neuralgia.
- It can also be used in treatment of digitalis induced arrhythmia and in status epilepticus.

Side effects:

- Hypertrophy of gums, Hirusitism
- Hypersensitivity, Hyperglycemia
- Hydantoin syndrome, Cerebellar atrophy
- Megaloblastic anemia, Osteomalacia
- Ophthalmoplegia, Lymphoma
- Hepatocellular damage
- Phenytoin follows saturation kinetics, Depresses CNS

CARBAMAZEPINE

- Carbamazepine is derivative of tricyclic antidepressants having similar profile to that of phenytoin.
- It is effective in most forms of epilepsy (except absence seizures); particularly effective in psychomotor epilepsy.
- It is also useful in trigeminal neuralgia, neuropathic pain, post-herpetic neuralgia, diabetes insipidus of pituitary origin, manic depressive psychosis and in the treatment of alcohol withdrawal syndrome.

Unwanted effects: sedation, dizziness, ataxia, mental disturbances, foetal malfunction, Aplastic anemia, hyponatremia, and water retention.

SODIUM VALPROATE

- Sodium valproate is an antiepileptic drug, which **blocks sodium channels.**
- It produces increase in GABA levels by inhibiting GABA-aminotransferase.
- It stimulates GABA synthetase and increase GABA. It also blocks T-type calcium channels.
- It is a broad spectrum antiepileptic, effective against all types of seizures.
- It is also used in bipolar mood disorder.
- It is the DOC for absence seizure, akinetic seizures and infantile seizures.

Side effects include: anorexia, drowsiness, vomiting, ataxia, tremors, and alopecia, thinning of hair, hypersensitivity reactions, hepatotoxicity and teratogenecity.

ETHOSUXIMIDE

- It has specificity for the treatment of absence seizure.
- It acts by inhibiting T type calcium channels.
- It also inhibits Na+/K+ ATPase and GABA-transaminase.

Most common side effects are: GI disorders, nausea, vomiting, hiccups, euphoria, skin rashes etc.

CLONAZEPAM

It is a benzodiazepine used for the treatment of absence seizures, akinetic seizures, and myoclonic seizures. It reduces symptoms of infantile seizures. Common side effects include: sedation, drowsiness, hysteria, etc. It may develop physical and psychological dependence in prolonged use.

GABAPENTIN AND PREGABALIN

These are centrally acting GABA analogs. Both modify synaptic/presynaptic release of GABA. Gabapentin is used for partial seizure and neuropathic pain. But side effects include somnolence, dizziness, and ataxia. Pregabalin is used as antiepileptic, analgesic.

TOPIRAMATE

- Topiramate is used to treat epilepsy in both children and adults.

- It can also be used as an antidepressant.
- In children it is also indicated for treatment of Lennox-Gastaut syndrome.
- It is now frequently prescribed for, the prevention of migraines. It has been used by psychiatrists to treat bipolar disorder.
- Topiramate enhances GABA-activated chloride channels. In addition, topiramate inhibits excitatory neurotransmission, through actions on kainate and AMPA receptors.
- It is also an inhibitor of carbonic anhydrase, particularly subtypes II and IV. As topiramate inhibits carbonic anhydrase, the concomitant use of other inhibitors of carbonic anhydrase (e.g. acetazolamide) may lead to an increased risk of renal stones.
- Acute myopia and secondary angle closure glaucoma, in a small subset of patients who take topiramate regularly, may cause transient (reversible), or permanent, loss of vision.
- Another serious side-effect is the development of osteoporosis in adults and children (bones affected break more easily) and rickets (abnormal, deformed growth of bones) in children.

MANAGEMENT OF STATUS EPILEPTICUS

Diazepam 10 mg IV over 5 minutes, can be repeated twice more, at 15 min interval.

Or

Lorazepam 4 mg IV bolus, repeated once after 10 min.

This is followed by Phenytoin/ fosphenytoin 18-20 mg/kg IV at a rate not more than 50 mg/min as it is short acting.

If still seizure continues, then phenobarbitone 10-20 mg/kg IV slowly. Midazolam can be used in a loading dose of 0.2 mg/kg and then infusin at a rate 0.05-0.2 mg/kg/h.

EXAMPLES OF DRUGS WHICH CAN CAUSE SEIZURES

- Lignocaine
- Cocaine
- Ketamine
- Enflurane
- Ether
- Haloperidol
- Ephedrine
- Amphetamine
- Isoniazid
- Penicillin
- Methotrexate
- Cyclosporine

DRUG OF CHOICE OF DIFFERENT EPILEPTIC SYNDROMES

DOC for generalized tonic lonic seizures: Valproic acid

DOC for absence seizures: Ethoxsuccimide, valproic acid

DOC for atonic seizures: Valproic acid

DOC for myoclonic epilepsy: Valproic acid

DOC for partial seizures: Carbamazepine

DOC for status epilepticus: IV lorazepam

DOC for febrile seizures: Rectal diazepam

DOC for eclampsia: Magnesium sulfate

DOC for infantile spasms: Vigabatrin/ethox succimide

ADVANTAGES OF BENZODIAZEPINES OVER BARBITURATES

- High margin of safety (i.e. 10 times the normal dose can be given without harmful effects).
- Least drug interactions, since no effect on the drug metabolising cytochrome P450 enzyme system in the liver.
- Selectivity of action (i.e. like barbiturates, benzodiazepines are not a general CNS depressant – they act mainly on limbic system).
- Lack of interactions (i.e. neither enzyme inhibitors nor enzyme inducers).
- Do not cause hyperalgesia.
- Fewer incidences of drug dependence/addiction.
- Less severe withdrawal syndrome.
- Less severe tolerance.
- Least changes in sleep pattern.

LOCAL ANAESTHETIC

Local anaesthetic is a drug that produces reversible depression of nerve conduction without loss of consciousness. It also causes reversible absence of pain sensation.

Classification of local anaesthetics according to their chemical structure.

- **Esters:** Benzocaine, Procaine/Proparacaine, chloroprocaine, tetracaine, piperocaine, proparacaine, benzocaine.
- **Amide:** Bupivacaine, Levobupivacaine, Lidocaine/Lignocaine, Dibucaine Mepivacaine.

Classification of local anaesthetics according to their duration of action.

- **Short acting (less than 30 min) and less potent:** Procaine, Chlorprocaine
- **Intermediate acting (1-2 hours) and intermediate potent:** Lidocaine, Prilocaine
- **Long acting (3-6 hours) and potent:** Bupivacaine, Ropivacaine, Tetracaine

MECHANISM OF ACTION OF LOCAL ANESTHETICS

- They prevent generation and conduction of nerve impulse by blocking initiation and propagation of action potential by preventing voltage dependent increase in Na+ conductance.

- They block voltage dependent sodium channels directly. As a result blockade of nerve impulses takes place (e.g., those mediating pain).

Prolongation of the actions of local anesthetics

Local anesthetics actions can be prolonged by using vasoconstrictors like Epinephrine, Phenylephrine along with it. Epinephrine decreases the rate of absorption and reduces systemic toxicity of local anesthetics.

Major Side Effects of Local Anesthetics

CNS: Light headedness, agitation, confusion, auditory disturbances, visual disturbances, tremors, convulsions, respiratory arrest.

CVS: Myocardial depression, bradycardia, hypotension, Cardiac arrhythmia.

Hypersensitivity reactions: Rashes, dermatitis, asthma etc.

VARIOUS USES OF LOCAL ANESTHETICS

- **Surface anesthesia:** For Skin & mucous membrane (lidocaine, tetracaine)
- **Infiltration anesthesia:** For suturing wound, incisions, excisions
- **Nerve Block:** For tooth extraction, eye operation
- **Spinal anesthesia:** Operation of lower abdomen, cesarean section
- **Epidural Anesthesia:** Thoracic abdominal surgery

PARKINSON'S DISEASE

Parkinson's disease occurs due to the loss of brain cells that produce dopamine. Early signs and symptoms of Parkinson's disease include:

- tremors or trembling, slow movement (bradykinesia)
- akinesia(no movement)
- body rigidity and stiffness,
- problems walking
- difficulty in writing
- mask like face

DRUGS USED IN THE TREATMENT OF PARKINSONISM

- **Dopaminergic precursors:** Tyrosine, L-DOPA (levodopa)
- **COMT inhibitors:** Entacapone, Opicapone, Tolcapone
- **DOPA decarboxylase inhibitors:** Benserazide, Carbidopa
- **MAO B inhibitors:** Selegiline, Rasagiline
- **DA receptor agonist:** Apomorphine, Bromocriptine, Pramipexole
- **Antimuscarinics:** Benzhexol, Benztropine, Procyclidine

ROLE OF LEVODOPA + CARBIDOPA IN PARKINSONISM

- Plasma half life of levodopa is prolonged.
- Dopamine dose is reduced to ¼.
- Effective Levodopa dosage is attained quickly.
- Concentration of dopamine is reduced, nausea and vomiting is less.

- Cardiac side effects are minimized.
- On-off effect is reduced.
- Degree of improvement is high.

BROMOCRIPTINE

It is ergot alkaloids which is D2 receptor agonist. It inhibits prolactin release.

Uses:

- Parkinsonism
- Hyperprolactinemia
- Acromegaly
- Acute cocaine withdrawal syndrome

COMT INHIBITORS

Tolcapone and entacapone inhibit methylation of levodopa. They inhibit catecholamine o-methyl transferase enzyme. They reduce clinical symptoms of 'wearing off' in patients using levodopa+carbidopa combinations.

MAO-B INHIBITOR/ SELEGILINE IN PARKINSONISM

Selegiline is a selective inhibitor of MAO-B, which causes accumulation of dopamine in brain. It prevent breakdown of dopamine in brain.

BENZTROPINE IN PARKINSONISM

Benztropine is a central acting anticholinergic agent used to reduce tremors and rigidity caused by excessive cholinergic activities.

CHAPTER-3

DRUGS ACTING ON "ANS"

The autonomic nervous system is part of peripheral nervous system that acts unconsciously in body. It regulates various body functions such as the heart rate, digestion, regulation of BP, regulation of respiration, exocrine and endocrine secretions, sexual arousal, urination, contractions and relaxations of smooth muscles etc. The autonomic nervous system is divided into three parts:

- Sympathetic nervous system [Major neurotransmitter is NE]
- Parasympathetic nervous system [Major NT is Ach]
- Enteric nervous system

Cholinomimetic (cholinergic/ parasympathomimetic): A drug that mimics the effects produced by stimulation of parasympathetic nervous system. Examples: Acetylcholine, Pilocarpine, Arecholine, Muscarine.

Sympathomimetic (adrenergic): A drug that mimics the effects produced by stimulation of sympathetic nervous system. Examples: Adrenaline, Isoprenaline, Dopamine, Noradrenaline

SYNTHESIS, STORAGE, RELEASE AND DEGRADATION OF ACETYLCHOLINE

Synthesis: Acetylcholine is synthesized in certain neurons (mainly cholinergic) from the compounds choline and acetyl-CoA by enzyme choline acetyltransferase.

Storage: After its synthesis, acetylcholine is packaged into storage vesicles and is stored at the nerve ending.

Release: Acetylcholine is released into synaptic cleft, when an action potential arrives.

Degradation: The enzyme acetylcholinesterase converts acetylcholine into the inactive metabolites choline and acetate.

CHOLINESTARASES AND ANTICHOLINESTERASES

- Cholinesterase is a family of enzymes present in nervous tissue, muscle. It hydrolyzes acetylcholine into choline and acetic acid.
- Anticholinesterases are the drugs that inhibit cholinesterase, resulting in increased levels of ACh everywhere in the body.

DIFFERENT CHOLINERGIC RECEPTORS AND THEIR LOCATIONS

- **Nicotinic acetylcholine receptors:** These are responsive to nicotine. These are present in skeletal muscles and autonomic ganglia.
- **Muscarinic acetylcholine receptors:** These are particularly responsive to muscarine. These are present in heart, smooth muscles, blood vessels, different glands and eyes.

MUSCARINIC RECEPTORS AND THEIR ASSOCIATED FUNCTIONS

Five types of muscarinic receptors are found. They are M1, M2, M3, M4, and M5.

- **M1 (neuronal):** Present in CNS, gastric glands and salivary glands (**Function:** Gastric secretion)
- **M2 (cardiac):** Present in Heart, Smooth muscles (**Function:** decrease heart rate)
- **M3 (glands, smooth muscles):** Present in exocrine glands, GI smooth muscles, eye, and blood vessel. (**Function:** Increase Glandular secretions (sweat, saliva, ocular), Increase motility, vasodilatation)
- **M4 (CNS):** Present in CNS (**Function:** Enhanced locomotion)
- **M5 (CNS):** Present in CNS (**Function:** Not Known)

NICOTINIC RECEPTORS AND THEIR ASSOCIATED FUNCTIONS

Two types of nicotinic receptors are present: N_M and N_N.

- **N_M:** Present in the neuromuscular junction and skeletal muscle. **Function:** Skeletal Muscle contraction
- **N_N:** Present in the autonomic ganglion. **Function:** Stimulation of Autonomic ganglia

PARASYMPATHOMIMETICS (CHOLINERGIC AGONISTS, CHOLINOMIMETIC)

Direct acting agents	**Indirect acting agents (Anticholinesterases:**	
	Reversible	**Irreversible**
Acetylcholine, Arecholine,	Physostigmine, Neostigmine,	Parathion, Malathion,

Bethanechol. Carbachol, Muscarine, Pilocarpine	Pyridostigmine, Edrophonium	Ecothiophate, Tabun, Sarin, Soman

PHARMACOLOGICAL ACTIONS AND USES OF ACETYLCHOLINE

Pharmacological actions:

- **M1 (neuronal):** Gastric secretion increases so digestion enhance.
- **M2 (cardiac):** Decreases heart rate, decreases force of contraction, decreases conduction velocity.
- **M3 (glands, smooth muscles):** Increases glandular secretions (sweat, saliva, ocular), increases motility, vasodilatation, miosis (decrease pupil size).
- **M4 (CNS):** Enhances locomotion
- **N_M:**Inducesskeletal muscle contraction
- **N_N:** Stimulates Autonomic ganglia

  Uses: No clinical use

CARBACHOL

Carbachol: Carbachol is completely absorbed from the gastro intestinal tract and is stable towards hydrolysis by cholinesterase enzyme; therefore it can be given both orally and parenteraly with almost similar dosage.

Pharmacodynamics

It has similar actions to those of acetylcholine with pronounced effects on the gastro intestinal tract and the urinary bladder

Indications

- Glaucoma
- Retention of urine (postoperative)
- Paralytic ileus

PILOCARPINE

Pharmacokinetics

This drug is readily absorbed from the gastrointestinal tract and it is not hydrolyzed by cholinesterase enzyme. It is excreted partly destroyed and partly unchanged in the urine.

Pharmacodynamics: The drug directly stimulates the muscarinic receptors to bring about all the muscarinic effects of acetylcholine.

Indications:

- Glaucoma

PHYSOSTIGMINE

Pharmacokinetics

This drug is completely absorbed from the gastrointestinal and is highly distributed throughout the body; it can pass the blood brain barrier.

Pharmacodynamics

Inhibits the enzyme cholinesterase; therefore, it increases and prolongs the effect of endogenous acetylcholine at the different sites. It has no direct effect on cholinergic receptors.

Indications

- Glaucoma
- Atropine over dosage

NEOSTIGMINE

Pharmacokinetics

This drug is poorly absorbed from the gastro intestinal tract and is poorly distributed throughout the body; it cannot pass the blood brain barrier.

Pharmacodynamics

Just like physostigmine, it inhibits cholinesterase enzyme; but unlike physostigmine, it has a direct nicotinic action on skeletal muscles.

Indications

- Myasthenia gravis
- Paralytic Ileus
- Reversal of effect of muscle relaxants, e.g. tubocurarine
- Post-operative urine retention

ORGANOPHOSPHATES

Organophosphates such as echothiophate, isofluorophate, etc. combine with cholinesterase irreversibly and thus hydrolysis is very slow. They may be used in glaucoma. Other organophosphates like Parathion and Malathion are used as insecticides. Poisoning with organophosphates is an important cause of morbidity and mortality all over the world. It usually results from Occupational exposure as in persons engaged in spraying insecticides, Accidental exposure, and Ingestion of any of these compounds with suicidal intent.

PARASYMPATHOMIMETICS

- **Bethanechol:** It is used in postoperative/ postpartum nonobstructive urinary retention, and in neurogenic bladder to promote urination.
- **Pilocarpine:** It is used as eye drops for open angle glaucoma.

THERAPEUTIC USES OF ANTICHOLINESTERASE AGENTS

- **Physostigmine:** It is used along with pilocarpine in glaucoma. It is also used as antidote in belladonna poisoning.
- **Neostigmine:** It is indicated in myasthenia gravis.
- **Pyridostigmine:** It is indicated in myasthenia gravis.
- **Rivastigmine, donepezil and galantamine:** Used in Alzheimer's disease.
- **Neostigmine: W**ith **atropine to stop respiratory paralysis (cobra bite).**

CONTRAINDICATIONS TO THE USE OF CHOLINE ESTERS

Choline- esters are contraindicated in:

a. **Bronchial asthma** because they may induce bronchial constriction and increase bronchial secretions
b. **Hyperthyroidism** because of the danger of inducing atrial fibrillation

c. **Peptic ulcer** disease because of the increase in gastric acid secretion
d. **Coronary insufficiency** because the hypertension produced will further compromise coronary blood flow
e. Mechanical intestinal and urinary outlet obstruction.

ORGANOPHOSPHOROUS POISONING

Organophosphates are used as insecticides, medicines.

Symptoms of organophosphate poisoning include

- Increased saliva production, Increased tear production
- Diarrhea, Vomiting, Miosis, Sweating, Muscle tremors, Confusion

Treatment: Treatment of organophosphate poisoning includes atropine (Anticholinergic activity), pralidoxime (Cholinesterase reactivator), and diazepam (benzodiazepines).

The following steps are followed in treatment:

- Complete rest to affected individual
- Atropine (2 mg IV slowly) and repeated every 10-12 minutes till pupils are dilated
- Oximes (pralidoxime) I gram in 5 ml distilled water IV. If this is not available, blood transfusion may need to be considered.
- Frusemide 40-80 mg. IV
- Care of respiration
- General supportive measures

PARASYMPATHOLYTICS/ ATROPINIC/ ANTICHOLINERGIC DRUGS

Antimuscarinic drugs:

Atropine, Biperiden. Clomipramine, Clozapine, Desipramine,	Dicyclomine, Diphenhydramine, Doxepin, Imipramine, Meclizine	Nortriptyline, Olanzapine, Scopolamine, Trimipramine,

Antinicotinic agents:

Bupropion, Dextromethorphan, Doxacurium,	Hexamethonium, Mecamylamine, Tubocurarine

THERAPEUTIC CLASSIFICATION OF ANTICHOLINERGIC DRUGS

- **Anti-asthmatics:** Ipratropium bromide, Tiotropium
- **Antidote to cholinergic poisoning:** Atropine sulphate
- **Antidiarrhoeal:** Atropine sulphate, Diphenoxylate
- **Anti-Parkinsonism:** Benzhexol, Benztropine, Biperidine, Orphenadine, Procyclidine
- **Antispasmodic:** Atropine sulphate, Clidineum bromide, Hyoscine butylbromide, Pipenzolate bromide
- **Anti-ulcer:** Pirenzepine, Telenzepine

- **As pre-anaesthetic medication and in motion sickness:** Atropine sulphate, Hyoscine butylbromide
- **Mydriatics and cycloplegics:** Atropine sulphate, Cyclopentolate hydrochloride, Eucatropine hydrochloride, Homatropine hydrobromide, Tropicamide.

PHARMACOLOGICAL ACTIONS OF ATROPINE

- **M1 (neuronal):** Gastric secretion decreases, digestion process decreases.
- **M2 (cardiac):** increases heart rate, increases force of contraction, increases conduction velocity.
- **M3 (glands, smooth muscles):** decreases Glandular secretions [sweat (body temp increases, hot and dry skin), saliva (dry mouth), ocular (eye pain)], decreases motility (constipation), vasoconstriction, increases pupil size (mydriasis), smooth muscle relaxation.

  Atropine produces photophobia Atropine blocks the cholinergic nerve supply and causes dilation of pupil. Atropine paralyses the ciliary smooth muscles causing increase in the focal length of thelens, thus the individual can see the things only at long distance. As muscles of sphincter of iris are paralysed, individual cannot constrict the pupil for viewing near objects or in response to bright light. Thus atropine produces photophobia.

HYOSCINE (SCOPOLAMINE)

This drug has the same effect as atropine except for some differences which includes:-

- It has shorter duration of action
- It is more depressant to the CNS.
- All other properties are similar to atropine. It has certain advantage over atropine. These include:
    - Better for preanesthetic medication because of strong antisecretory and antiemetic action and also brings about amnesia.
    - Can be used for short- travel motion sickness.

Synthetic atropine derivatives: There are a number of synthetic atropine derivatives, which are used in the treatment of various conditions, their actions are similar to that of atropine but have fewer side effects. These groups of drugs include

- Mydriatic atropine substitutes, this group of drugs have shorter duration of action than atropine and are used locally in the eye; drugs included: Homatropine, Eucatropine etc.
- Antiseccretory antispasmodic atropine substitutes: Effective more localized to the Gl. Drugs include: propantheline and hyoscine
- Antiparkinsonian atropine substitute: drugs like Benztropine, Trihexyphenidyl
- Atropine substitutes which decrease urinary bladder activity like oxybutynin

- Atropine substitutes used in bronchial asthma drugs like ipratropium

- **What are the uses of parasympatholytics?**
  - **Pirenzepine:** It is used in
    - peptic ulcer
    - irritable bowel syndrome
    - traveler's diarrhea
    - to reduce salivary secretion in heavy metal poisoning
    - Parkinsonism
  - **Atropine:** It is used for treating some cases of sinus bradycardia and partial heart block.
  - **Atropine methonitrate:** It is used in abdominal colics , hyperacidity
  - **Ipratropium bromide**: It is used for the treatment COPD.
  - **Tiotropium bromide:** It is also used for the treatment COPD.
  - **Propantheline:** It is used for the treatment of peptic ulcer and gastritis.
  - **Clidinium:** It has antisecretory and antispasmodic properties. It is used along with benzodiazepines for treatment of diseases like nervous dyspepsia, gastritis, irritable bowel syndrome, colic, and peptic ulcer.
  - **Dicyclomine:** It has antispasmodic property. It directly relaxes smooth muscles in muscle cramps.
  - **Oxybutynin:** It is a smooth muscle relaxant and has local anesthetic properties.

- **Isopropamide:** It is used in hyperacidity, nervous dyspepsia, and irritable bowel syndrome.
- **Hyoscine:** It is indicated in motion sickness.

ATROPINE/BELLADONNA POISONING AND ITS MANAGEMENT

Atropabelladonnais a plantthat contains alkaloids like atropine and hyosciamine. Belladonnapoisoning occurs due to over dosage of belladonna.

Symptoms of belladonna poisoning include: Dryness of themouth, Thirst, Mydriasis, Tachycardia, Delirium, and Stupor.

Treatment: The treatment normally starts with gastrointestinal decontamination with activated charcoal. The antidote for belladonna poisoning is physostigmine. Pilocarpine is also used.

DRUGS USED FOR MYASTHENIA GRAVIS

Myasthenia gravis is an autoimmune disorder, which causes weakness of skeletal muscle (generally muscles of eye and face). It is caused due to impaired communication between nerves and muscles. This occurs due to development of antibodies directed to the nicotinic receptors at the muscle endplate.

Signs and symptoms include

- Weakness of arm or leg muscles
- Double vision
- Drooping eyelids
- Difficulties with speech and in chewing
- Difficulties in swallowing
- Difficulties in breathing

Treatment: Neostigmine 15 mg orally 6 hourly is administered in initial therapy to get maximum relief from weakness. Immunosuppressants like methotrexate, cyclosporine are also used.

THERAPEUTIC USES OF ERGOT ALKALOIDS

Migraine:

- Acute attack: Ergotamine is used.
- Prevention: Ergonovine and methysergide are used.

Postpartum haemorrhage: Ergotamine and ergonovine are used.

EXAMPLES OF ENDOGENOUS CATECHOLAMINES

Catecholamines are synthesized in neurons and in the chromaffin cells of the adrenal medulla. Examples: **dopamine, noradrenaline and adrenaline**.

DIFFERENT ADRENERGIC RECEPTORS/ADRENOCEPTORS

The adrenergic receptors are G protein-coupled receptors. Two types of adrenergic receptors are:

- **α receptors:** α_1 and α_2.
- **β receptors**: β_1, β_2 and β_3.

DISTRIBUTION OF ADRENOCEPTOR SUBTYPES

Type	Tissue : Actions

Alpha1	Most vascular smooth muscles: Contraction Pupillary dilator muscle: Mydriasis Heart: Increased force of contraction
Alpha2	Adrenergic nerve terminals: Inhibition of transmitter release Platelets: Aggregation
Beta1	Heart: Increased rate and force of contraction
Beta2	Respiratory, uterine, and vascular smooth muscle: Relaxation Human liver: Glycogenolysis
Beta3	Fat cells: Lipolysis

CLASIFICATION OF SYMPATHOMIMETIC DRUGS ACCORDING TO THEIR MOA.

- **Direct acting adrenergic agonists:** Epinephrine, Norepinephrine, Dopamine, Isoprotrenol, Dobutamine, Clonidine, Phenylephrine.
- **Indirect acting adrenergic agonists:** Amphetamine, Tyramine, Methylamphetamine, Hydroxyamphetamine.
- **Mixed action adrenergic agonists:** Ephedrine, Metaraminol.

CLASSIFICATION OF SYMPATHOMIMETIC DRUGS ACCORDING TO THEIR THERAPEUTIC USES

- **Anorectics:** Fenfluramine, Sibutramine, Dexfenfluramine
- **Bronchodilators:** I**soprenaline, Salmeterol, Salbutamol, Terbutaline**
- **Cardiac stimulant:** Adrenaline, Dobutamine, Isoprenaline
- **CNS stimulants:** Amphetamine, Methamphetamine, Dexamphetamine
- **Nasal decongestants:** Phenylephrine, Pseudoephedrine.
- **Uterine relaxant and vasodilators**: Salbutamol, Terbutaline.

IMPORTANT PHARMACOLOGICAL ACTIONS OF ADRENALINE

Adrenaline is a potent stimulant of both α and β adrenoceptors so its effects on different target organs are complex.

- **Blood vessels:** It reacts with α1, α2, β1, and β2 adrenoceptors.
- It constricts blood vessels in the skin (α1).
- It dilates muscular arterioles (β2).
- At low concentration dilation occurs (β2).
- At high concentration constriction occurs (α1).
- **Blood pressure:** Large doses increase BP due to vasoconstriction (α1), but low doses decrease BP (β2).
- **Heart:** Increases HR, Increases FC of heart (β1).
- **Bronchi:** It is a potent bronchodilator.
- **Metabolism:**
- Adrenaline increases glucose production (β2).
- Produces Fight or flight response.

- Inhibits of insulin secretion (α2).

DETAILED PHARMACOLOGY OF ADRENALINE

This is the prototype of adrenergic drugs and is produced in the body by the cells of the Adrenal medulla and by chromaffin tissues.

Pharmacokinetics

Adrenaline is rapidly destroyed in the gastrointestinal tract, conjugated, and oxidized in the liver. It is therefore ineffective when given orally and should be given intramuscularly or subcutaneous. Intravenous injection is highly dangerous and is likely to precipitate ventricular fibrillation. The drug may however, be given by nebulizer for inhalation when its relaxing effect on the bronchi is desired or it may be applied topically to mucus membranes to produce vasoconstriction. Because of the extensive metabolism of the drug in liver, little is excreted unchanged in the urine.

Pharmacodynamics

Adrenaline directly stimulates all the adrenergic receptors both and brings about effects of sympathetic nerve stimulation. Its action may be divided in to two, depending on the type of receptor stimulated.

- The α effects consist of vasoconstriction in skin and viscera, mydriasis, platelet aggregation and some increase in blood glucose.

- The ß effects consists of increased contractility and rate of heart with a decreased refractory period (ß1), vasodilatation in muscles and coronary vessels (ß2), bronchial relaxation (ß2) uterine relaxation (ß2), hyperglycemia, lactic acidemia and increased circulating free fatty acids.

Indications

- Acute bronchial asthma
- Anaphylaxis
- Local haemostatic to stop bleeding in epistaxis
- With local anesthesia to prolong the action
- Cardiac arrest

Adverse reactions of adrenaline

- Anxiety, restlessness, headache, tremor
- Anginal pain
- Cardiac arrhythmias and palpitations
- Sharp rise in blood pressure
- Sever vasoconstriction resulting in gangrene of extremities
- Tearing, conjunctival hyperemia
- Cerebral haemorrhage
- Pulmonary edema
- Tissue necrosis

Contra indications

- Coronary diseases
- Hyperthyroidism
- Hypertension

- Digitalis therapy
- Injection around end arteries

PHARMACOLOGY OF NORADRENALINE

Noradrenaline is the neurochemical mediator released by nerve impulses and various drugs from the postganglionic adrenergic nerves. It also constitutes 20% of the adrenal medulla catecholamine output.

Pharmacokinetics

Like adrenaline, noradrenaline is ineffective orally so it has to be given intravenously with caution. It is not given subcutaneous or intramuscularly because of its strong vasoconstrictor effect producing necrosis and sloughing. The metabolism is similar to adrenaline; only a little is excreted unchanged in urine.

Pharmacodynamics

Noradrenaline is a predominantly α receptor agonist with relatively less β agonist action when compared to adrenaline.

Indication

Noradrenaline is used as hypertensive agent in hypotensive states. E.g. During spinal anesthesia or after sympathectomy.

Adverse effects include:

- Anxiety, headache, bradycardia are common side effects
- Severe Hypertension in sensitive individuals
- Extravasation of the drug causes necrosis and sloughing.

PHARMACOLOGY OF EPHEDRINE IN DETAIL

Pharmacokinetics

Ephedrine in absorbed from the gastrointestinal tract and from all parenteral sites. It has a good distribution throughout the body and is resistant to hydrolysis by the liver enzymes. Major proportion of the drug is excreted unchanged in the urine. Because of its stability to metabolism it has long duration of action than the catecholamines.

Pharmacodynamics

Ephedrine stimulates both α and β receptors. This effect is partly by a direct action on the receptors and partly indirectly by releasing noradrenaline from its tissue stores the effect of the drug to various organs and systems is similar to that of adrenaline. It is also a mild CNS stimulant.

Indications:

- Bronchial asthma: - usually as a prophylactic for prevention of attacks
- Nasal decongestion
- Mydriasis
- Heart block
- Nocturnal enuresis
- Whooping cough
- Myasthenia gravis (stimulates NM transmission)
- In skin allergies (counteract the effects of histamine by causing vasoconstriction)

Side effects

The side effects are similar to those of adrenaline; but in addition it may produce insomnia and retention of urine.

Contraindications

- Coronary diseases
- Hyperthyroidism
- Hypertension
- Digitalis therapy
- Injection around end arteries

CLASSIFICATION OF ALPHA -ADRENERGIC ANTAGONISTS

- **α1 Selective Antagonists:** Prazosin, Terazosin, Doxazosin.
- **α2 Selective Antagonist:** Yohimbine.
- **α1 And α2 Non Selective:** Phenoxybenzamine, Phentolamine, Ergotamine

PHARMACOLOGY OF PRAZOSIN

This is an effective drug for the management of hypertension. It has high affinity for alpha1 receptor and relatively low affinity for the alpha2 receptor. Prazosin leads to relaxation of both arterial and venous smooth muscles due to the blockage of alpha1 receptors. Thus, it lowers blood pressure, reduces venous return and cardiac output. It also reduces the tone of internal sphincter of urinary bladder.

Indications:

- Essential hypertension
- Raynaud's syndrome
- Benign prostatic hyperplasia

IMPORTANT USES OF ALPHA-BLOCKERS

- For treatment of high blood pressure (hypertension)
- For treatment of problems with passing urine in men who have enlargement of the prostate gland.
- In BPH (Benign Prostrate of Hypertrophy)
- In pheochromocytoma
- For the treatment of Erectile dysfunction
- In Raynaud's disease

β-ADRENERGIC ANTAGONISTS

- **β-1 Selective Antagonist**: Metoprolol, Alebutolol, Atenolol, Esmolol.
- **β-2 Selective Antagonists:**Butoxamine.
- **β1 and β2 Non Selective Antagonist**: Propanolol, Pindolol, Sotalol, Timolol, Nadolol.
- **α and β Non Selective Antagonist:**Lobetalol.
- **Centrally Acting Sympatholytics:** Methyldopa, Clonidine, Guanabenz.
- **Adrenergic Neuron Blocker:** Reserpine, Guanithidine, Guanadrel.

IMPORTANT USES OF β-ADRENERGIC ANTAGONIST

- **Angina pectoris:** β blockers are indicated in angina.
- **Anxiety:** Propranolol produces antianxiety effect.
- **Cardiac arrhythmia:** β blockers suppress extrasystoles and tachycardias**.**

- **CHF:** β blockers like metoprolol, bisoprolol, nebivolol, carvedilolare useful in selected patients of CHF with dilated cardiomyopathy.
- **Glaucoma:** Beta blockers are used for all types of glaucoma.
- **Hypertension:** β blockers are useful in hypertensive cases.
- **Migraine:** Propranolol is most effective drug for prophylaxis of migraine.
- **MI:** Beta blockers are found to be beneficial in MI.
- **Thyrotoxicosis:** Propranolol is useful during thyroid storm.

PHARMACOLOGY OF PROPRANOLOL

Propranolol is a non- selective β adrenergic blocker; it has also other actions like membrane stabilization.

Pharmacokinetics

Propranolol is almost completely absorbed following oral administration. However, the liver, leaving only 1/3 rd of the dose to reach the systemic circulations, metabolizes most of the administered dose. It is bound to plasma to the extent of 90-95%. It is excreted in the urine.

Pharmacodynamics

The drug has the following main actions.

1. Cardiovascular system
    - Bradycardia
    - Reduces force of contraction
    - Reduces blood pressure

2. Respiratory system
    - Bronchoconstriction
3. Metabolic system
    - Hypoglycemia
4. Central nervous system
    - Anti-anxiety action
5. Eye
    - Decrease the rate of Aqueous humor production
6. Kidneys:
    - Decrease renin secretion

Indications

- Cardiac arrhythmias
- Hypertension
- Prophylaxis against angina
- Myocardial infarction
- Thyrotoxicosis
- Anxiety states (suppression of the physical manifestations of situational anxiety)
- Prophylaxis against migraine attacks
- Glaucoma

Adverse reactions

- GI disturbances like nausea, vomiting
- Heart failure
- Heart block
- Hypotension and severe bradycardia
- Bronchospasm

- Allergic reaction
- Vivid dreams night mare and hallucinations
- Cold hands
- Withdrawal symptoms in case of abrupt discontinuation
- Masking of hypoglycemia in diabetic patients

Contraindications and Precautions:

- Bronchial asthma
- Diabetes mellitus
- Heart failure
- Peripheral vascular disease

MANAGEMENT OF GLAUCOMA

Introduction: It is a chronic progressive optic neuropathy caused by a group of ocular conditions which lead to damage of the optic nerve with loss of visual function. It is the second major cause of blindness. It occurs due to increase in IOP (Intra Ocular pressure). IOP depends on the balance between production and removal of aqueous humor.

Classification: According to appearance of the angle, glaucoma is classified into two types:

- **Open angle Glaucoma:** It is caused by the slow clogging of the drainage canals, resulting in increased intra ocular pressure. It has a wide and open angle between the iris and cornea. It is observed in 90 % of glaucoma patients. It is the most common type of Glaucoma. It causes slow damage to the optic nerve causing gradual and irreversible loss of vision.

- **Closed angle Glaucoma**: It is caused by blocked drainage canals, resulting in a sudden rise in intraocular pressure. It is a less common form of glaucoma. It has a closed or narrow angle between the iris and cornea. It is also called narrow-angle glaucoma.

Management:

Open angle Glaucoma Management:

- Timolol Maleate 0.5% twice daily if patient is not Asthmatic or not Hypertensive, according to response.
- Latanoprost 0.005 % /Travoprost 0.004 % (Prostaglandin analogues) one Drop Once Daily in the Evening if patient is Asthmatic or Hypertensive, according to response.
- Acetazolamide 250-1000 mg /day orally can be given.
- Trabeculectomy can be done surgically.

Closed angle Glaucoma Management:

- Systemic - Intravenous Mannitol 20% 1-2 gm per Kg over ½ an hr.
- Acetazolamide 250-1000mg per day in divided doses should be given.
- One drop of 2% Pilocarpine placed in the eye every 5 min till pupil constricts, then One drop QID.
- One drop of Timolol Maleate 0.5 % twice daily.

BIPHASIC RESPONSE, DALE'S REVERSAL AND RE-REVERSAL PHENOMENON IN PHARMACOLOGY.

Biphasic response:

Adrenaline acts on - α1, α2, β1, β2, β3 receptors.

α1 receptor is present in blood vessels and causes vasoconstriction after adrenaline administration. So blood pressure increases.

β2 receptor is present in blood vessels and adrenaline causes vasodilatation by binding to β2 receptor, so there is decrease in blood pressure takes place.

When adrenaline is given intravenously, initially the concentration of adrenaline is high.So it will act on both α1, β2. But actions of α1 (vasoconstriction), will be more than actions of β2 (vasodilatation). So there will be rise in blood pressure.

Within few second level of adrenaline will decrease due to its rapid metabolism and neuronal re- uptake. So at lower concentration only action of β2 will be more.So only fall in Blood pressure seen.

So at this level it is observed initially rise in blood pressure and then after fall in blood pressure. This is called biphasic response (It is not vasomotor reversal of dale)

Vasomotor reversal of dale:

After biphasic response if non-selective alpha blocker is administered, it blocks the alpha receptors, hence α1 mediated vasoconstriction. Now, if adrenaline is given again, only β2mediated action occur because α1 receptors are blocked by alpha blocker. So only fall in blood presser is seen, rather than biphasic response. This phenomenon is called vasomotor reversal of Dale.

So in vasomotor reversal, it is observed that

- First give adrenaline and observe biphasic response
- second give non-selective alpha blocker

- At last we give adrenaline again and observe only fall in BP due to unopposed β2 mediated action.

Vasomotor Re-reversal:

- First give adrenaline intravenously and observe biphasic response.
- Now, second step, give non Selective Beta Blocker (instead of non-selective alpha blocker). It blocks the β2 receptors, hence β2 mediated vasodialatation will be blocked.

Now, if give Adrenaline again, only α1 mediated action occur-vasoconstriction - rise in blood pressure (why? because β2 receptors are blocked by beta blocker). So only rise in blood presser is seen, rather than biphasic response. This phenomenon is called Re-reversal of Vasomotor reversal of Dale.

CHAPTER-4

PHARMACOLOGY OF CARDIOVASCULAR SYSTEM

Some Terminologies

- **Antianginal Drugs:** drugs that treat angina by reducing the amount of oxygen the heart needs and/or by increasing the supply of oxygen to the heart
- **Antiarrhythmic Drugs:** a group of drugs used to treat cardiac arrhythmias
- **Antilipemic Drugs:** drugs used to lower abnormally high blood levels of fats such as triglycerides and cholesterol
- **Arrhythmia:** disturbance of normal heart function characterized by irregularities in rate, rhythm, or both
- **Atherosclerosis:** a disorder in which lipid deposits accumulate on the lining of the blood vessels, eventually producing degenerative changes and obstruction of blood flow
- **Atrial Fibrillation(atrial fib or AF):** a common irregular rhythm that causes the atria to contract abnormally
- **Atrial Flutter:** regular, rapid contractions of the heart's atria (the upper chambers of the heart)

- **Cardiac Glycosides:** a group of drugs derived from digitalis, a substance that occurs naturally in foxglove plants and in certain kinds of toads
- **Congestive Heart Failure:** a condition in which a weakened heart cannot pump enough blood to meet the body's needs; often called "heart failure"
- **Coronary Artery Disease(CAD):** a condition in which coronary arteries (vessels supplying blood and oxygen to the heart) are narrowed or blocked with fatty deposits
- **Diuretics:** drugs used to promote the excretion of water and electrolytes by the kidneys
- **Heart Block:** a delay or complete block of the electrical impulse as it travels from the heart's sinus node to the ventricles, causing an irregular or slower heartbeat
- **Hypertensive Crisis**: a condition of impending organ damage from severely high blood pressure
- **Inotropic:** affecting the force or energy of muscle contractions
- **Negative Chronotropic Effect:** the slowing of the heart's rate of contraction (or beating) through the use of cardiotonic drugs
- **Negative Dromotropic Effect:** the slowing of the conduction of the electrical impulses that cause the heart to beat through the use of cardiotonic drugs
- **Neurotransmitters:** chemical substances that are released at nerve endings to help transmit nerve impulses; also called neurohormones
- **Paroxysmal Atrial Tachycardia (PAT):** an arrhythmia marked by alternating brief periods of tachycardia and normal sinus rhythm

- **Paroxysmal Supraventricular Tachycardia** (**PSVT)—**a rapid heart rate, usually with a regular rhythm, that originates above the ventricles
- **Phosphodiesterase (PDE) Inhibitors**: a class of drugs used for short-term management of heart failure or long-term management in patients awaiting transplant surgery
- **Positive Inotropic Effect:** the increased force in the contraction of the heart muscle (myocardium) through the use of cardiotonic drugs
- **Premature Atrial Contractions (PACs):** usually harmless extra beats that originate in the atria
- **Premature ventricular contractions (PVCs**)—usually harmless skipped heartbeats
- **Statins:** the common name for HMG-CoA reductase inhibitors, a class of drugs that are used to treat high cholesterol
- **Supraventricular Arrhythmias**: abnormal heart rhythms that originate above the bundle branches of the heart's conduction system
- **Sympathetic Nervous System:** the branch of the autonomic nervous system that regulates the expenditure of energy and has key effects in stressful situations
- **Ventricular Fibrillation (V-Fib):** a disorganized firing of electrical impulses from the ventricles that causes the ventricles to quiver and to be unable to contract or pump blood to the body
- **Ventricular Tachycardia (V-Tach):** a rapid rhythm originating from the ventricles (the lower chambers of the heart) that prevents

the heart from adequately filling with blood and pumping enough blood to the body

- **Anemia:** a decrease in the number of red blood cells
- **Anticoagulant Drugs:** drugs used to reduce the ability of the blood to clot
- **Antiplatelet Drugs:** drugs used to prevent the formation of blood clots in arteries
- **Darbepoetin Alfa:** a glycoprotein that stimulates the production of red blood cells
- **Epoetin Alfa:** a glycoprotein that stimulates the production of red blood cells
- **Erythropoietin:** a hormone that stimulates bone marrow cells to produce red blood cells
- **Folic Acid:** a B vitamin that is important for normal functioning of red and white blood cells
- **Hematinic Drugs:** drugs used to increase the level of hemoglobin in the blood
- **Hematologic Drugs:** drugs used to treat disorders of the blood and blood tissues
- **Hemoglobin:** a molecule in red blood cells that contains iron and allows the transport of oxygen
- **Heparin:** an anticlotting (antithrombolytic) agent that is used to treat and prevent clot formation
- **Intrinsic Factor:** a protein produced by the gastric glands in the stomach that is needed for the metabolism of vitamin B12
- **Iron:** a mineral needed for producing hemoglobin

- **Megaloblastic Anemia:** anemia resulting from a deficiency of vitamin B12 or folic acid
- **Pernicious Anemia:** a condition characterized by decreased gastric production of hydrochloric acid and intrinsic factor deficiency
- **Plasma:** the liquid component of blood
- **Platelets:** substances in the blood that help with blood clotting
- **Red Blood Cells:** cells in the blood that move oxygen from the lungs to other body tissues
- **Thrombolytic Drugs:** drugs that act to dissolve preexisting blood clots vitamin B12 deficiency
- **White Blood Cells:** immune system cells in the blood that fight infection

HYPERTENSION

Hypertension is defined as an elevation of arterial blood pressure above an arbitrarily defined normal value. The American Heart Association defines hypertension as arterial blood pressure higher than 140/90mmHg (based on three measurements at different times).

Hypertension may be classified in to three categories, according to the level of diastolic blood pressure:

- **Mild hypertension** with a diastolic blood pressure between 95-105 mmHg
- **Moderate hypertension** with a diastolic blood pressure between 105 – 115mmHg

- **Severe hypertension** with a diastolic blood pressure above 115mmHg.

Other classification

- **Primary hypertension:** Patients in whom no specific cause of hypertension can be found are said to have essential hypertension or primary hypertension (accounts for 80-90 % of cases).
- **Secondary hypertension:** It arises as a consequence of some other conditions such as, atherosclerosis, renal disease, endocrine diseases and others. The central issue of antihypertensive therapy is to lower arterial blood pressure, irrespective of the cause.

NON-PHARMACOLOGICAL THERAPIES OF HYPERTENSION

- Exercise
- Cessation ofsmoking
- Decrease in excessive consumption ofalcohol
- Psychological methods (relaxation, meditation, Yoga)
- Dietary decrease in saturatedfats.
- Low sodium chloridediet
- Weightreduction

CLASSIFICATION OF ANTIHYPERTENSIVE DRUGS

All patients with hypertension require drug treatment to achieve sustained reduction of blood pressure. Antihypertensive drugs lower blood pressure by decreasing either cardiac output (CO) or total peripheral vascular resistance (PVR) or both although changes in one can indirectly affect the other.

Classification:

- **Angiotensin converting enzyme (ACE) inhibitors:** Captopril, Enalapril
- **Angiotensin (AT1 receptor) antagonists:** Losartan, Telmisartan
- **Calcium channel blockers:** Felodipine, Amlodipine, Nifedipine
- **Diuretics:** Hydrochlorothiazide, Chlorthalidone, Furosemide,
- **β Adrenergic blockers:** Propranolol, Metoprolol, Atenolol
- **β + α adrenergic blockers:** Labetalol**,** Carvedilol
- **α Adrenergic blockers:** Prazosin, Terazosin, Doxazosin
- **Central sympatholytics:** Clonidine, Methyldopa
- **Vasodilators:** Hydralazine, Minoxidil, Diazoxide, Sodium Nitroprusside

USE OF DIURETICS IN HYPERTENSION

Diuretics act on kidneys by increasing the amount of salt and water that comes out through your urine. Too much salt in blood vessels, increases blood pressure. Diuretics lowerblood pressure by flushing salt out of your body, taking this unwanted extra fluid with it.

Thiazide diuretics: They reduce blood pressure by reducing blood volume and cardiac output as a result of a pronounced increase in urinary water and electrolyte particularly sodium excretion. With chronic administration (6-8weeks), they decrease blood pressure by decreasing peripheral vascular resistance as the cardiac output and blood volume return gradually to normal values. Thiazides are

appropriate for most patients with mild or moderate hypertension and normal renal and cardiac function.

Loop diuretics: Loop diuretics are more potent than thiazides as diuretics. The antihypertensive effect is mainly due to reduction of blood volume. Loop diuretics are indicated in cases of severe hypertension which is associated with renal failure, heart failure or liver cirrhosis.

Potassium sparing diuretics: They are used as adjuncts with thiazides or loop diuretics to avoid excessive potassium depletion and to enhance the natriuretic effect of others. The diuretic action of these drugs is weak when administered alone.

Diuretics are used in

- Elderly patients
- Obese patients
- Isolated systolic hypertension condition

Diuretics are contraindicated in

- Young hypertensive patients
- Diabetic patients
- Hypertension with gouty arthritis, Hyperlipidemia

USE OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEIS) IN HYPERTENSION

Angiotensin Converting Enzyme helps in the formation of Angiotensin-II. Angiotensin-II causes vasoconstriction, so BP increases. Angiotensin

converting enzyme inhibitors inhibit ACE. Angiotensin –II formation stops. Vasodilatation takes place and relief from high BP occurs.

ADVERSE EFFECTS OF CAPTOPRIL

The adverse effects include

- **C**ough
- **A**ngioedema/Agranulocytosis
- **P**roteinuria/ Potassium excess
- **T**aste changes
- **O**rthostatic hypotension
- **P**regnancy contraindication/ Pancreatitis/ Pressure drop (fi rst dose hypertension)
- **R**enal failure (and renal artery stenosis contraindication)/Rash
- **I**ndomethacin inhibition
- **L**eukopenia/ Liver toxicity

USE OF ARBS / AT_1 RECEPTOR ANTAGONISTS IN HYPERTENSION

AT_1 receptor involves in the action of Angiotensin-II & III, Vasoconstriction occurs. **AT_1 receptor antagonists** competitively antagonize AT_1 receptors and inhibit stimulation of Angiotensin-II, Angiotensin-III. Vasodilatation takes place, so relief from hypertension occurs.

USE OF METHYLDOPA IN HYPERTENSION

Methyldopa is metabolized in CNS to methyl-inorepinephrine, which stimulates α_2 adrenergic receptors in brain. This leads to decrease

sympathetic outflow from the vasomotor centre in CNS and reduces blood pressure.

Adverse effect of methyldopa:

Adverse effects are Sedation**,** cognitive impairment, lethargy, dryness of mouth, headache, weight gain, impotence, and hypersensitivity reaction.

USE OF ALPHA BLOCKERS IN HYPERTENSION

α blockers cause blood vessels to dilate, thereby lowering blood pressure. They reduce arteriolar resistance and increase venous capacitance.

USE OF BOTH ALPHA AND BETA BLOCKERS IN HYPERTENSION.

Labetalol is highly selective for postsynaptic α1- adrenergic, and non-selective for **β** -adrenergic receptors. It is about equipotent in blocking both **β**1- and **β**2- receptors and found beneficial in hypertension during pregnancy.

USE OF NITROPRUSSIDE IN HYPERTENSION

It is a direct acting vasodilator that acts on both resistance and capacitance vessels. It reduces total peripheral resistance, reduces cardiac output, and reduces myocardial work.

USE OF CALCIUM CHANNEL BLOCKERS IN HYPERTENSION

Calcium channel blockers are drugs used to lower blood pressure. They work by decreasing the movement of calcium into the cells of the heart

and blood vessel walls, which makes it easier for the heart to pump and widens blood vessels.

OR

The mechanism of action in hypertension is inhibition of calcium influx in to arterial smooth muscle cells, resulting in a decrease in peripheral resistance. Verapamil has the greatest cardiac depressant effect and may decrease heart rate and cardiac output as well.

Adverse Effects of Calcium Channel Blockers

The most important toxic effects for calcium channel blockers are

- cardiac arrest
- bradycardia
- atrioventricular block
- congestive heart failure

LINES OF TREATMENT OF PRIMARY HYPERTENSION

The initial step in treating hypertension may be non-pharmacologic. Dietary salt restriction may be effective treatment for about half of the patients with mild hypertension. Weight reduction even without salt restriction normalizes blood pressure in up to 70% of obese patients with mild to moderate hypertension. Regular exercise may also be helpful in some hypertensive patients.

When non-pharmacologic approaches do not satisfactorily control blood pressure, drug therapy begins in addition to non-pharmacological approaches.

The selection of drug(s) depends on various factors such as the severity of hypertension, patient factors (age, race, coexisting diseases,etc.). For

most patients with mild hypertension and some patients with moderate hypertension mono- therapy with either of the following drugs can be sufficient.

- Thiazide diuretics
- Beta blockers
- Calcium channel blockers
- Angiotensin converting enzyme inhibitors

Beta-blockers are preferred in young patients, high renin hypertension and patients with tachycardia or angina and hypertension. Black patients respond well to diuretics and calcium channel blockers than to beta-blockers and ACE inhibitors.

If mono-therapy is unsuccessful, combination of two drugs with different sites of action may be used. Thiazide diuretics may be used in conjunction with a beta-blocker, calcium channel blocker or an angiotensin converting enzymeinhibitor.

If hypertension is still not under control, a third drug e.g. vasodilator such as hydralazine may be combined.

When three drugs are required, combining a diuretic, a sympathoplegic agent or an ACE inhibitor, and a direct vasodilator or calcium channel block is effective.

The treatment of hypertensive emergencies is usually started with furosemide given by parenteral route at dose of 20-40mg. In addition, parenteral use of diazoxide, sodium nitroprusside, hydralazine, trimethaphan, labetalol can be indicated.

ANTI-ANGINAL DRUGS

CLASSIFICATION

- **Nitrates:** (a) Short acting: Glyceryl trinitrate (b) Long acting: Isosorbide mononitrate
- **β Blockers:**Propranolol, Metoprolol, Atenolol
- **Calcium channel blockers**: Amlodipine, Nifedipine, Verapamil, Diltiazem
- **Potassium channel opener:**Nicorandil
- **Others**: Dipyridamole, Trimetazidine, Ranolazine

USE OF ORGANIC NITRATES IN ANGINA PECTORIS

They dilate the veins. They reduce preload as a result venous return reduces. This leads to reduction of cardiac work and oxygen demand. Thus they are useful in angina.

ROLE OF CALCIUM CHANNEL BLOCKER IN ANGINA PECTORIS

They dilate coronary artery so there is increase in coronary blood flow. They also decrease myocardial oxygen demand.

ROLE OF BETA BLOCKERS IN ANGINA PECTORIS

They have negative chronotropic and negative inotropic effects. So they decrease myocardial oxygen requirement at rest and during exercise. They also reduce arterial BP.

COAGULANTS

A) Vitamin K:

- K_1 (from plants, Soluble fats): Phytonadione
- K_2 (produced by bacteria): Menaquinones
- K_3 (Synthetic): Menadione, Acetomenaphthone (Fat Soluble);

Menadione sod bisulfate, Menadione sod diphosphate (Water soluble)

B) Miscellaneous: Fibrinogen (human), Antihaemophilic factor, Ethamsylate

MECHANISM OF COAGULANT ACTION

Vitamin K acts as cofactor at a last stage in the synthesis by liver coagulation proteins –prothrombin (factor II), factors VII, IX & X.

THERAPEUTIC USES OF VITAMIN K

- Prolonged Antibiotic use.
- Overdose of oral anticoagulants.
- Newborn or Premature infants.
- Malabsorption syndrome/obstructive Jaundice.

ANTICOAGULANTS

Parenteral Anticoagulants

Heparin

- **Low Mol Wt Heparins:** Enoxaparin, Dalteparin, Tinzaparin, Ardeparin, Nadoparin, Raviparin
- **Synthetic Heparin:** Fondaparinux

- **Miscellaneous group:** Lepirudin, Bivalirudin, Argatroban, Danaparoid

Oral Anticoagulants

- **Coumarin Derivatives:** Dicumarol, Ethyl biscoumacetate, Warfarin, Acenocumarol
- **Indandione Derivatives:** Phenindione, Anisindione

INDIVIDUAL DRUGS

Heparin: It is present together with histamine in all tissues containing mast cells. Richest source include Lung, Liver, Intestinal Mucosa. It is obtained from beef lung & pig intestinal mucosa. Duration of action of heparin is short (1-5hrs).

MOA of Heparin: It acts indirectly by activating plasma antithrombin III (AT III, a serine proteinase inhibitor). The heparin-AT III complex then binds to clotting factors of the intrinsic and common pathways (Xa, IIa, IXa, XIa, XIIa and XIIIa) and inactivates them but not factor VIIa operative in the extrinsic pathway.

LOW MOLECULAR WEIGHT HEPARIN

They produce lesser effect on thrombin, platelet function, on coagulation.

Advantages of LMWH: These can be given in subcutaneous route. They have better bioavailability (70-90%). Their effects are more consistent & dosing is less frequent (can be used as OD dose).

SYNTHETIC HEPARIN DERIVATIVES

Fondaparinux: It is a synthetic pentasaccharide. **It causes an AT-III mediated inhibition of Factor Xa, interrupts the blood coagulation cascade and inhibits thrombin formation.** Bioavailability in sc route is 100%, and $t_{1/2}$ is 17-21 hours. It is indicated for treatment of pulmonary embolism.

MISCELLANEOUS PARENTERAL ANTICOAGULANTS

They act by binding the thrombin directly.

- **Hirudin:** Hirudin is a specific irreversible inhibitor of thrombin.
- **Lepirudin:** Lepirudin is the recombinant form of hirudin. It is used in patients with heparin-induced thrombocytopenia and associated thromboembolic diseases. Adverse effects include hemorrhage, and haematuria.

DIFFERENCES BETWEEN HEPARIN & WARFARIN

Heparin	Warfarin
1. It is a parenteral anticoagulant (sc/iv). 2. Source: bovine lungs 3. Anticoagulation action is by accelerating AT-III and inactivating Factors IIa & Xa. 4. Duration of action is shorter. Continuous monitoring of coagulant parameters in blood after administration. 5. It is safer in pregnancy. 6. But it causes thrombocytopenia, haemorrhage. 7. Heparin antagonist is Protamine Sulfate. 8. They are given initially before the warfarin administration. 9. Site of action: blood 10. Protein binding: nil 11. Half life: 40-90min	1. It is an oral anticoagulant. 2. Source: semi synthetic 3. Anticoagulant action is by inhibiting the Vit K reductase which indirectly inhibits the synthesis of coagulant factors. 4. Onset of action is slower & Duration of action is longer. 5. It is not safer in pregnancy → it causes skeletal abnormalities in fetus. 6. It also causes necrosis of soft tissues. 7. Warfarin antagonist is Vit K_1-Phytonadione. 8. Heparin should be given before the warfarin administration to avoid necrosis of soft tissues. 9. Site of action: Liver 10. Protein binding: Extensive 11. Half life: 15-70hr

Adverse Effects of Warfarin

- It may produce teratogenecity, transient Alopecia.
- Dermatitis and diarrhea are common adverse effects.

Adverse Effects of Heparin

- Thrombocytopenia, Osteoporosis, Transient Alopecia, Hypersensitivity.

THERAPEUTIC USES OF ANTICOAGULANTS

- Used for treatment of **deep vein thrombosis**&**pulmonary embolism.**
- They are used in **myocardial infarction** and **coronary angioplasty**.
- They are used in **unstable angina AND rheumatic heart disease**.
- For thetreatment of **disseminated intravascular coagulation**&**peripheral embolism.**
- They are used during **cardiac bypass surgery.**
- They are used **during haemodialysis.**
- They are used for **anticoagulation in pregnancy.**

ANTIPLATELET AGENTS

Anti platelet drugs include thromboxane A_2 inhibitors, ADP receptor inhibitors, glycoprotein IIb/IIIa receptor blockers and phosphodiesterase inhibitors.

- **Thromboxane-A_2 inhibitor:** Aspirin
- **ADP receptor inhibitors:** Clopidogrel, Ticlopidine
- **Glycoprotein IIb/IIIa receptor blockers:** Abciximab, Eptifibatide, Tirofiban
- **Phosphodiesterase inhibitors:** Dipyridamole, Cilostazol

MECHANISM OF ACTION OF ASPIRIN

Aspirin irreversibly inhibits the enzyme cyclooxygenase (COX), resulting in reduced platelet production of TXA_2 (TXA_2 is a powerful vasoconstrictor that initiates the platelet release reaction).

WRITE MECHANISM OF ACTION OF DIPYRIDAMOLE

Dipyridamole inhibits **platelet phosphodiesterase enzyme** and causes an increase in cyclic AMP production. It also potentiates the action of PGI_2.

THROMOLYTICS/ FIBRINOLYTICS

Thrombolytic drugs dissolve blood clots by **activating plasminogen,** which forms a cleaved product called plasmin.

Plasmin is a proteolytic enzyme capable of breaking cross-links between fibrin molecules, which provide the structural integrity of blood clots. Thrombolytic drugs are also called as **plasminogen activators** and **fibrinolytics.**

There are three major classes of fibrinolytic drugs:

- tissue plasminogen activator: **Alteplase, Retaplase, Tenecteplase**
- **Streptokinase**
- **Urokinase**

DRUGS USED FOR CONGESTIVE HEART FAILURE

- **ACE inhibitor:** They relax blood vessels and lower blood pressure. This improves blood flow. So heart can able to pump more blood to other body parts without working harder.
- **ARB:** Improves quality of life in patients with heart failure.
- **Digitalis:** Digitalis increases blood flow throughout body and reduce edema.
- **Beta adrenergic agonists:** They improve pulmonary function and cardiovascular hemodynamics.
- **Diuretics:** Diuretics help kidneys to remove more water and salt (sodium) from body, which help relieve swelling.
- **Vasodilators:** Theydilate blood vessels so blood pressure reduces. This helps heart to pump blood easily.
- **Beta-blockers:** Beta-blockers slow the heart rate and allow more time for heart to fill with blood.
- **Calcium-channel blockers:** They relax blood vessels and increase the supply of blood and oxygen to the heart.

PHARMACOLOGY OF DRUGS USED FOR CONGESTIVE HEART FAILURE

Congestive heart failure occurs when there is an inability of the heart to maintain a cardiac output sufficient to meet the requirements of the metabolising tissues.

Heart failure is usually caused by one of the following:

- Ischaemic heartdisease
- Hypertension

- Heart muscle disorders
- Valvular heartdisease

Treatment:

Drugs used to treat heart failure can be broadly divided into:

- Drugs with positive inotropiceffect
- Drugs without positive inotropiceffect

A. Drugs with positive inotropiceffect: Drugs with positive inotropic effect increase the force of contraction of the heart muscle. These include:

- Cardiacglycosides
- Bipyridinederivatives
- Sympathomimetics
- Methylxanthines

Cardiacglycosides: Cardiac glycosides comprise a group of steroid compounds that can increase cardiac output and alter the electrical functions. Commonly used cardiac glycosides are digoxin and digitoxin. The mechanism of inotropic action of cardiac glycosides is **inhibition of the membrane-bound Na^+/K^+ ATPase often called the "Sodium Pump".** This results in an increased intracellular movement of sodium and accumulation of sodium in the cells. As a consequence of the higher intracellular sodium, decreased transmembrane exchange of sodium and calcium will take place leading to an increase in the intracellular calcium that acts on contractile proteins. All cardiac glycosides exhibit similar pharmacodynamic properties but do differ in their

pharmacokinetic properties. For example, digitoxin is more lipid soluble and has long half-life than digoxin.

Therapeutic uses of cardiac glycosides include:

- Congestive heartfailure,
- Atrialfibrillation,
- Atrial flutter,and
- Paroxysmal atrial tachycardia.

Toxicity of cardiac glycosides includes:

- Gastrointestinal effects such as anorexia, nausea, vomiting,diarrhoea
- Cardiac effects such as bradycardia, heart block,arrhythmias
- CNS effects such as headache, malaise, hallucinations, delirium, visual disturbances (yellowvision)

Mild toxicities such as gastrointestinal and visual disturbance can be managed by reducing the dose of the drug.

For the management of arrhythmias or serious toxicity, potassium supplementation, administration of anti-arrhythmic drugs (e.g. lidocaine), and use of digoxin antibodies can be helpful.

Bipyridine derivatives: e.g. amrinone,milrinone.

These drugs possess both positive inotropic effect and vasodilatoreffects.The suggested mechanism of action is **inhibition of an enzyme known as phophodiesterase, which is responsible for the inactivation of cyclic AMP.** Inhibition of this enzymes result in an

increase in cAMP.

Bipyridine derivatives are used in cases of heart failure resistant to treatment with cardiac glycosides and vasodilators.

Beta - adrenergic stimulants e.g. dobutamine,dopamine

The increase in myocardial contractility by beta stimulants increases the cardiac output. However, positive chronotropic effect of these agents minimizes the benefit particularly in patients with ischaemic heart disease. The positive inotropic effect of dobutamine is proportionally greater than its effect on heart rate. It is reserved for management of acute failure or failure refractory to other oralagents.

Methylxanthines, e.g. theophylline in the form ofaminophylline

Aminophylline has a positive inotropic effect, bronchodilating effect and a modest effect on renal blood flow. It is used for management of acute left ventricular failure or pulmonary edema.

B. Drugs without positive inotropic effect: Theseinclude:

- Diuretics, e.g. hydrochlorothiazide,furosemide
- Vasodilators, e.g. hydralazine, sodiumnitroprusside
- Angiotensin converting enzyme inhibitors e.g. captopril,enalapril

Diuretics: Diuretics are first line drugs for treatment of patients with heart failure. In mild failure, a thiazide may be sufficient but are ineffective at low glomerular filtration rates. Moderate or severe failure requires a loopdiuretic.In acute failure, diuretics play important role by

reducing ventricular preload. The reduction in venous pressure causes reduction of edema and its symptoms and reduction of cardiac size which leads to improved efficiency of pump function.

Vasodilators: The vasodilators are effective in acute heart failure because they provide a reduction in preload (through venous dilation), or reduction in after-load (through arteriolar dilation), or both. Hydralazine has a direct vasodilator effect confined to arterial bed. Reduction in systemic vascular resistance leads to a considerable rise in cardiac output.

Sodium nitroprusside is a mixed venous and arteriolar dilator used also for acute reduction of blood pressure.

Vasodilator agents are generally reserved for patients who are intolerant of or who have contraindications to ACE inhibitors.

Angiotensin converting enzyme (ACE) inhibitors: Because of the pervasive involvement of angiotensin II in the undesirable compensatory responses to heart failure, reduction of this peptide has positive effects on the course of thedisease. These drugs reduce after load by reducing peripheral resistance and also reduce preload by reducing salt and water retention by way of reduction in aldosterone secretion. They are nowadays considered a head of cardiac glycosides in the treatment of chronic heart failure.

The following are essential for long-term management of chronic heart failure:

- Modify cardiovascular risk factor profile, e.g. cigarette smoking,

obesity, salt intake Underlying causes should be treated, e.g. anemia, hypertension, valvular disease If this proves inadequate, diuretic should be given.

- Give ACE inhibitor and digitalis (ACE inhibitors may be used before digitalis). In patients with persisting symptoms give vasodilators besides increasing the dose of diuretic and ACE inhibitors.

MANAGEMENT OF DIGOXIN TOXICITY

Digoxin toxicity: features

- Arrhythmias (especially AV block).
- Nausea, vomiting, diarrhoea.
- Headache; dizziness.
- Seizures.
- Xanthopsia (yellow vision).
- Skin reactions.
- Impotence.

Digoxin toxicity: causes

- Electrolyte disturbances (↓ K+; ↓ Mg++; ↑ Ca++).
- Renal impairment.
- Hypothyroidism.
- Drug-induced (ACEI Ca-channel blockers; amiodarone; quinidine; cyclosporine).

Management of Digoxin toxicity:

- Prevent absorption: gastric lavage; activated charcoal (if patient comes within 6–8hrs of ingestion).
- Correct electrolyte disturbances (↓ K+; ↓ Mg++; ↑ Ca++). K+ should not be raised above the level of 5 mEq/L.
- For bradyarrhythmia: Atropine.
- For symptomatic bradycardia that has failed to respond to atropine:

Temporary pacemaker:

- For supraventricular tachycardia (SVT): Verapamil.
- For ventricular tachycardia (VT): Lignocaine; phenytoin.

DRUGS USED FOR ACUTE MYOCARDIAL INFARCTION

- **For Pain, anxiety and apprehension**: An opioid analgesic (morphine/pethidine) or diazepam
- **Oxygenation**: By O2 inhalation and assisted respiration, if needed.
- **Maintenance of blood volume:** Slow i.v. infusion of saline/low mw dextran.
- **Correction of acidosis**: by i.v. Sodium bicarbonate infusion.
- **Prevention and treatment of arrhythmias:**Prophylactic i.v. infusion of beta blocker. Tachyarrhythmias may be treated with i.v. lidocaine, procainamide
- **Pump failure:** Drugs used for this purpose are: (a) Furosemide, (b) Vasodilators: Drugs like GTN (i.v.), or nitroprusside (c) Inotropic agents: dopamine or dobutamine i.v. infusion

- **Prevention of thrombus extension, embolism, and venous thrombosis**: Aspirin (162–325 mg) should be given. This is continued at 80–160 mg/day. Anticoagulants (heparin followed by oral anticoagulants) are used primarily to prevent deep vein thrombosis.
- **Thrombolysis and reperfusion**: Fibrinolytic agents, i.e. plasminogen activators—streptokinase/ urokinase/alteplase to achieve reperfusion ofthe infarcted area
- **Prevention of remodeling and subsequent CHF**: ACE inhibitors/ARBs are DOC.
- **Prevention of future attacks**:

  (a) Platelet inhibitors—aspirin or Clopidogrel given

  (b) β blockers—reduce risk of reinfarction, CHFand mortality.

  (c) Control of hyperlipidaemia: dietary substitution with unsaturated fats, and statins.

PHARMACOTHERAPY OF CARDIAC ARRHYTHMIA

Electrophysiology of cardiac muscle: the pathophysiological mechanisms responsible for the genesis of cardiac arrhythmias are not clearly understood. However, it is generally accepted that cardiac arrhythmias arise as the result of either of

- Disorders of impulse formation and/ or
- Disorders of impulse conduction.

Pharmacotherapy of cardiac arrhythmias

Antiarrhythmic drugs are used to prevent or correct cardiac arrhythmias (tachyarrhythmias). Drugs used in the treatment of cardiac arrhythmias are traditionally classified into:

Class (I): Sodium channel blockers which include quinidine, lidocaine, phenytion, flecainide, etc.

Class (II): Beta adrenergic blockers which include propranolol, atenolol, etc.

Class (III): Potassium channel blockers e.g. amiodarone, bretylium.

Class (IV): Calcium channel blockers e.g. verapamil, etc.

Class (V): Digitalis e.g.digoxin.

Class – I drugs (Sodium channel blocker)

- **Quinidine:** It blocks sodium channel so that there is an increase in threshold for excitability. It is well absorbed orally. Adverse effects: It has low therapeutic ratio. Main **adverse effects** are SA block, cinchonism, severe headache, diplopia and photophobia.
- **Lidocaine,** which is used commonly as a local anaesthetic blocks both open and inactivated sodium channel and decreases automaticity. It is given parenterally. **Adverse effects**: excessive dose cause massive cardiac arrest, dizziness, drowsiness, seizures, etc.
- **Flecainide:** It is a procainamide analogue and well absorbed orally. It is used in ventricular ectopic beats in patients with normal left ventricular function.

Class –II drugs: Beta-adrenergic receptor blockers

- **Propranolol:** Myocardiac sympathetic beta receptor stimulation increases automaticity, enhances A.V. conduction velocity and shortens the refractory period. Propranolol can reverse these effects. Beta blockers may potentiate the negative inotropic action of other antiarrhythmics.

Therapeutic uses: This is useful in tachyarrhythmias, in pheochromocytoma and in thyrotoxicosis crisis. It is also useful in patients with atrial fibrillation and flutter refractory to digitalis.

Class – III: Potassium channel blockers

- **AMIODARONE:** This drug is used in the treatment of refractory supraventriculat tachyarrhythmias and ventricular tachyarrhythmias. It depresses sinus, atrial and A.V nodal function.

The **main adverse effects** of this drug are anorexia, nausea, abdominal pain, tremor, hallucinations, peripheral neuropathy, and A.V. block

Class IV drugs: Calcium channel blockers

- Verapamil: this drug acts by blocking the movement of calcium ions through the channels. It is absolutely contraindicated in patients on beta blockers, quinidine or disopyramide. It is the drug of choice in case of paroxysmal supraventricular tachycardia for rapid conversion to sinus rhythm.

Class - V drugs:

- Digoxin causes shortening of the atrial refractory period with small doses (vagal action) and a prolongation with the larger doses (direct action). It prolongs the effective refractory period of A.V node directly and through the vagus. This action is of major importance in slowing the rapid ventricular rate in patients with atrial fibrillation.

DIURETICS

Diuretics: These are the drugs that act on the renal tubule to promote the excretion of Na+, Cl- and H_2O.

They are used to treat Hypertension, Acute pulmonary oedema, Heart Failure, Liver cirrhosis and ascites, Renal Failure, Acute hypercalcaemia

Osmotic Diuretics:

Mannitol: It is a pharmacologically inert drug.

MOA: It is filtered by the glomerulus but not reabsorbed resulting in an increase in the osmolarity of the kidney tubule. So there is decrease in water reabsorption in the proximal tubule, loop of Henle and collecting duct.

Use: It is used to prevent acute renal failure by increasing H_2O excretion. It decreases intra-cranial pressure and intra-ocular pressure.

ADR: Nausea, Vomiting, Dehydration**,** Hyponatraemia**,** Hypernatraemia**,** Pulmonary Oedema

Carbonic anhydrase Inhibitors:

Acetazolamide: generally weak diuretic.

MOA: It acts on the proximal tubule to prevent the reabsorption of HCO_3^- and Na^+. This result in less water being reabsorbed due to the low osmolarity of the proximal tubule cells. High concentration of HCO_3^- in the distal tubule also causes a reduction in K^+ loss. Urine is therefore very alkaline.

USE: Metabolic alkalosis,Renal stones, Decrease intra-ocular pressure in glaucoma.

ADR: Hypokalaemia**,** Metabolic acidosis

Loop Diuretics

Frusemide: It is a powerful diuretic.

MOA: It prevents the reabsorbtion of sodium and chloride ions in the ascending loop of Henle and is associated with a decrease in Ca^{2+} and Mg2+ reabsorption. This results in a lower osmolarity of the interstitium and hence less water will be reabsorbed in the descending limb and collecting duct. Its overall effect is excretion of a large amount of Water, Na^{+}, Ca^{2+} and K^{+}.

USE: Oedema, Moderate Hypertension, Hypercalcaemia, Hyperkalaemia

ADR: Hypovolaemia & Hypotension, K+ loss (Ca2+/Mg2+), Metabolic Alkalosis, Hypokalaemia.

Thiazides

Bendrofluazide

MOA: It inhibits Na^{+} and Cl^{-} absorption in the early part of the distal tubule and so increase magnesium Mg^{2+} loss and Ca^{2+} reabsorption. This results in a decrease in water reabsorption in the collecting duct and therefore a moderate increase in urine volume and Na+, Cl- & K+ loss (Mg2+ loss).

USE: Cardiac failure, Hypertension, Severe resistant oedema, Idiopathic hypercalciuria - stone formation, Nephrogenic diabetes insipidus.

ADR: diabetes mellitus (due to inhibition of insulin secretion), metabolic alkalosis, gout, hypokalaemia.

Potassium Sparing Drugs

Spironolactone: Spironolactone is used in hyperaldosteronism (primary and secondary).

Amiloride: Amiloride is used with other diuretics that result in K^+ loss.

MOA: They block aldosterone from binding to its receptor and amiloride inhibits the aldosterone sensitive Na^+ channels, both resulting in an increase in Na^+ loss, and K^+ reabsorption. Decreased water reabsorption in the collecting duct takes place. It also increases uric acid loss.

ADR:

- **Amiloride:** Hyperkalaemia, Metabolic Acidosis
- **Spironolactone**: Gynaecomastia, Menstrual disorders, Testicular Atrophy

LIPID LOWERING AGENTS

Classification:

HMG-CoA reductase inhibitors (Statins): Lovastatin, Simvastatin, Pravastatin, Atorvastatin, Rosuvastatin,

Bile acid sequestrants (Resins): Cholestyramine, Colestipol

Lipoprotein lipase activators (PPARα activators, Fibrates): Clofibrate, Gemfibrozil, Bezafibrate, Fenofibrate.

Lipolysis and triglyceride synthesis inhibitor: Nicotinic acid.

Sterol absorption inhibitor: Ezetimibe.

a. Statins (HMG-CoA Reductase Inhibitors): Lovastatin, pravastatin, simvastatin, fluvastatin, atrovastatin and **rosuvastatin.**

- Statins lower triglycerides and raise HDL cholesterol. They are taken at night because cholesterol synthesis is greatest at that time.
- **MOA:** Statins act by inhibiting cellular cholesterol production, decreasing the intracellular pool of cholesterol.
- **Side effects**: gastrointestinal discomfort, myalgia.They are contraindicated inconditions likeliver diseases, in pregnancy and breast-feeding.

b. Bile Acid Binding Resins: Cholestyramine and **colestipol** can cause rise of triglycerides. Resins can be combined with niacin or statins. Colesevelam causes less gastrointestinal side effects. **Side effects** are GIT disorders like bloating and constipation.

c. Cholesterol Absorption Inhibitor: Ezetimibe blocks the absorption of cholesterol. It is used alone or in combination with statins. Side effects include diarrhea.

d. Nicotinic Acid (Niacin): Niacin can decrease triglycerides, increase HDL, and decrease LDL in higher doses. It may cause severe liver toxicity, angioedema, bronchospasm and anaphylaxis.

e. Fibrates: Gemfibrozil and **fenofibrate** are lipid lowering fibrates. They decrease serum triglycerides, LDL cholesterol and increase HDL cholesterol in patients with hypertriglyceridemia. Side effects are mainly gastrointestinal disorders. They are contraindicated in pregnancy and breastfeeding.

CHAPTER-5

DRUGS ACTING ON RESPIRATORY SYSTEM

CLASSIFICATION OF DRUGS USED IN ASTHMA

Bronchodilators

- **Selective β_2- Agonists:** Salbutamol, Terbutaline, Remiterol, Fenoterol, Salmeterol, Formoterol, Bambuterol
- **Non-selective sympathomimetics:** Epinephrine, Ephedrine, Isoprenaline, Orciprenaline (Metaproterenol), Isoetharine
- **Anticholinergics:** Ipatropium, Tiotropium, Oxitropium
- **Methyl Xanthines:** Theophylline, Aminophylline, diprophylline, Choline theophyllinate

Corticosteroids

- **Oral:** Prednisone, methyl prednisolone
- **Parenteral:** Methyl prednisolone, Hydrocortisone
- **Inhalational:** Beclomethasone, Fluticasone, Triamcinolone, Budesonide, Flunisolide

Mast Cell Stabilisers: Sodium Ceromoglycate, Nedocromil, Ketotifen

Leukotriene Modulators

- **5-Lipoxygenase Inhibitor:** Zileuton
- **LTD4 – Receptor Antagonists:** Zafirlukast, Montelukast, Iralukast

Monoclonal Anti-IgE Antibody: Omalizumad

Miscellaneous: Nitric oxide donors, Calcium channel blockers

PHARMACOLOGY OF DRUGS USED FOR BRONCHIAL ASTHMA

Bronchodilators: They relieve asthmatic symptoms & improve pulmonary functions by relaxing the bronchial smooth muscle. They provide a rapid symptomatic relief but don't control the disease process. They are termed as relievers. These includes Non-selective sympathomimetics, Selective β2 agonists, Methylsanthines, Antimuscarinic drugs

Selective β2 – Agonists: They activate β2 adrenorecptors present on airway muscle and enhance the release of cAMP by activating adenylyl cyclase enzyme. They relax airway smooth muscle and inhibit the release of bronchoconstricting chemical mediators from mast cells. Terbutaline is only safest drug in Pregnancy.

Adverse Effects: Muscle tremors (due to stimulation of β2 in skeletal muscle), Tachycardia (due to the stimulation of chronotropic β2 receptors & in high doses β1 receptors in the heart), Restlessness

Non-selective Sympathomimetics: Epinephrine, Ephedrine, Isproterenol, Orciprinaline

Isoproterenol is a non-selective but it is not used because of side effects (tremors & tachycardia), it also disturbs the ventilation: perfusion ration of lungs leading to hypoxaemia & respiratory acidosis.

Anticholinergics: Ipratropium, Oxitropium & Tiotropium are used but are less effective bronchodilators then β2 agonists. They cause bronchodilation by binding to M3 receptors on airway smooth muscle. They also decreases the mucus secretion. Combination of Ipratopium

with β2 agonist (Salbutamol) produces longer duration of action and is beneficial in severe asthma. Side effects include bad taste & dryness of mouth.

Methylxanthines: (Teophylline, Aminophylline, Diprophylline, Choline theophyllinate). Their beneficial effects are mediated through increased cAMP, which leads to bronchodilation. Theophylline exhibits bronchodilatory, anti-inflammatory & immunomodulatory effects. Theophylline mainly used in the management of asthma and to treat COPD. It is also used to relieve dyspnoea from congestive heart failure. They are used as combination therapy with β2 agonists. Adverse Effects include Nausea, Vomiting with normal therapeutic doses.

Corticosteroids: Corticosteroids have been used in the management of asthma & they provide long term stabilization of the symptoms due to their anti-inflammatory effects. They are called as "Controllers." They are combined with β2 agonists and the combination is the first choice in asthma. They enhance β2 receptor response by up-regulating the β2 recptors in lung cells & leukocytes. They inhibit the release of prostaglandins & leukotrienes (LTC4, LTD4 & LTE4). They prevent smooth muscle contraction, vascular permeability & airway secretions.

Mast Cell Stabilizers: These are nonbronchodilating, nonsteroidal drugs used for prophylactic asthma. These drugs prevent degranulation & subsequent release of chemical mediators from mast cells. They stabilize mast cells by preventing transmembrane influx Ca+2 ions provoked by antigen IgE antibody reaction on the mast cell membrane.

These are reserved for prophylactic use in the management of chronic asthma.

Leukotriene Modulators: The effects of Leukotrienes can be blocked by inhibiting leukotriene synthesis. Example: Zileuton.

The effects of Leukotrienes can be blocked by blocking their stimulator effects on cys LT receptor. Example: Zafirlukast, Montelukast, Iralukast, Pranlukast. These drugs mainly used as adjuvants with inhaled corticosteroids in poorly responding patients. They reduce the dosage of β2 agonists & inhaled corticosteroids for maintenance.

ANTITUSSIVES

Antitussives are medicines that suppress coughing, also known as cough suppressants. Antitussives are thought to work by inhibiting a coordinating region for coughing located in the brain stem, disrupting the cough reflex arc; although the exact mechanism of action is unknown.

Many antitussives, including pholcodine, codeine, and dextromethorphan, are derived from opioids. Pholcodine and codeine may cause drowsiness and constipation and codeine may be addictive. Dextromethorphan can increase serotonin levels and may interact with other medicines that also increase serotonin. Benzonatate is a nonnarcotic antitussive that anesthetizes certain receptors located in the breathing passages, reducing the urge to cough.

NASAL DECONGESTANTS

Nasal decongestants help reduce swelling in the passageways of your nose, which relieves the feeling of pressure and improves the flow of air.

Decongestants come in pill form or nasal sprays.

Nasal decongestants constrict dilated blood vessels within the nose, reducing swelling which allows air to flow more freely, relieving symptoms of congestion.

Examples

Short-acting nasal decongestants

- ephedrine
- levmetamfetamine or L-desoxyephedrine
- Naphazoline
- Phenylephrine
- Propylhexedrine

Long-acting decongestants (8 to 12 hours)

- xylometazoline
- oxymetazoline

Side effects of nasal decongestants include:

- Burning
- Stinging
- Dryness
- Local irritation

CHAPTER-6

AUTACOIDS

CLASSIFICATION OF AUTACOIDS

Amine autacoids: Histamine, 5-Hydroxytryptamine (Serotonin)

Lipid derived autacoids: Prostaglandins, Leukotrienes, Platelet activating factor

Peptide autacoids: Plasma kinins (Bradykinin, Kallidin), Angiotensin

In addition, cytokines (interleukins, TNFα, GM-CSF, etc.) and several peptides like gastrin, somatostatin, vasoactive intestinal peptide and many others may be considered as autacoids.

HISTAMINE

It is a potent tissue amine widely distributed in plant and animal tissues and in the venoms of bees. In man, it is formed by decarboxylation of histidine and major portion is stored in mast cells and basophils.

Mechanisms of Action: It acts on 2 major types of receptors

- Stimulation of H1 receptors results in smooth muscle contraction, increased vascular permeability, and mucus production. These effects are blocked competitively by H1 antagonists.
- Activation of H2 receptors increases gastric acid production, and this effect is blocked by H2 blockers such as cimetidine.

Both types of receptors are involved in vascular dilatation and edema formation.

Pharmacological Actions:

- **Cardiovascular system:** Histamine produces dilatation of capillaries and venules accompanied by a fall in blood pressure. The

mechanism is direct relaxation of the smooth muscles of blood vessels. This effect cannot be adequately reversed by antihistaminic agents but by adrenaline. It also has positive inotropic and chronotropic actions on the heart, impairs AV conduction, and increases coronary blood flow.

- **Smooth Muscles**: Histamine directly stimulates the smooth muscles of various tissues including the bronchi and uterus. Histamine-induced bronchospasm is effectively antagonized by adrenaline.
- **Exocrine Glands**: It is a powerful stimulant of HCl secretion by the gastric mucosa.
- **CNS**: Histamine is formed locally in the brain and is believed to be a "waking amine", acting by "increasing the sensitivity of large cerebral areas to excitation inputs"
- **Miscellaneous** actions include induction of itching and pain.

Histamine has no valid therapeutic use currently. But it plays very important role in anaphylaxis and other forms of allergic reactions. Its release may be induced by various agents including certain venoms, drugs, trauma (thermal, chemical, radiation), and antigen-antibody reactions.

H1 RECEPTOR ANTAGONISTS

Classification of H1 receptor antagonists:

1. Potent and sedative: such as diphenhydramine and promethazine.

2. Potent but less sedative: such as cyclizine and chlorpheniramine
3. Less potent and less sedative: such as pheniramine
4. Non-sedative: such as terfenadine, loratadine, and cetrizine.

The newer generation agents are relatively free of central depressant effects.These agents may also possess anti-emetic effects.

Pharmacological Actions:

1. Antihistaminic Actions:-they block histamine effects at various sites.
2. Other Effects: are independent of the antihistaminic effects and vary widely according to the drug used.

Most of them produce CNS depression resulting in sedation, drowsiness, inability to concentrate, and disturbances of coordination. But very few agents such as phenindamine may produce stimulation.Anti-motion sickness effects are exhibited by promethazine, diphenhydramine, and dimenhydinate.Promethazine and mepyramine have significant local anesthetic effect. Majority possess atropine-like effects. Some have central antimuscarinic actions which is useful in the treatment of Parkinsonism.

Pharmacokinetics:

They are well-absorbed following oral and parenteral administration. And are mainly metabolized by the liver; degradation products are removed in the urine.

Therapeutic Uses:

1. Allergic Disorders:-Including urticaria, seasonal hay fever, atopic and contact dermatitis, mild blood transfusion reactions.

2. Other uses:

- Diphehydramine and promethazine are used as hypnotics.
- Diphenhydramine and orphenadrine are effective in the treatment of Parkinsonism.
- Dimehydrinate and promethazine are employed in the prevention and treatment of motion sickness, other vomiting disorders associated with labyrinthine dysfunction as well as nausea and vomiting associated with pregnancy.
- Diphenhydramine is frequently used in the treatment of cough as combination preparation with other agents.

Adverse Effects: Are usually mild. Most common is sedation. The most common anticholinergic adverse effect is dryness of the mouth. They may themselves occasionally cause allergic reactions.

SEROTONIN AND SEROTONIN AGONISTS

5-Hydroxytreptamine (Serotonin): It is widely distributed in plants and animals. Highest concentration in mammals is found in the pineal gland, acting as a precursor for melatonin. It is synthesized from the amino acid tryptophan and acts on several types of receptors.

Pharmacolocial Actions:

5-HT causes constriction of renal, splanchnic, meningeal, and pulmonary arteries and veins and venules, but dilatation of the blood

vessels of skeletal musles, coronaries, and skin capillaries. It has weak direct ino-chronotropic effect on the myocardium. It also stimulates smooth muscles, especially of the intestines. Serotonin is widely distributed in the CNS, serving as a neurotransmitter. Altered functions may be responsible for disturbances in sleep, mood, sexual behavior, motor activity, pain perception, migraine, temperature regulation, endocrine control, psychiatric disorders and extra-pyramidal activity.

SEROTONIN AGONISTS

Sumatriptan is a selective agonist of 5-HT1 receptors and is highly effective in treating acute attacks of migraine, but is not useful in the prevention. It relieves the nausea and vomiting, but the headache may recur, necessitating repeated administrations.

It is administered orally or by the subcutaneous route. The bioavailability of oral dose is only 14 %; thus, the oral dose is several times larger than the subcutaneous dose.

Adverse effects include flushing and heat at the injection site, neck pain, dizziness, and tingling of the hands. The drug is contraindicated with symptomatic ischemic heart diseases, angina, and hypertension as it may cause coronary vasoconstriction.

Buspirone, another serotonin agonist, is a useful effective anxiolytic agent.

SEROTONIN ANTAGONISTS

- **Methysergide** blocks the actions of 5-HT on a variety of smooth muscles. It also has a weak direct vasoconstrictor effect. It is an effective prophylactic agent for migrainous headaches. But has no effect in treating acute attacks, even may worsen the condition. Adverse reactions include gastrointestinal irritation, drowsiness, vertigo, and psychic disturbances.
- **Cyproheptadine** is a potent antagonist of 5-HT and to a smaller extent of histamine and acetylcholine. It stimulates appetite probably by acting directly on the hypothalamus. It can block the release of hydrocortisone, and the production of aldosterone. It is mainly used to relieve the itching associated with skin disorders such as allergic dermatitis. The common adverse reaction is drowsiness.
- **Ondansetron** is specific 5-HT3 receptor antagonist. Given orally or intravenously, it is useful in the management of nausea and vomiting associated with cytotoxic therapy. Adverse reactions include headache, constipation, and allergic reactions.
    - **Prochlorperazine and haloperidol** have anti-5-HT activity and are sometimes used for resistant acute attacks.

PROSTAGLANDINS

Prostaglandins were named so because of their presumed origin from the prostate gland. Human seminal fluid is the richest known source, but they are also present in various tissues. The prostaglandins are synthesized from polyunsaturated fatty acids at their sites of action. PG

E2 and PG F2 are the two main prostaglandins. They are released in the body by mechanical, chemical, and infectious insults.

They play an important role in the development of the inflammatory response in association with other mediators.

Pharmacological Actions:

- Smooth muscle: most stimulate myometrium and are known to be important in the initiation and maintenance of labor. Prostaglandin E has bronchodilator action.
- GIT: they increase intestinal motility. PG E inhibits gastric acid secretion and has cytoprotective action on the gastroduodenal mucosa. Both PG E and F produce contraction of the longitudinal muscle of the gut. They also stimulate intestinal fluid secretion, resulting in diarrhea.
- CVS: PGE is peripheral vasodilator and powerful natriuretic. PGF constricts arterioles and veins.
- Platelets: Thromobxane causes platelet aggregation and vasoconstriction. PG I (prostacycline) is found in the vascular endothelium and is a potent inhibitor of platelet aggregation and is a vasodilator.
- Miscellaneous: Prostaglandins are important in pain generation and perception. PGE and PGI produce hyperalgesia associated with inflammation. In addition, PG E is a potent pyrogenic substance.

Natural prostaglandins have no therapeutic application because of short duration of action, but their derivatives such as carboprost, dinoprostone and misoprostol find clinical application.

Therapeutic uses include cervical ripening and labor induction, control of postpartum hemorrhage, induction of abortion, and prophylaxis of NSAID-induced peptic ulcers. They are also finding several other uses more recently such as erectile dysfunction, glaucoma, etc.

Adverse Effects include fever, diarrhea, abdominal cramps, headache, nausea, and vomiting.

CHAPTER-7

HORMONE

HORMONES

Hormone is a substance of intense biological activity that is produced by specific cells in the body and is transported through circulation to act on its target cells. Hormones regulate body functions to bring about a programmed pattern of life events and maintain homeostasis in the face of markedly variable external/internal environment.

Functions:

a) **Availability of fuel:** Insulin, Glucagon, Growth hormone
b) **Metabolic rate:** Triiodothyronine, Thyroxine

c) Somatic growth: Growth hormone, Insulin-like growth factors

d) Sex and reproduction: Gonadotropins, Androgens, Estrogens, Progestins

e) Circulating volume: Aldosterone, Antidiuretic hormone

f) Adaptation to stress: Glucocorticoids, Adrenaline

g) Calcium balance: Parathormone, Calcitonin, Vitamin D

CLASSIFICATION OF HORMONES ACCORDING TO THEIR LOCATION

- **Pituitary**

Anterior Pituitary:

- Growth hormone
- Prolactin
- Adrenocorticotropic hormone
- Thyroid stimulating hormone
- Follicle stimulating hormone
- Luteinizing hormone.

Posterior Pituitary:

- Oxytocin
- Antidiuretic hormone (ADH, Vasopressin).

- **Thyroid:**
  - Thyroxine (T4),
  - Triiodothyronine (T3),
  - Calcitonin.
- **Parathyroid:** Parathormone (PTH).
- **Pancreas (Islets of Langerhans):**

- Insulin,
- Glucagon.

➢ **Adrenals**

Adrenal Cortex:

- Glucocorticoids (hydrocortisone),
- Mineralocorticoids (aldosterone),
- Sex steroids (dehydroepiandrosterone)

Adrenal Medulla:

- Adrenaline,
- Noradrenaline

➢ **Gonads:**

- Androgens (testosterone),
- Estrogens (estradiol),
- Progestins (progesterone)

SITES AND MODE OF ACTIONS OF HORMONES

The hormones act on their specific receptors present on or within their target cells. These receptors are present **on cell membrane, in the cytoplasm, or in the nucleus.**

a) On the cell membrane: A hormone binds to receptor in membrane → increases cAMP → Produces biological effects

b) In the cytoplasm: A steroidal hormone binds to receptor in cytoplasm → migrates to nucleus →bind to DNA→ produces response by synthesizing various proteins.

c) In the nucleus: Thyroid hormones bind to nuclear receptors→ produces response by synthesizing various proteins.

CORTICOSTEROIDS

The adrenal cortex secretes steroidal hormones which have glucocorticoid, mineralocorticoid and weakly androgenic activities.

Glucocorticoids:

a) **Short acting (8-12 hours):** Hydrocortisone, Cortisone
b) **Intermediate acting (12-36 hours):** Prednisolone, Prednisone, Methyl Prednisolone, Triamcinolone
c) **Long acting (36-72 hours):** Betamethasone, Dexamethasone
d) **Local acting:** Beclomethasone, Fluticasone, Budesonide

Mineralcorticoids: Aldosterone, Fludrocortisone, Desoxycorticosterone acetate

PHARMACOLOGICAL ACTIONS OF GLUCOCORTICOIDS

- **Carbohydrate metabolism:** hyperglycemia occurs, decrease sensitivity to insulin. So contraindicated in diabetes mellitus.
- **Protein metabolism:** Muscle wasting occurs, lympholysis, loss of bone matrix takes place. So contraindicated in osteoporosis.
- **Fat metabolism:** Prolonged use produces moon face, buffalo hump, fish mouth with thin limbs.
- **Calcium metabolism:** Anti-vit-D action, inhibit Ca^{2+} absorption from gut, ↓ blood Ca^{2+} level.

- **Water metabolism:** Sodium and water retention, edema and hypertension on prolonged use.
- **CVS:** Glucocorticoids restrict capillary permeability, maintain tone of arterioles and myocardial contractility. Applied topically, they cause cutaneous vasoconstriction.
- **Skeletal muscles** Optimum level of corticosteroids is needed for normal muscular activity. Weakness occurs in both hypo- and hypercorticism, but the causes are different.
- **CNS** Mild euphoria is quite common with pharmacological doses of glucocorticoids.
- **Stomach:** Secretion of gastric acid and pepsin is increased: may aggravate peptic ulcer.
- **Lymphoid tissue and blood cells:** Glucocorticoids enhance the rate of destruction of lymphoid cells
- **Inflammatory responses:** Inflammatory response is suppressed by glucocorticoids.
- **Immunological and allergic responses:** They suppress all types of hypersensitization and allergic reactions.

DIFFERENT USES OF GLUCOCORTICOIDS

A. Replacement therapy

Acute adrenal insufficiency

Chronic adrenal insufficiency (Addison's disease

Congenital adrenal hyperplasia (Adrenogenital syndrome)

B. Pharmacotherapy

Rheumatoid arthritis, Rheumatic fever, Gout, Systemic lupus erythematosus, polyarteritis nodosa, Dermatomyositis, nephrotic syndrome, glomerulonephritis, anaphylaxis, angioneurotic edema, urticarial, serum sickness, allergic conjunctivitis, rhinitis, Autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, active chronic hepatitis, Bronchial asthma, aspiration pneumonia, pulmonary edema from drowning, severe lepra reaction, bacterial meningitis, Pneumocystis carinii pneumonia, allergic conjunctivitis, iritis, iridocyclitis, keratitis, eczematous skin diseases, pemphigus vulgaris, exfoliative dermatitis, Stevens-Johnson syndrome, Ulcerative colitis, Crohn's disease, inflammatory bowel diseases, Cerebral edema, acute lymphatic leukaemia, Hodgkin's disease, Organ transplantation and skin allograft, Septic shock, Thyroid storm

DIFFERENT CONTRAINDICATIONS OF GLUCOCORTICOIDS

Peptic ulcer, Diabetes mellitus, Hypertension, Viral and fungal infections, Tuberculosis and other infections, Osteoporosis, Herpes simplex keratitis, Psychosis, Epilepsy, CHF, Renal failure, Glaucoma.

DIFFERENT TYPES OF DIABETES MELLITUS

Diabetes Mellitus: Hyperglycaemia is the end point for all types of DM. All forms of DM occur due to either a decrease in the circulating levels of insulin (insulin deficiency) or insulin resistance. The main 3 symptoms of DM are an excessive urine production (polyuria), an excessive thirst (polydipsia) & an excessive eating (polyphagia).

Type1 DM: It is called "Insulin Dependent Diabetes Mellitus" or "juvenile-onset diabetes". Commonly occurs before puberty or in youngsters below 20 years of age & persists throughout their life. IDDM is an autoimmune disease of the pancreatic beta – cells. Clinical features: hyperglycaemia with polyuria, polydipsia, polyphagia, & ketoacidosis. Diabetic ketoacidosis is the end result of insulin deficiency in uncontrolled type-1 diabetes.

Type2 DM: This is called "Non-Insulin Dependent Diabetes Mellitus". 90 – 95 % of diabetics have type 2 diabetes. Usually occurs in people who are over 40 & overweight. This type of diabetes develops due to peripheral resistance to insulin. Clinical features: same as type – 1 but it doesn't cause ketoacidosis. But they develop hyperoosmolar coma, a condition charaterised by severe hyperglycaemia, & dehydration (Management: give insulin quickly followed by IV fluids)

Type 3 DM: This is due to other causes of hyperglycaemia e.g., chronic pancreatitis or chronic drug therapy with glucocorticoids, thiazide diuretics, diazoxide, growth hormne, & with some protease inhibitors (e.g., saquinavir)

Type 4 DM: It also called "Gestatinal Diabetes Mellitus" (GDM). It is observed in 4-5% of all pregnancies. Elevated blood sugar levels are seen in 2nd& 3rd trimester of pregnancy due to insulin resistance by placental hormones.

ACTIONS OF INSULIN

Insulin is a proteinaceous hormone, consisting of 51 amino acid residues in the form of two linked peptide chains of 21 and 30 amino acids respectively.

- It is antagonistic to glucagon and it decreases the level of glucose in the blood.
- It acts by increasing the rate at which glucose is transported out of the blood and into cells and by stimulating muscle cells to take up sugar from the blood and convert it into glycogen.
- Insulin is primarily regulated by feedback from the blood glucose concentration.
- When the blood sugar level drops, the secretion of insulin is suppressed and when the blood sugar increases, the secretion of insulin in stimulated.
- It promotes protein synthesis in tissues from amino acids.
- Insulin reduces catabolism of proteins, thus functions as an anabolic hormone.
- It increases the synthesis of fats in the adipose tissue from fatty acids.

- Insulin reduces the breakdown and oxidation of fats.

Mechanism of action: Insulin binds to alpha subunits insulin receptor and then activates tyrosine kinase activity of beta subunits. After that phosphorylation takes place which promotes entry of glucose into cells.

DIFFERENT INSULIN PREPARATIONS

A. **Ultra-short acting insulins:** They are **Insulin lispro, Insulin aspart & Insulin glulisine**. These are human origin insulins and modified to have rapid absorption from subcutaneous tissue. Their action starts within 10- 20 min & lasts for 3-4 hrs. These are soluble insulins, dispensed as clear solutions at neutral pH & given i.v. also. These are mostly used in combination with one of the long acting insulins to provide immediate insulin following a meal & to maintain a baseline level of insulin between the two meals.
B. **Short acting insulins:** These are **Regular insulin, Prompt Insulin-Zn Suspension or Semilente.** Their effect starts within 30 min & lasts for 5 – 8 hrs. These are soluble crystalline Zn-Insulins made by recombinant DNA techniques which are identical to human insulin. **Regular Insulin** is designed to control post-meal hyperglycaemia & is also for Diabetic ketoacidosis & during the perioperative management of insulin-requiring diabetics. **Semilente** is also a fast acting preparation but it is cloudy, so can't be given by i.v route & should be mixed only with lente or ultralente insulin.
C. **Intermediate acting Insulins:** These are **NPH or Isophane insulin & Lente Insulin.** These have slower onset (1-3 hrs) but longer duration of action (16-20 hrs). NPH insulin is a cloudy complex in

which the insulin is conjugated with modifier protein- Protamine. **NPH** insulin has a **N**eutral pH, contains **P**rotamine. **Isophane insulin** is like NPH insulin. Lente Insulin is a mixture of 30% Semilente (short acting insulin – rapid onset of action) and 70% Ultralente (longer acting insulin- delayed onset & prolonged duration of action). Lente insulin doesn't contain Protamine. They are not given i.v and are used to control diabetes in a variety of situations except for diabetic ketoacidosis

D. **Longer acting insulins:** These are **Ultralente & Insulin Glargine.** Ultralente is a cloudy Zn-suspension at neutral pH in acetate buffer. It is usually combined with semilente preparation & given s.c. Insulin Glargine is a newer long acting insulin , it doesn't have Zn or Protamine. Insulin glargine must not be mixed with any other form of insulin for injection. It causes lesser hypoglycaemia at night.

USES OF INSULIN

- Patients with Type – 1 diabetes: NPH insulin is often combined with short acting Regular insulin & is administered s.c. before meals.
- Many patients with diabetes Type – 2 diabetes ultimately require insulin therapy
- For GDM not controlled by diet
- For emergency treatment of diabetic ketoacidosis (diabetic coma).

SIDE EFFECTS OF INSULIN

- **Hypoglycemia:** Brain damage may occur in turn. Prompt administration of glucose (sugar/candy by mouth, intravenous

glucose or intramuscular glucagon) is the emergency treatment of hypoglycemia.

- **Rebound hyperglycemia:** This can follow excessive insulin administration and results from the release of insulin-opposing hormones (glucagon, adrenaline, glucocorti-coids, growth and thyroid hormones).
- **Immunological complications:** Regular insulin administration can lead to the formation of antibodies against insulin or non-insulin protein contaminants. This in turn may cause insulin resistance or insulin allergy. Immunological complications primarily occur with bovine insulin and are uncommon with the currently avail-able highly-purifi ed human insulin.
- **Lipodystrophy/lipohypertrophy** at the site of injection.

ORAL HYPOGLYCEMIC AGENTS

A) Drugs acting by the release of insulin [insulin secretagogues]:

This group includes **sulfonylureas** and **meglitinides**. These drugs inhibit ATP sensitive K+channels and cause depolarization of b cells resulting in the release of insulin. These drugs are effective only if 30% or more of the b cells in the pancreas are available. Major limitation of these drugs is that like insulin, these can also cause hypoglycemia.

Mechanism of action:

Sulfonylureas and meglitinides inhibit ATP sensitive K+ channels

↓

K+ cannot go out resulting in more positive charge in β-cells

↓

Depolarization starts

↓

Leads to opening of Ca2+ channels and thus entry of Ca2+ in β-cells

↓

Release of insulin from granules

↓

Decrease in blood glucose

Sulfonylureas:

1st Generation: Tolbutamide, Chlorpropamide, Acetohexamide, Tolazamide

2nd Generation: Glibenclamide or Glyburide, Glipizide, Gliclazide, Glimepiride

- Tolbutamide is the shortest acting whereas chlorpropamide is the longest acting sulfonylurea.
- Second generation drugs are more potent than the first generation agents. Sulfonylureas can cause weight gain (less chance with glipizide and gliclazide).
- All these drugs can cause hypoglycemia (maximum with chlorpropamide and with glyburide).

- Chlorpropamide has additional actions as well. It can cause dilutional hyponatremia (ADH like action), cholestatic jaundice and disulfram like reaction (intolerance to alcohol).
- Gliclazide has additional antiplatelet action also.
- Glimepiride exerts beneficial effects with regard to ischemic preconditioning.

Meglitinides

- These drugs have similar mechanism to cause release of insulin.
- **Nateglinide and repaglinide**are the drugs in this group.
- These drugs are used for the treatment of post prandial hyperglycemia due to their rapid onset and short duration of action.
- These drugs can also result in hypoglycemic episodes.

B) Drugs Acting by Other Mechanisms: These drugs do not cause hypoglycemia because these are not increasing serum insulin concentration.

Biguanides:

- **Metformin** and **phenformin** are biguanides and are preferred agents for obese patients.
- These drugs decrease blood glucose by activating AMPK (Adenosine Mono Phosphate-activated protein Kinase) that helps in decreasing the production (inhibit gluconeogenesis and glycogenolysis) and increasing the utilization (stimulation of glycolysis and tissue uptake of glucose).
- These drugs also inhibit the intestinal absorption of glucose.

- Metformin is drug of choice for type 2 diabetes mellitus.
- Lactic acidosis (more with phenformin) and megaloblastic anemia (more with metformin) due to vitamin B12 defciency are the major adverse effects of these drugs.
- Other contra-indications include cardiac failure, and chronic hypoxic lung disease.
- Metformin is also useful for polycystic ovarian disease (PCOD). Metformin is the only oral agent that has been demonstrated to reduce macrovascular events in type 2 DM. It is first-line therapy for type 2 diabetes.

Thiazolidinediones:

- **Troglitazone, pioglitazone** and **rosiglitazone** are the drugs in this group that act as agonists of a nuclear receptor; peroxisome proliferator activated receptor gamma (PPARγ).
- It regulates the transcription of genes involved in glucose and lipid metabolism. Important genes that are up regulated by PPAR-γ are: Adiponectin, Fatty acid transport protein, Insulin receptor substrate, GLUT– 4.
- These drugs are used to reverse insulin resistance in type II DM. These drugs also tend to increase HDL.
- Troglitazone was withdrawn due to serious hepatotoxicity and monitoring of hepatic function is recommended for other glitazones also.
- Glitazones have been reported to cause weight gain, edema and plasma volume expansion. Therefore, these should be avoided in

CHF patients. Rosiglitazone increases the risk of angina and MI. So, pioglitazone is preferred agent from this group.

- Rosiglitazone increases total and LDL cholesterol as well as HDL-cholesterol whereas pioglitazone increases HDL-cholesterol without affecting total and LDL-cholesterol.
- Pioglitazone is associated with increased risk of bladder cancer on long term use. Both of these can result in: Weight gain, Edema, Increase in fracture risk in women, Anemia.

α-Glucosidase inhibitors:

- Complex carbohydrates (polysaccharides and sucrose) are absorbed after conversion to simple carbohydrates by α glucosidase. Inhibitors of this enzyme (**acarbose, voglibose and miglitol)** decrease carbohydrate absorption from the GIT.
- Major adverse effect of these drugs is flatulence due to fermentation of unabsorbed carbohydrates.
- Acarbose can decrease blood glucose in both type 1 as well as type 2 diabetes.
- However, apart from insulin, the only drug approved for treatment of both type 1 as well as type 2 diabetes is pramlintide.

GONADAL HORMONES

Estrogen, progesterone and testosterone are principal gonadal hormones. Estrogen and progesterone are produced by ovaries whereas testosterone is mainly formed by testes.

Estrogens: Natural estrogens include estradiol (principal and most potent estrogen), estrone and estriol (weakest). Major site of estrogen production in premenopausal female is ovary whereas in post menopausal female, estrogen is produced mainly by peripheral organs like liver, kidney, brain and adipose tissue. Ethinyl estradiol, mestranol (both steroidal), diethylstilbesterol and genistein (non-steroidal) also possess estrogenic activity. Estrogen stimulates synthesis of progesterone receptors whereas progesterone inhibits the synthesis of estrogen receptors.

Actions of estrogens:

- Growth and development of female reproductive system.
- Increased risk of breast, endometrial and cervical carcinoma.
- Feedback inhibition of gonadotropin (LH/FSH) secretion.
- Stimulation of CTZ to cause nausea and vomiting.
- Increased predisposition to deep vein thrombosis and pulmonary embolism.
- Glucose intolerance and sodium and water retention.
- Maintain bone mass by decreasing the bone resorption.
- Increased risk of gall bladder stones and cholestatic jaundice.
- Can result in hepatic adenoma on prolonged use.
- Vasodilation by increasing the production of NO.

Progestins: Progesterone is the most important progestin in humans. It is primarily secreted by corpus luteum. Synthetic progestins may be classifed as:

- **1st generation:** Norethindrone, Norethinodrel, Lynestrenol
- **2nd generation:** Norgestrel, Levonorgestrel
- **3rd generation:** Desogestrel, Norgestimate, Gestodene
- **4th generation:** Nomegestrol, Drospirenone

Actions of Progesterone:

- Progesterone increases basal insulin levels and the insulin response to glucose.
- These can act as competitors of aldosterone causing decrease in Na+ reabsorption.
- Progesterone increases LDL and opposes benefcial effect of estrogen on lipid profle.
- It has depressant effect on the brain.
- It causes growth of breast tissue and also participates in LH surge.
- Progestins decrease the chances of endometrial carcinoma and are added to HRT to decrease this adverse effect of estrogens.
- Third generation agents are also known as impeded androgens because they lack androgenic activity.

USES OF ESTROGEN AND PROGESTRERONE

Major use of estrogen is for hormone replacement therapy (HRT) in post menopausal females. Progesterone is added to HRT to decrease the risk of endometrial carcinoma. Estrogens can reverse all the features of its defciency. Another important use of estrogens is as a component of oral contraceptives. These can be used in the treatment of dysfunctional uterine bleeding (DUB), if it is due to estrogen withdrawal. Estrogens

reduce testosterone production due to feed back inhibition of LH secretion. This property has been utilized for the treatment of testosterone dependent tumors like prostatic carcinoma. But now a days, GnRH agonists and antagonists are preferred for this indication.

Major indications of progesterone are for oral contraception and hormone replacement therapy, for which these are combined with estrogens. Progestins are added to decrease the risk of endometrial and ovarian carcinoma. Progestins are also used for secondary amenorrhea, abnormal uterine bleeding, and premature labour and luteal phase support to treat infertility.

ORAL CONTRACEPTIVES

These contain both estrogen and progestin. Most commonly used estrogen in combined OCPs is ethinyl estradiol.

Most commonly used progesterone in combined OCPs is **levonorgestrel (LNG)**

Combined OCPs:

- **Monophasic:** Content of estrogen and progesterone remain same in all the pills (for 21 days).
- **Biphasic:** Content of progesterone is different in pills for first 10 days and that for 11-21 days
- **Triphasic:** Content of progesterone is gradually increased. It is lowest in first phase (1-6 days), moderate in second phase (7-11 days) and further increased in third phase (12-21 days).

- **Biphasic and triphasic pills** permit reduction in progesterone content without compromising efficacy. These pills decrease the risk of breakthrough bleeding.

Mechanism of action: Main mechanism of combined OCPs is to cause feedback inhibition of pituitary (causing abolition of LH surge) resulting in inhibition of ovulation. Other mechanisms include thickening of cervical mucus, decreased motility and secretions of the fallopian tubes and making endometrium unfavourable for implantation.

Combined OCPs are started on first day of menstrual cycle and given for 21 days. To allow withdrawal bleeding, iron tablets are given (without hormones) for next seven days.

Ovulation returns within 3 months of stopping OCP use in 90% of cases.

Progesterone Only Pills (Minipills): These contain low dose of progestin without any estrogen. These are less effective than combined OCPs. Minipills are preferred in women where estrogen is contra-indicated.Minipills are oral contraceptives of choice for Lactating women, Sickle cell anemia, Seizure disorder Progesterone only pills are given daily without any break. Thickening of cervical mucus is major mechanism of minipills.

Adverse Effects of OCPs:

- Nausea, mastalgia, breakthrough bleeding and edema are related to the amount of estrogen in the preparation.

- Migraine is made worse with the use of OCPs.
- Failure of withdrawal bleeding is another important adverse effect.
- Breakthrough bleeding is the most common problem with the use of progesteroneonly pills. Chances of this bleeding decrease with biphasic and triphasic pills.
- Weight gain can occur with the use of progestins containing androgenic properties. Desogestrel and norgestimate cause less weight gain.
- Acne and hirsutism may worsen by progestins containing androgenic properties.
- Risk of venous thromboembolism, MI and stroke is increased with the use of OCPs because estrogen increases the clotting factors (VII, VIII, IX and X) and decreases anticlotting factors (antithrombin III).
- Cholestatic jaundice, gall bladder disease and incidence of hepatic adenomas are increased with OCP use.
- Chances of breast and cervical carcinoma are increased whereas endometrial and ovarian carcinomas are decreased by OCP use. Progesterone is responsible for decreasing the risk of these cancers.

TESTOSTERONE

Most important androgens are testosterone and dihydrotestosterone (DHT). Less potent androgens include androstenidione and dehydroepiandrostenidione (DHEA). Testosterone is converted to DHT by 5-α reductase and to estradiol by aromatase.

Actions of testosterone:

- F – Fedback inhibition of LH
- I – Internal genitilia development
- S – Spermatogenesis
- H – Hematopoiesis

Actions of DHT:

- Development and maturatin of external genitalia (scrotum, penis, urethra etc.) in male.
- Male behaviour and changes of puberty.
- Growth and hypertrophy of prostate in the elderly.
- Growth of hair follicles (pubic, axillary and beard) during puberty.
- Loss of scalp hair in adults
- Activation of sebaceous glands.

Uses

- Long acting derivatives like testosterone enanthate (i.m.) are indicated for hypogonadal men to compensate for the decreased endogenous secretion.
- Long term oral therapy is associated with liver adenomas and carcinomas. It can also be administered by transdermal route. Polycythemia and hypertension (due to erythropoietic action) may be a problem.
- These can also be used to reduce breast engorgement during postpartum period.

- Sometimes, these are used for chemotherapy of breast tumors in premenopausal females.
- These are frequently abused by athletes due to their anabolic properties.
- These agents have been used to stimulate growth in boys with delayed puberty.
- Androgens have been used in the treatment of osteoporosis.

Adverse Effects

- Masculinising actions (hirsutism, amenorrhoea, clitoral enlargement and deepening of voice) in females.
- Increased risk of atherosclerosis due to decrease in HDL and increase in LDL cholesterol.
- Use of androgens during pregnancy may result in masculinization of the female fetus and under-masculinization of the male fetus.
- Sodium retention and edema can occur rarely, so caution is advised in patients with heart and kidney disease.
- 17-alkyl substituted compounds (methyltestosterone and fluoxymestrane) are more likely to cause cholestatic jaundice and peliosis hepatica.
- Increased chances of acne, erythrocytosis, gynaecomastia and azoospermia.
- Androgens are contraindicated in pregnant females, infants, carcinoma of the male breast and prostate and patients with cardiac and renal diseases.

ANTIANDROGENS

Drugs in this group can act by inhibiting the synthesis, activation or action of androgens.

- **Steroid synthesis inhibitors:** Ketoconazole inhibits the synthesis of adrenal and gonadal hormones but its usefulness in the treatment of prostatic carcinoma is limited by serious toxicity on prolonged use. It can cause gynaecomastia due to increase in estradiol: testosterone ratio. Abiraterone is an orally active prodrug that acts by inhibiting 17-α-hydroxylase and 17, 20-lyase. It reduces the synthesis of cortisol and androgens, and is approved for castration resistant refractory prostate cancer.
- **5-α reductase inhibitors:** Most of the actions of testosterone are mediated by its conversion to DHT by 5-α reductase. Important amongst these are growth of prostate, male pattern baldness and hirsutism in females. Finasteride and dutasteride are 5-α reductase inhibitors useful in the treatment of BHP, male pattern baldness and hirsutism by reducing the production of DHT.
- **Androgen receptor inhibitors:** Cyproterone and cyproterone acetate act as antagonists of androgen receptors. Latter compound has marked progestational activity that inhibits feedback enhancement of LH and FSH. These drugs are useful in the treatment of hirsutism and as a component of contraceptive pills. Flutamide, bicalutamide, enzalutamide and nilutamide are other anti-androgens that act by same mechanism. These are useful for the treatment of prostatic carcinoma. Flutamide can cause

gynaecomastia and reversible liver damage. These drugs can also be combined with GnRH agonists (like leuprolide) to reduce the initial flare up reaction.

- **Spironolactone:** It is an aldosterone antagonist that also competes with DHT for its receptor. It can be used for the treatment of hirsutism.

THYROID HORMONES

Thyroid gland contains follicular cells and parafollicular (C) cells. Follicular cells secrete thyroid hormones (T3 and T4) whereas the parafollicular cell is responsible for the secretion of calcitonin.

Actions:

- Thyroid hormones are required for the normal growth and development. The most remarkable action is metamorphosis of tadpole to frog: the tail is used-up to build lungs, limbs and other organs.
- Congenital deficiency of T4 and T3 resulting in cretinism emphasizes their importance. Deficiency of thyroid hormones leads to cretinism in children and myxedema in adults.
- These are catabolic hormones and increase the breakdown of fats (to FFA), carbohydrates (cause hyperglycemia) and proteins (cause weight loss). These are calorigenic and increase basal metabolic rate (BMR).
- Thyroid hormones stimulate the heart (increase rate, contractility and cardiac output). In hyperthyroidism, atrial fibrillation can occur.

- T3, T4 have profoundfunctional effect on CNS. Mental retardation isthe hallmark of cretinism; sluggishness and otherbehavioral features are seen in myxoedema.Hyperthyroid individuals are anxious, nervous,excitable, exhibit tremors and hyperreflexia.
- Propulsive activity of gut is increasedby T3/T4. Hypothyroid patients are often constipated, while diarrhoea is common in hyperthyroidism.
- Hypothyroid patients suffer from some degree of anaemia which is restored only by T4 treatment. Thus, T4 appears tobe facilitatory to erythropoiesis.
- Thyroid has an indirecteffect on reproduction. Fertility is impaired inhypothyroidism and women suffer from oligomenorrhoea. Normal thyroid function is requiredfor maintenance of pregnancy and lactation.

Mechanism of action: Both T3 and T4 penetrate cells by active transport and produce majority of their actions by combining with a nuclear thyroid hormone receptor (TR) which belongs to the steroid and retinoidsuperfamily of intracellular receptors.

Uses: Main uses of thyroid hormones are hypothyroidism (cretinism, myxedema and myxedema coma).

- **Cretinism**: It is due to failure of thyroid development or a defect in hormone synthesis (sporadic cretinism) or due to extreme iodine deficiency (endemic cretinism). Treatment with thyroxine (8–12 μg/kg) daily should be started as early as possible, because mental retardation that has already ensued is only partially reversible.

- **Adult hypothyroidism (Myxoedema**): This is one of the commonest endocrine disorders which develop as a consequence of autoimmune thyroiditis or thyroidectomy; it may accompany simple goiter if iodine deficiency is severe.Antibodies against thyroid peroxidase orthyroglobulin are responsible for majority of casesof adult hypothyroidism. Important drugs that cancause hypothyroidism are 131I, iodides, lithium andamiodarone. Treatment with T4 is most gratifying.It is often wise to start with a low dose—50 μgof l-thyroxine daily and increase every 2–3 weeksto an optimum of 100–200 μg/day (adjusted byclinical response and serum TSH levels). Furtherdose adjustments are made at 4–6 week intervalsneeded for reaching steady-state. Individualization of proper dose is critical, aiming atnormalization of serum TSH levels. Increase indose is mostly needed during pregnancy.
- **Myxoedema coma**: It is an emergency; characterized by progressive mental deterioration due to acute hypothyroidism: carries significant mortality. Rapid thyroid replacement is crucial. Though liothyronine (T3) acts faster, its use is attended by higher risk of cardiac arrhythmias, angina, etc. Drug of choice is l-thyroxine (T4) 200–500 microgram i.v. followed by 100 microgram i.v. OD till oral therapy can be instituted. Some authorities recommend adding low dose i.v. T3 10 microgram 8 hourly in younger patients with no arrhythmia or ischaemia. Alternatively oral T4 500 microgram loading dose followed by 100–300 microgram daily may be used, but in severe hypothyroidism, oral absorption is delayed and inconsistent.

- **Nontoxic goiter:**It may be endemic or sporadic. Endemic is due to iodine deficiency which may be accentuated by factors present in water (excess calcium), food or milk (goitrin, thiocyanates). A defect in hormone synthesis may be responsible for sporadic cases. In both types, deficient production of thyroid hormone leads to excess TSH→thyroid enlarges, more efficient trapping of iodide occurs and probably greater proportion of T3 is synthesized --> enough hormone to meet peripheral demands is produced so that the patient is clinically euthyroid. Thus, treatment with T4 is in fact replacement therapy in this condition as well, despite no overt hypothyroidism. Full maintenance doses must be given.

THYROID INHIBITORS

Antithyroid drugs (also called thionamides) are most often used to treat an overactive thyroid (hyperthyroidism) caused by Graves' disease. These drugs block the formation of thyroid hormone by the thyroid gland.

Classification

- Drugs that Inhibit Thyroid Hormone Synthesis (Thioamides): Methimazole, Carbimazole
- Drugs that Inhibit Iodide Trapping (Ionic inhibitors): Thiocyanate, Perchlorates
- Drugs that Inhibit Hormone Release: Iodides, Lithium
- Drugs that Destroy Thyroid Tissue: Radioactive Iodines

- Drugs that Inhibit Peripheral Conversion of T4 to T3: Amiodarone, β-blockers, Corticosteroids

FUNCTIONS OF ANTITHYROID DRUGS

Antithyroid drugs decrease the levels of the two hormones produced by the thyroid, thyroxine (T4) and triiodothyronine (T3).

USES:

- As a short-term treatment in people with Graves' hyperthyroidism, to prepare for thyroid surgery or radioiodine.
- To treat hyperthyroidism associated with toxic multinodular goiter or a toxic adenoma.
- To treat women with hyperthyroidism during pregnancy.
- For long-term treatment of hyperthyroidism due to Graves' disease or toxic multinodular goiter or toxic adenoma when patients prefer to avoid definitive therapy with radioiodine or surgery.

UTERINE STIMULANTS (OXYTOCICS, ABORTIFACIENTS)

These drugs increase uterine motility, especially at term.

1. Posterior pituitary hormone: Oxytocin, Desamino Oxytocin

2. Ergot alkaloids: Ergometrine (Ergonovine), Methylergometrine

3. Prostaglandins: PGE2, PGF2α, 15-methyl PGF2α, Misoprostol

4. Miscellaneous Ethacridine, Quinine.

OXYTOCIN

Oxytocin is a nonapeptide secreted by the posterior pituitary along with vasopressin (ADH). Both are released by stimuli appropriate for oxytocin, i.e. coitus, parturition, suckling; or for ADH, i.e. hypertonic saline infusion, water deprivation, haemorrhage, etc., or nonspecific, i.e. pain and apprehension.

Actions:

1. Uterus: Oxytocin increases the force and frequency of uterine contractions. With low doses, full relaxation occurs in between contractions; basal tone increases only with high doses. Increased contractility is due to hightened electrical activity of the myometrial cell membrane. Estrogens sensitize the uterus to oxytocin; increase oxytocin receptors.

Mechanism of action: Action of oxytocin on myometrium is independent of innervation. There are specific G-protein coupled oxytocin receptors which mediate the response mainly by depolarization of muscle fibres and influx of Ca2+ ions as well as through phosphoinositide hydrolysis and IP3 mediated intracellular release of Ca2+ ions. The number of oxytocin receptors increases during later part of pregnancy. Oxytocin increases PG synthesis and release by the endometrium which may contribute to the contractile response.

2. Breast: Oxytocin contracts the myoepithelium of mammary alveoli and forces milk into the bigger milk sinusoids—'milk ejection reflex' (milk letdown in cattle) is initiated by suckling so that it may be easily sucked by the infant. Oxytocin has been used in milch cattle to facilitate milking.

3. CVS: Conventional doses used in obstetrics have no effect on BP, but higher doses cause vasodilatation → brief fall in BP, reflex tachycardia and flushing.

4. Kidney Oxytocin in high doses exerts ADH-like action—urine output is decreased: pulmonary edema can occur if large amounts of i.v. fluids and oxytocin are infused together. Conventional doses are without any effect.

Physiological role:

1. Labour: Oxytocin is released during labour and the uterus is highly sensitive to it at this time. PGs and PAF are complementary to oxytocin.

2. Milk ejection reflex: Suckling induces oxytocin release from pituitary which contracts the myoepithelial cells. These cells in breast are more sensitive than myometrium to oxytocin.

3. Neurotransmission: Oxytocin appears to function as a peptide neurotransmitter of oxytocinergic neurones in the hypothalamus and brainstem to regulate autonomic outflow.

Unitage and preparations 1 IU of oxytocin = 2 μg of pure hormone. Commercially available oxytocin is produced synthetically. OXYTOCIN, SYNTOCINON 2 IU/2 ml and 5 IU/ml inj., PITOCIN 5 IU/0.5 ml inj.

Uses

1. Induction of labour: Labour needs to be induced in case of postmaturity or prematurely in toxaemia of pregnancy, diabetic mother, erythroblastosis, ruptured membranes or placental insufficiency. For

this purpose oxytocin is given by slow i.v. infusion: 5 IU is diluted in 500 ml of glucose or saline solution (10 milli IU/ml) — infusion is started at a low rate and progressively accelerated according to response (0.2–2.0 ml/ min). Usually a total of 2–4 IU is needed.

2. Uterine inertia: When uterine contractions are feeble and labour is not progressing satisfactorily—oxytocin can be infused i.v. to augment contractions. It should not be used to hasten normally progressing labour. Too strong contraction can be catestrophic: use should only be made in selected cases and by experienced people. Oxytocin is the drug of choice and is preferred over ergometrine/PGs for the above two purposes:

(a) Because of its short t½ and slow i.v. infusion, intensity of action can be controlled and action can be quickly terminated.

(b) Low concentrations allow normal relaxation in between contractions—foetal oxygenation does not suffer.

(c) Lower segment is not contracted: foetal descent is not compromised.

(d) Uterine contractions are consistently augmented.

3. **Postpartum haemorrhage, Caesarean section:**Oxytocin 5 IU may be injected i.m. or by i.v. infusion for an immediate response, especially in hypertensive women in whom ergometrine is contraindicated. It acts by forcefully contracting the uterine muscle which compresses the blood vessels passing through its mesh work to arrest haemorrhage from the inner surface exposed by placental separation.

4. **Breast engorgement**It may occur due to inefficient milk ejection reflex. Oxytocin is effective only in such cases; an intranasal spray may

be given few minutes before suckling. It does not increase milk production.

5. Oxytocin challenge test: It is performed to determine uteroplacental adequacy in high risk pregnancies. Oxytocin is infused i.v. at very low concentrations till uterine contractions are elicited every 3–4 mins. A marked increase in foetal heart rate indicates uteroplacental inadequacy.

Adverse effects

(i) Injudicious use of oxytocin during labour can produce too strong uterine contractions forcing the presenting part through incompletely dilated birth canal, causing maternal and foetal soft tissue injury, rupture of uterus, foetal asphyxia and death.

(ii) Water intoxication: This occurs due to ADH like action of large doses given along with i.v. fluids, especially in toxaemia of pregnancy and renal insufficiency. It is a serious (may be fatal) complication.

Desamino-Oxytocin: It has been developed as a buccal formulation; action is similar to injected oxytocin, but less consistent. Its indications are:

Induction of labour: 50 IU buccal tablet repeated every 30 min, max 10 tabs.

Uterine inertia: 25 IU every 30 min. Promotion of uterine involution 25–50 IU 5 times daily for 7 days.

Breast engorgement: 25–50 IU just before breast feeding.

Carbetocin: It is a long-acting analogue of oxytocin that has been introduced recently for prevention of uterine atony after caesarean section and to control PPH.

Ergometrine, Methylergometrine

Only the amine ergot alkaloid ergometrine (ergonovine) and its derivative methylergometrine are used in obstetrics. Both have similar pharmacological property.

1. **Uterus**: They increase force, frequency and duration of uterine contractions. At low doses, contractions are phasic with normal relaxation in between, but only moderate increase in dose raises the basal tone, contracture occurs with high doses.
2. **CVS**Ergometrine and methylergometrine are much weaker vasoconstrictors than ergotamine and have low propensity to cause endothelial damage.
3. **CNS**No overt effects occur at usual doses.
4. **GIT**High doses can increase peristalsis. Methylergometrine is 1½ times more potent than ergometrine on the uterus, but other actions are less marked. It has thus replaced ergometrine at many obstetric units.

Adverse effects Ergometrine and methylergometrine are less toxic than ergotamine. When correctly used in obstetrics—hardly any complications arise. Nausea, vomiting and rise in BP occur occasionally. They can decrease milk secretion if higher doses are used

for many days postpartum; this is due to inhibition of prolactin release (dopaminergic action).

- **Use**

  1. The primary indication for ergometrine/ methylergometrine is to control and prevent postpartum haemorrhage (PPH): 0.2–0.3 mg i.m. at delivery of anterior shoulder reduces blood loss attending delivery and prevents PPH.

- After caesarean section/instrumental delivery —to prevent uterine atony.

  3. To ensure normal involution: A firm and active uterus involutes rapidly. To ensure this: 0.125 mg of ergometrine or methylergometrine has been given TDS orally for 7 days.

- Diagnosis of variant angina: A small dose of ergometrine injected i.v. during coronary angiography causes prompt constriction of reactive segments of coronary artery that are responsible for variant angina.

Prostaglandins

PGE2, PGF2α and 15-methyl PGF2α are potent uterine stimulants, especially in the later part of pregnancy and cause ripening of cervix. Since misoprostol (a PG analogue used for peptic ulcer) produces less side effects, it is being used for obstetric indications as well.

Ethacridine Available as 50 mg/50 ml solution for extra-amniotic infusion: 150 ml (containing 150 mg) is injected slowly for medical

termination of pregnancy in the 2nd trimester. This is an alternative method used occasionally.

UTERINE RELAXANTS (TOCOLYTICS)

These are drugs which decrease uterine motility. They have been used to delay or postpone labour, arrest threatened abortion and in dysmenorrhoea. Prevention of premature labour in those at higher risk due to past history has been attempted by administration of high dose progesterone in the later half of pregnancy, with some success. Suppression of premature labour may be needed to allow the foetus to mature, to allow time for initiating glucocorticoid therapy for foetal lung maturation or to transfer the mother in labour to a centre with proper facilities.

1. Adrenergic agonists

Ritodrine, the β2 selective agonist having more prominent uterine relaxant action is approved to suppress premature labour and to delay delivery in case of some exigency or acute foetal distress. For dependable action it is started as 50 μg/min i.v. infusion, the rate is increased every 10 min till uterine contractions cease or maternal HR rises to 120/min. Contractions are kept suppressed by continuing i.v. infusion or by 10 mg i.m. 4–6 hourly followed by 10 mg oral 4–6 hourly. However, treatment beyond 48 hours is not recommended, since risk to mother increases and benefit is uncertain. Use of ritodrine to arrest labour has been found to increase maternal morbidity. Foetal pulmonary edema can develop; volume of i.v. infusion should be kept to a minimum to avoid fluid overload. The neonate may develop

hypoglycaemia and ileus. It should not be used if mother is diabetic, having heart disease, or receiving β blockers or steroids.

2. Calcium channel blockers: Because influx of Ca2+ ions plays an important role in uterine contractions, Ca2+ channel blockers to reduce the tone of myometrium and oppose contractions. These drugs, especially nifedipine, which has prominent smooth muscle relaxant action, can postpone labour if used early enough. Oral nifedipine 10 mg repeated once or twice after 20–30 min, followed by 10 mg 6 hourly has been used. Tachycardia and hypotension are prominent at doses which suppress uterine contractions.

3. Oxytocin antagonist Atosiban is a peptide analogue of oxytocin that acts as antagonist at the oxytocin receptors.

4. Magnesium sulfate: Infused i.v. it is a first line drug for prevention and treatment of seizures in preeclampsia and eclampsia. It also acts as a tocolytic by competing with Ca2+ ions for entry into myometrium through both voltage sensitive as well as ligand gated Ca2+ channels.

5. Miscellaneous drugs: Ethyl alcohol, nitrates, progesterone, general anaesthetics and indomethacin (PG synthesis inhibitors) are the other drugs, which can depress uterine contractions.

CHAPTER-8

DRUGS ACTING ON DIGESTIVE SYSTEM

PHARMACOLOGY OF DRUGS USED FOR ACID PEPTIC DISEASE

Acid-peptic disease includes peptic ulcer (gastric and duodenal), gastroesophageal reflux and Zollinger – Ellison syndrome. Peptic – ulcer disease is thought to result from an imbalance between cell – destructive effects of hydrochloric acid and pepsin and cell-protective effects of mucus and bicarbonate on the other side. Pepsin is a proteolyic enzyme activated in gastric acid, also can digest the stomach wall. A bacterium, Helicobacter pylori is now accepted to be involved in the pathogenesis of ulcer.

In gastroesophageal reflux, acidic stomach contents enter into the esophagus causing a burning sensation in the region of the heart; hence the common name heartburn, or other names such as indigestion, dyspepsia, pyrosis, etc.

Zollinger-Ellison syndrome is caused a tumor of gastrin secreting cells of pancreas characterized by excessive secretion of gastrin that stimulates gastric acid secretion.

The disorders can be treated by drugs, which are able to:

- Neutralize gastric acid (HCl) e.g. magnesium hydroxide

- Reduce gastric acid secretione.g. cimetidine
- Enhance mucosal defences e.g sucralfate
- Exert antimicrobial action against H.pylori e.g. clarithromycin

The effective therapeutic approach of ucler is based on: “no acid, no ulcer”

Anti – ulcer drugs: drugs used in the prevention and treatment of peptic ulcer disease act mainly to decrease cell-destructive effects, increase cell – protective effects or both.

A: Gastric acid neutralizers (antacids)

Antacids are alkaline substances (weak bases) that neutralize gastric acid (hydrochloric acid). They react with hydrochloric acid in the stomach to produce neutral or less acidic or poorly absorbed salts and raise the PH of stomach secretion, and above PH of 4, pepsin is inactive. Antacids are divided into systemic and nonsystemic

- Systemic, e.g. sodium bicarbonate are absorbed into body fluids and may alter acid – base balance. It can be used in the treatment of metabolic acidosis.
- Non systemic, do not alter acid – base balance significantly. They are used as gastric antacids; and include aluminium, magnesium and calcium compounds e.g. (Al(OH)3, MgS2O3 , Mg(OH)2, CaCO3)

Gastric antacids differ in their potency, in onset of action, duration of action and adverse effects produced.

- Magnesium compounds have a relatively high neutralizing capacity, rapid onset of action, cause diarrhoea and hypermagnesemia.

- Aluminium compounds generally have a low neutralizing capacity, slow onset of action but long duration of action and may cause constipation.

Calcium compounds are effective and have a rapid onset of action but may cause hypersecretion of acid (acid - rebound) and milk-alkali syndrome (hence rarely used in peptic ulcer disease). All gastric antacids act chemically although some like magnesium trisiolicate can also act physically.

The most commonly used antacids, are mixtures of aluminium hydroxide and magnesium hydroxide.

Antacids act primarily in the stomach and are used to prevent and treat peptic ulcer. They are also used in the treatment of Reflux esophagitis and Gastritis

B. Gastric acid secretion inhibitors (antisecretory drugs):

HCl is secreted by parietal cells of the gastric mucosa which contain receptors for acetylcholine, histamine and gastrin that stimulate the secretion. Antagonists of acetylcholine, histamine and gastrin inhibit acid secretion.

Antisecretory drugs include:

• **H2-RECEPTORS BLOCKING AGENTS** such as cimetidine, ranitidine, famotidine, nizatidine.

Cimetidine is the proto type of the group.

Cimetidine dosage: PO 400mg 2 times/day, with meals and at bed time, or 800mg once daily at bed time for 6-8 weeks. Prophylaxis of recurrent ulcer, PO 400mg at bed time. High doses are used in the treatment of Zollinger-Ellison syndrome.

Common adverse effects: muscular pain, headache, dizziness, anti-androgenic effects at high doses such as impotence, gynecomastia, menstrual irregularities.

Drug interactions may occur when it is co-adminstered with warfarin, theophylline, phenytoin, etc. and and the effects of the latter drugs is enhanced because of inhibition of the metabolism of them.

PROTON PUMP INHIBITORS such as, omeprazole, lansoprazole, etc. inhibit H+ -K+-ATPase (proton pump) which is the common terminal step in the three secretagogues to release hydrogen ion into the gastric lumen.

Omeprazole dosage: - gastritis, gastroesophageal reflux disease, PO 20mg/day for 4-8 weeks; zollinger-Ellison syndrome, PO 60mg once

daily initially -120mg/day. Peptic ulcer disease, PO 10-60mg/day. Adverse effects include headache, diarrhea and nausea.

ANTICHOLINERGIC AGENTS such as pirenzepine, dicyclomine. Major clinical indication is prevention & treatment of peptic ulcer disease, Zollinger Ellison syndrome, reflux esophagitis.

Anticholinegic drugs are not used alone in the treatment of peptic ulcer. However, they are combined with H2-antagonists to further decrease acid secretion, with antacids to delay gastric empting and thereby prolong acid – neutralizing effects, or with any anti-ulcer drug for antispasmodic effect in abdominal pain.

C. Cytoprotective (mucosal protective) agents.

Locally active agents help to heal gastric and duodenal ulcers by forming a protective barrier between the ulcers and gastric acid, pepsin, and bile salts.

• They do not alter the secretion of gastric acid. These drugs include sucralfate and colloid bismuth compounds. (e.g. tripotassium, dicitratobismuthate)

• Colloidal bismuth compounds additionally exert bactericidal action against H.pylori. Other drugs that can to eradicate H.pylori such as amoxicillin, metronidazole, clarithromycin and tetracycline are included in the anti-ulcer treatment regimens.

• Protaglandins have both antisecretory and mucosal protective effects. Example: Misoprostol- used for prevention of NSAID – induced ulcer.

CHAPTER-9

PHARMACOLOGY OF LAXATIVES AND CATHARTICS (PURGATIVES)

Laxatives and cathartics (purgatives)

Laxatives and **cathartics** are drugs used orally to evacuate the bowels or to promote bowel elimination (defecation).

The term **laxative** means **mild effects**, and eliminative of soft formed stool.

The term **cathartic** means **strong effects** and **elimination of liquid** or **semi liquid** stool.

Both terms are used interchangeably because it is the **dose** that determines the effects rather than a particular drug.

Example:- castor oil laxative effect= 4ml

Cathartic effect = 15-60ml

Laxative and cathartics are arbitrarily classified depending on mode of action as:

• **Bulk forming laxatives:** are substances that are largely unabsorbed from the intestine. They include hydrophilic colloids such as psyllium, bran, methylcellulose, etc. When water is added, the substances swell and become gel-like which increases the bulk of the fecal mass that stimulates peristalsis and defecation.

Osmotic laxatives such as magnesium sulfate, magnesium hydroxide, sodium phosphate, etc. also belong to bulk – forming laxatives. These

substances are not efficiently absorbed, thus creating a stronger than usual solution in the colon which causes water to be retained. The increase in pressure and volume causes stimulation of peristalsis.

• **Stimulant (irritant) laxatives (cathartics):** are substances that are themselves irritant or contain an irritant substance to produce purgation. Individual drugs are castor oil, bisacodyl, phenolphthalein, cascara sagrada, glycerine, etc.

They are the strongest and most abused laxative products that act by irritating the GI mucosa and pulling water into the bowel lumen. The feces is moved too rapidly and watery stool is eliminated as a result. Glycerine can be administered rectally as suppository only.

Fecal softners – Decrease the surface tension of the fecal mass to allow water to penetrate into the stool. They have detergent – like property e.g. **docusate**. They may also decrease water absorption through intestinal wall.

Lubricant laxatives e.g. **liquid paraffin** (mineral oil). It lubricates the intestine and is thought to soften stool by retarding colonic absorption of fecal water. Used as retention enema.

Indications for use

Laxatives and cathartics are used:

1. To relieve constipation – bulk – forming
2. To prevent straining – stool softeners
3. To empty the bowel in preparation for bowel surgery or diagnostic procedures (saline or stimulant)
4. To accelerate elimination of potentially toxic substances from the GI tract (saline or stimulant)

5. To accelerate excretion of parasite after anthelmintic drugs (saline or stimulant) have been administered.

Constipation is a common problem in older adults and laxatives are often used or overused. Non drug measures to prevent constipation (e.g. increasing intake of fluid and high –fiber foods, exercise) are much preferred to laxatives.

ANTIEMETICS

- Antiemetic drug or Antivomiting drug are those drug which is responsible for the prevention of the vomiting.

Classification-

1. **Anticholinergic drug-** Hyoscine, Dicyclomine
2. **H1 Antihistaminics:** Promethadine, Cinnarizine
3. **Neuroleptics**- Haloperidol,Chlorpromazine
4. **Prokinetic drug-** Domperidone,Cisapride, Mosapride, Metochlopramide
5. **5-HT3 Antagonist-** Granisteron, Ondansteron
6. **Adjuvant Antiemetics-** Dexamethasone, Benzodiazepine.

PROKINETIC DRUG

- Domperidone, Metoclopramide etc. are belonging to this category.
- Prokinetic drug blocks Dopamine D2 receptor in CTZ.
- Prokinetic drug also enhances the gastro duodenal motility and increases gastric emptying are called Prokinetic drug.
- It also act by enhancing Acetylcholine (Ach) from cholinergic neuron in the gut.

- Prokinetic agents, or prokinetics, are medications that help control acid reflux. Prokinetics help strengthen the lower esophageal sphincter (LES) and cause the contents of the stomach to empty faster. This allows less time for acid reflux to occur.
- Prokinetics are typically used with other gastroesophageal reflux disease (GERD) or heartburn medications, such as proton pump inhibitors (PPIs) or H2 receptor blockers. Unlike these other acid reflux medications, which are generally safe, prokinetics may have serious, or even dangerous, side effects. They're often only used in the most serious cases of GERD.

Types of Prokinetics

1. Bethanechol: Bethanechol (Urecholine) is a medication that stimulates the bladder and helps you pass urine if you are having trouble emptying your bladder. It helps strengthen the LES, and makes the stomach empty faster. It also helps prevent nausea and vomiting. It is available in tablet form.

2. Cisapride: Cisapride (Propulsid) acts on serotonin receptors in the stomach. It was primarily used to improve muscle tone in the LES. However, because of its side effects, such as irregular heartbeat, it has been removed from the market in several countries.

3. **Domperidone** is a medicine that increases the movements or contractions of the stomach and bowel. Domperidone is also used to treat nausea and vomiting caused by other drugs used to treat Parkinson's disease.

CHAPTER- 10

CHEMOTHERAPY

CHEMOTHERAPY

It is defined as treatment of infectious diseases or malignancy with drugs to kill microorganisms or cancer cells with minimal damage to host. The infection may be due to bacteria, virus, fungus etc.

CLASSIFICATION OF ANTIMICROBIAL AGENTS ACCORDING TO THEIR STRUCTURE

- **Sulfonamides:** Sulfadiazine, Sulfasalazine
- **Diaminopyrimidines:** Trimethoprim, Pyrimethamine.
- **Quinolones:** Nalidixic acid, Norfloxacin, Ciprofloxacin, Ofloxacin.
- **B-Lactam antibiotics:** Penicillins, Cephalosporins, Monobactams.
- **Tetracyclines:** Oxytetracycline, Doxycycline,
- **Nitrobenzene derivative:** Chloramphenicol.
- **Aminoglycosides:** Streptomycin, Gentamicin, Amikacin, Neomycin,
- **Macrolide antibiotics:** Erythromycin, Clarithromycin, Azithromycin, Roxithromycin
- **Lincosamide antibiotics:** Lincomycin, Clindamycin.
- **Glycopeptide antibiotics:** Vancomycin, Teicoplanin.
- **Nitrofuran derivatives:** Nitrofurantoin, Furazolidone.
- **Oxazolidinone:** Linezolid.
- **Polypeptide antibiotics:** Polymyxin-B, Colistin, Bacitracin, Tyrothricin.

- **Nitroimidazoles:** Metronidazole, Tinidazole, etc.
- **Nicotinic acid derivatives:** Isoniazid, Pyrazinamide, Ethionamide.
- **Polyene antibiotics:** Nystatin, Amphotericin-B, Hamycin.
- **Azole derivatives:** Miconazole, Clotrimazole, Ketoconazole, Fluconazole.
- **Others:** Rifampin, Ethambutol, Thiacetazone, Clofazimine, Griseofulvin, etc.

CLASSIFICATION OF ANTIMICROBIAL AGENTS ACCORDING TO THEIR MECHANISM OF ACTION

- **Inhibition of cell wall synthesis:** Beta lactams, Cycloserine, Vancomycin, Bacitracin.
- **Cause leakage from cell membranes:** Polypeptides, Polyenes
- **Interference with DNA synthesis:** Acyclovir, Zidovudine.
- **Interference with intermediary metabolism:** Sulfonamides, Trimethoprim, Pyrimethamine, Metronidazole.
- **Inhibition of protein synthesis:** Tetracyclines, Chloramphenicol, Erythromycin.
- **Cause misreading of m-RNA code and affect permeability:** Streptomycin, Gentamicin, etc.
- **Inhibition of DNA gyrase:** Fluoroquinolones

CLASSIFICATION OF ANTIMICROBIAL AGENTS ACCORDING TO THEIR TYPE OF ACTION

- **Bacteriostatics:** Sulfonamides, Chloramphenicol, Ethambutol
- **Bacteriocidals:** Penicillins, Cephalosporins, metronizadole

CLASSIFICATION OF ANTIMICROBIAL AGENTS ACCORDING TO TYPE OF ORGANISMS THEY AFFECT

- **Antibacterial:** Penicillins, Aminoglycosides, Erythromycin.
- **Antifungal:** Griseofulvin, Amphotericin B, Ketoconazole, etc.
- **Antiviral:** Acyclovir, Amantadine, Zidovudine, etc.
- **Antiprotozoal:** Chloroquine, Pyrimethamine, Metronidazole, Diloxanide.
- **Anthelmintic:** Mebendazole, Pyrantel, Niclosamide, Diethyl carbamazine.

CLASSIFICATION OF CEPHALOSPORIN ANTIBIOTICS AND WRITE THEIR MECHANISM OF ACTION

- **First generation cephalosporins**: Cefadroxil, Cephalexin, Cefazolin, Cephradine.
- **Second generation cephalosporins**: Cefaclor, Cefuroxime, Cefotetan, Cefoxitin

- **Third generation cephalosporins**: Cefixime, Cefpodoxime, Ceftriaxone, Cefotaxime.
- **Fourth generation cephalosporins**: Cefepime, Cefluprenam, Cefozopran, Cefpirome.
- **Fifth generation cephalosporins**: Ceftaroline, Ceftobiprole.

MOA OF BETALACTAM ANTIBIOTICS

All β-lactam antibiotics **interfere with the synthesis of bacterial cell wall.** The bacteria synthesize UDP-NAM and UDP-NAG. The peptidoglycan residues are linked together forming long strands and UDP is split off. The final step is cleavage of the terminal D-alanine of the peptide chains by transpeptidases; the energy so released is utilized for establishment of cross linkages between peptide chains of the neighbouring strands. This cross linking provides stability and rigidity to the cell wall. The β-lactam antibiotics inhibit the transpeptidases so that cross linking (which maintains the close knit structure of the cell wall) does not take place. These enzymes and related proteins constitute the penicillin binding proteins (PBPs) which have been located in the bacterial cell membrane.

USES OF CEPHALOSPORINS

Currently cephalosporins are one of the most commonly used antibiotics. Among them they cover a wide range of gram-positive and

gram negative bacteria including some anaerobes but not B. fragilis, or MRSA, enterococci, mycobacteria and chlamydia. Their indications are:

1. **As alternatives to penicillins** for ENT, upper respiratory and cutaneous infections, one of the first generation compounds may be used.

2. Respiratory, urinary and soft tissue infections caused by gram-negative organisms, especially Klebsiella, Proteus, Enterobacter, Serratia. Cephalosporins preferred for these infections are cefuroxime, cefotaxime, ceftriaxone.

3. Penicillinase producing staphylococcal infections.

4. Septicaemias caused by gram-negative organisms: an aminoglycoside may be combined with a cephalosporin.

5. Surgical prophylaxis: the first generation cephalosporins are popular drugs. Cefazolin (i.m. or i.v.) is employed for most types of surgeries including those with surgical prosthesis such as artificial heart valves, artificial joints, etc.

6. Meningitis: Optimal therapy of pyogenic meningitis requires bactericidal activity in the CSF, preferably with antibiotic concentrations several times higher than the MBC for the infecting organism. For empirical therapy before bacterial diagnosis, i.v. cefotaxime/ceftriaxone is generally combined with ampicillin or vancomycin or both. Ceftazidime + gentamicin is the most effective therapy for Pseudomonas meningitis.

7. Gonorrhoea caused by penicillinase producing organisms: ceftriaxone is a first choice drug for single dose therapy of gonorrhoea if the penicillinase producing status of the organism is not known.

Cefuroxime and cefotaxime have also been used for this purpose. For chancroid also, a single dose is as effective as erythromycin given for 7 days.

8. Typhoid: Currently, ceftriaxone and cefoperazone injected i.v. are the fastest acting and most reliable drugs for enteric fever. They are preferred over fluoroquinolones (especially in children) for empirical therapy, since many S. typhi strains are resistant to chloramphenicol, ampicillin, cotrimoxazole, and FQs.

9. Mixed aerobic-anaerobic infections in cancer patients, those undergoing colorectal surgery, and obstetric complications: cefuroxime, cefaclor or one of the third generation compounds is used.

10. Hospital acquired infections, especially respiratory and other infections in intensive care units, resistant to commonly used antibiotics: cefotaxime, ceftizoxime or a fourth generation drug are used.

11. Prophylaxis and treatment of infections in neutropenic patients: ceftazidime or another third generation compound, alone or in combination with an aminoglycoside.

CLASSIFICATION OF PENICILLIN ANTIBIOTICS AND WRITE THEIR MECHANISM OF ACTION

- **Natural Penicillin:** Penicillin G
- **Acid resistant alternative to Pn G:** Penicillin V
- **Penicillinase reistant penicillins:** Methicillin, Oxacillin, Cloxacillin
- **Extended Spectrum Penicillins**

- **Amino Penicillins:** Ampicillin, Bacampacillin, Amoxycillin
- **Carboxy penicillins:** Carbenicillin, Carfecillin, Ticarcillin
- **Ureido Penicillins:** Piperacillin, Mezlocillin
- **Mecillinan:** Amdinocillin

MOA: Cell Wall Synthesis inhibition. All β-lactam antibiotics **interfere with the synthesis of bacterial cell wall.** The bacteria synthesize UDP-NAM and UDP-NAG. The peptidoglycan residues are linked together forming long strands and UDP is split off. The final step is cleavage of the terminal D-alanine of the peptide chains by transpeptidases; the energy so released is utilized for establishment of cross linkages between peptide chains of the neighbouring strands. This cross linking provides stability and rigidity to the cell wall. The β-lactam antibiotics inhibit the transpeptidases so that cross linking (which maintains the close knit structure of the cell wall) does not take place. These enzymes and related proteins constitute the penicillin binding proteins (PBPs) which have been located in the bacterial cell membrane.

PENICILLIN G

Penicillin G has narrow spectrum of activity, only limited to Gm +ve microorganisms. Different preparations include: Sod Penicillin G (Crystalline penicillin), Procaine Penicillin G, Benzathine Penicillin G.

Uses

- Streptococcal infections
- Pneumococcal infections
- Meningococcal infections

- Gonorrhoea
- Syphilis
- Diptheria

Adverse Effects: Pain at i.m. injection site, nausea on oral ingestion, thrombophlebtis of injected vein, mental confusion, muscular twitchings, convulsions, coma, hallucinations, convulsions. Hypersensitivity reactions like rash, itching, urticaria, fever, wheezing, angioneurotic edema, serum sickness, exfoliative dermatitis are also seen.

USES OF AMPICILLIN

- Urinary tract infections
- Respiratory tract infections
- Meningitis
- Gonorrhoea
- Typhoid fever
- Bacillary dysentery
- Cholecystitis
- Subacute bacterial endocarditis
- H. pylori infection
- Septicaemias and mixed infections
- ANUG (Acute necrotizing ulcerative gingivitis)

AMINOGLYCOSIDES

- Streptomycin
- Gentamicin
- Sisomicin
- Kanamycin
- Tobramycin
- Amikacin
- Neomycin
- Soframycin

MOA:

- Aminoglycosides bind to **30S ribosomal units of the bacteria and prevent the formation of "initiation complex"** which is the essential for protein synthesis**.** Once inside the bacterial cell, streptomycin binds to 30S ribosomes, but other aminoglycosides bind to additional sites on 50S subunit, as well as to 30S-50S interface.
- They freeze initiation of protein synthesis, prevent polysome formation and promote their disaggregation to monosomes so that only one ribosome is attached to each strand of mRNA.
- Binding of aminoglycoside to 30S-50S juncture causes distortion of mRNA codon recognition resulting in misreading of the code: one or more wrong amino acids are entered in the peptide chain and/or peptides of abnormal lengths are produced.

- Different aminoglycosides cause misreading at different levels depending upon their selective affinity for specific ribosomal proteins.

TOXICITIES AND CONTRAINDICATIONS OF AMINOGLYCOSIDES

- **Ototoxicity**: Aminoglycosides cause impairment of 8th cranial nerve endolymph & perilymph of the inner ear leading to vestibular & cochlear damage. Cochlear Damage means hearing loss due to failure in the generation of sensory cells. So deafness is permanent. Vestibular damage causes nausea, vomiting dizziness, nystagmusm, vertigo & ataxia.
- **Nephrotoxicity:** It is tubular damage resulting in loss of urinary concentrating power, low g.f.r., nitrogen retention, and albuminuria. Aminoglycosides attain high concentration in the renal cortex & toxicity is related to the total amount of the drug.
- **Neuromuscular Blockade:** Aminoglycosides displaces Ca^{+2} from NM junction, block the postsynaptic NM receptor & inhibits Ca^{+2} mediated release of acetylcholine from cholinergic nerve endings and decrease the sensitivity of the muscle end plates to Ach. Myasthenia Gravis is precipitated with aminoglycosides.

Contraindications

- Avoided during pregnancy due to risk of foetal ototoxicity.
- Avoid using with other ototoxic drugs like high ceiling diuretics (frusemide), minocycline.

- Avoid using with nephrotoxic drugs like Amphotericin B, Vancomycinm, Cephalothin, Cyclosporine and Cisplastin.
- Avoid in renal damage patients & in renal insufficiency and also in older aged patients.
- Cautious use of muscle relaxants with Aminoglycosides.

STREPTOMYCIN

Streptomycin is mainly used as a first-line agent for treatment of tuberculosis.

Adverse Reactions: Disturbance of **vestibular function (vertigo, loss of balance) is common.**

Thefrequency and severity of this disturbance are proportionate to the age of the patient, the blood levels of the drug, and the duration of administration.

Vestibular dysfunction may follow a fewweeks of unusually high blood levels or months of relatively low blood levels. Vestibular toxicity tends to be irreversible. Streptomycin given during pregnancy can cause **deafness** in the newborn.

GENTAMICIN

Gentamicin inhibits many strains of staphylococci and coliforms and other gram-negative bacteria. It is a synergistic companion with beta-lactam antibiotics, against Pseudomonas, Proteus, Enterobacter, Klebsiella, Serratia, Stenotrophomonas, and other gram-negative rods that may be resistant to multiple other antibiotics.

Gentamicin is also used concurrently with penicillin G for bactericidal activity in endocarditis due to viridans streptococci. Creams, ointments, or solutions gentamicin sulfate are for the treatment of infected burns, wounds, or skin lesions.

AMIKACIN

Amikacin is a semisynthetic derivative of kanamycin; it is less toxic than the parent molecule. It is resistant to many enzymes that inactivate gentamicin and tobramycin, and it therefore can be employed against some microorganisms resistant to the latter drugs. Strains of multidrug resistant Mycobacterium tuberculosis, including streptomycin-resistant strains, are usually susceptible to amikacin.

MACROLIDES

- Azithromycin
- Clarithromycin
- Roxithromycin
- Erythromycin

MOA: Erythromycin acts by inhibiting bacterial protein synthesis. It combines with 50S ribosome subunits and **interferes with 'translocation'.**

After peptide bond formation between the newly attached amino acid and the nacent peptide chain at the acceptor (A) site, the elongated

peptide is translocated back to the peptidyl (P) site, making the A site available for next aminoacyl tRNA attachment.

This is prevented by erythromycin and the ribosome fails to move along the mRNA to expose the next codon. As an indirect consequence, peptide chain may be prematurely terminated: synthesis of larger proteins is suppressed.

ERYTHROMYCIN

Erythromycin is poorly soluble in water but dissolves readily in organic solvents. They Erythromycins are usually dispensed as various esters and salts.

Antimicrobial Activity: Erythromycin is effective against gram-positive organisms, especially pneumococci, streptococci, staphylococci, and corynebacteria. Mycoplasma, Legionella, Chlamydia trachomatis, Helicobacter, Listeria, Mycobacterium kansasii, and Mycobacterium scrofulaceum are also susceptible. Gram-negative organisms such as Neisseria species, Bordetella pertussis, Treponema pallidum, and Campylobacter species are susceptible.

Pharmacokinetics: Erythromycin base is destroyed by stomach acid and must be administered with enteric coating. Food interferes with absorption. Stearates and esters are fairly acidresistant and somewhat better absorbed. Large amounts of an administered dose are excreted in the bile and lost in feces. Absorbed drug is distributed widely except to the brain and cerebrospinal fluid.

Adverse Reactions

Gastrointestinal Effects: Anorexia, nausea, vomiting, and diarrhea.Liver Toxicity: Erythromycins, particularly the estolate, can produce acute cholestatic hepatitis (reversibile).

Drug Interactions: Erythromycin metabolites inhibit cytochrome P450 enzymes; hence increase the serum concentrations of theophylline, oral anticoagulants, and terfenadine. It increases serum concentrations of oral digoxin by increasing its bioavailability.

USES OF ERYTHROMYCIN

A. As an alternative to penicillin

1. Streptococcal pharyngitis, tonsillitis, mastoiditis and community acquired respiratory infections
2. Diphtheria
3. Tetanus: as an adjuvant to antitoxin, toxoid therapy.
4. Syphilis and gonorrhea
5. Leptospirosis

B. As a first choice drug for

1. Atypical pneumonia caused by Mycoplasma pneumonia
2. Whooping cough
3. Chancroid

C. As a second choice drug in

1. Campylobacter enteritis
2. Legionnaires' pneumonia
3. Chlamydia trachomatis infection of urogenital tract
4. Penicillin-resistant Staphylococcal infections

CLARITHROMYCIN

Clarithromycin is derived from erythromycin. It is better absorbed compared with erythromycin. Clarithromycin and erythromycin are virtually identical with respect to antibacterial activity except that clarithromycin has high activity against H. influenzae, M. leprae and T. gondii. Clarithromycin penetrates most tissues, with concentrations equal to or exceeding serum concentrations. It is metabolized in the liver. A portion of active drug and major metabolite is eliminated in the urine. It has drug interactions similar to those described for erythromycin. The advantages of clarithromycin compared with erythromycin are lower frequency of gastrointestinal intolerance and less frequent dosing.

AZITHROMYCIN

The spectrum of activity and clinical uses of azithromycin is identical to those of clarithromycin.It is rapidly absorbed and well tolerated orally. Azithromycin does not inactivate cytochrome P450 enzymes like erythromycin.

CLINDAMYCIN

Clindamycin is active against streptococci, staphylococci, bacteroides species and other anaerobes, both grampositive and gram-negative. It resembles erythromycin in activity and mechanisms of resistance. Clindamycin is well absorbed orally and about 90% protein-bound. Excretion is mainly via the liver, bile, and urine. It penetrates well into most tissues.

Clinical uses: Clindamycin is used for the treatment of severe anaerobic infection caused by Bacteroides. It is used for prophylaxis of endocarditis in patients with valvular heart disease who are undergoing certain dental procedures. Clindamycin plus primaquine is an effective for moderate to moderately severe Pneumocystis carinii pneumonia. It is also used in combination with pyrimethamine for AIDS-related toxoplasmosis of the brain.

Adverse effects: Diarrheas, nausea, and skin rashes, impaired liver functions are common. Severe diarrhea and enterocolitis is caused by toxigenic C difficile (infrequently part of the normal fecal flora but is selected out during administration of oral antibiotics).

TETRACYCLINS AND THEIR MECHANISM OF ACTION

- Tetracycline
- Oxytetracycline
- Doxycycline
- Minocycline

MOA: Inhibit protein synthesis by binding to 30S ribosomes of organism.Subsequent to such binding, attachment of aminoacyl-t-RNA to the acceptor (A) site of mRNA-ribosome complex is interferred with. As a result, the peptide chain fails to grow.

THERAPEUTIC USES OF TETRACYCLINE

- Chlamydial nonspecific urethritis/endocervicitis,
- Lymphogranuloma venereum

- Granuloma inguinale
- Atypical pneumonia
- Cholera
- Brucellosis
- Plague
- Relapsing fever
- Rickettsial infections

SULFONAMIDE ANTIBIOTICS AND THEIR MOA

Classification:

- **Short-acting:** Sulfacetamide, Sulfadiazine, Sulfadimidine, Sulfisoxazole
- **Intermediate-acting:** Sulfadoxine, Sulfamethoxazole, Sulfamoxole
- **Long-acting:** Sulfadimethoxine, Sulfamethoxypyridazine
- **Ultra long-acting:** Sulfadoxine, Sulfametopyrazine

MOA: Both sulfonamides and trimethoprim (not a sulfonamide) sequentially interfere with folic acid synthesis by bacteria. Folic acid functions as a coenzyme in the transfer of one-carbon units required for the synthesis of thymidine, purines, and some amino acids and consist of three components: a pteridine moiety, PABA, and glutamate. The sulfonamides, as structural analogues, competitively block PABA incorporation; sulfonamides inhibit the enzyme dihydropteroate synthase, which is necessary for PABA to be incorporated into dihydropteroic acid, an intermediate compound in the formation of

folinic acid. Since the sulfonamides reversibly block the synthesis of folic acid, they are bacteriostatic drugs. Humans cannot synthesize folic acid and must acquire it in the diet; thus, the sulfonamides selectively inhibit microbial growth.

VANCOMYCIN

Vancomycin is active only against gram-positive bacteria, particularly staphylococci. It inhibits cell wall synthesis. Vancomycin is poorly absorbed from the intestinal tract and is administered orally only for the treatment of antibiotic-associated enterocolitis caused by Clostridium difficile. Parenteral doses must be administered intravenously. The drug is widely distributed in the body. Ninety percent of the drug is excreted by glomerular filtration.

Clinical Uses: Parenteral vancomycin is indicated for sepsis or endocarditis caused by methicillin-resistant staphylococci. It irritates the tissues surrounding the injection site and is known to cause a red man or red neck syndrome.

BACITRACIN

Bacitracin is active against gram-positive microorganisms. It inhibits cell wall formation. It is markedly nephrotoxic if administered systemically, thus limited to topical use. Bacitracin is poorly absorbed.

CYCLOSERINE

Cycloserine inhibits many gram-positive and gram-negative organisms, but it is used almost exclusively to treat tuberculosis caused by strains of M tuberculosis resistant to first-line agents. It is widely distributed in

tissues. Most of the drug is excreted in active form into the urine. Cycloserine causes serious dose-related central nervous system toxicity with headaches, tremors, acute psychosis, and convulsions.

CHLORAMPHENICOL

Chloramphenicol is a bacteriostatic broad-spectrum antibiotic that is active against both aerobic and anaerobic gram-positive and gram-negative organisms. It is active also against rickettsiae.

Haemophilus influenzae, N. meningitidis, and some strains of Bacteroides are highly susceptible, and for them chloramphenicol may be bactericidal. Clinically significant resistance emerges and may be due to production of chloramphenicol acetyltransferase, an enzyme that inactivates the drug.

Pharmacokinetics: Following oral administration, chloramphenicol is rapidly and completely absorbed. It is widely distributed to virtually all tissues and body fluids. The drug penetrates cell membranes readily. Excretion of active chloramphenicol and of inactive degradation products occurs by way of the urine. A small amount of active drug is excreted into bile or feces. Newborns less than a week old and premature infants clear chloramphenicol inadequately.

Clinical Uses: Because of potential toxicity, bacterial resistance, and the availability of other effective drugs, chloramphenicol may be considered mainly for treatment of serious rickettsial infections, bacterial meningitis caused by a markedly penicillin-resistant strain of pneumococcus or meningococcus, and thyphoid fever.

Adverse Reactions

- Gastrointestinal disturbances
- Bone marrow disturbances
- Toxicity for newborn infants
- Interaction with other drugs

ANTI TUBERCULAR DRUGS

- **1st Line Drugs:** INH (Isonicotinic Acid Hydrazide), Rifampicin (or Rifampin), Pyrizinamide, Streptomycin, Ethambutol, Thiacetazone
- **2nd Line Drugs:** Amikacin, Kanamycin, Clarithromycin, Azithromycin

PHARMACOLOGY OF ANTITUBERCULAR DRUGS

- **Isoniazid (Isonicotinic Acid Hydrazide):** It is an ideal drug; cheapest, most effective, more potent, more bactericidal, least-toxic, quick acting. It inhibits the synthesis of Mycolic acid (essential components of M. cell wall). It also supresses the formation of DNA & RNA. Adverse effects includePeripheral neuritis & Hepatotoxicity.
- **Rifampicin (Rifampin):** It binds strongly to the Beta subunits of bacterial "DNA-dependent RNA polymerase" and inhibits RNA synthesis of bacteria. Adverse effects includehepatitis, rashes, GI disturbances, dizziness, fatigue & flu-like syndrome.

- **Ethambutol:** Itinhibits Arabinosyl transferase enzyme to prevent polymerisation of arabinoglycans in mycobacterial cell wall. It is commonly included along with the other 1st line drugs in thetreatment of TB. Adverse effects are mild GIT intolerance, rashes, fever and dizziness.
- **Pyrizinamide:** Itinhibits mycobacterial fatty acid synthase-I enzyme and disrupts mycolic acid synthesis needed for cell wall synthesis. Hepatotoxicity is the major adverse effect. It is avoided during pregnancy
- **Streptomycin:** It inhibits protein synthesis of bacteria.
- **Ethionamide**: It is rarely used due to intense gastric irritation & neurological toxicity (peripheral neuritis & optic neuritis), hapatotoxic. It blocks the synthesis of Mycolic acid and static drug.

PHARMACOLOGY OF RIFAMPIN

MOA: Rifampin binds strongly to the bacterial DNA-dependent RNA polymerase and thereby **inhibits RNA synthesis.**

Pharmacokinetics: It is well absorbed after oral administration and excreted mainly through the liver into bile. Rifampin is distributed widely in body fluids and tissues. It is relatively highly proteinbound, and so adequate cerebrospinal fluid concentrations are achieved only in the presence of meningeal inflammation.

Uses: Rifampin is used in the treatment of mycobacterial infections. Rifampin causes a **harmless orange color to urine**, sweat, and tears.

Occasional adverse effects include rashes, thrombocytopenia, nephritis, cholestatic jaundice and occasionally hepatitis.

Rifampin induces microsomal enzymes (cytochrome P450), which increases the elimination of anticoagulants, anticonvulsants, and contraceptives. Administration of rifampin with ketoconazole, or chloramphenicol results in significantly lower serum levels of these drugs.

NALIDIXIC ACID

Nalidixic acid is the first antibacterial quinolone. It is not fluorinated and is excreted too rapidly to have systemic antibacterial effects. They inhibit normal transcription and replication of bacterial DNA. Because of their relatively weak antibacterial activity, these agents were useful only for the treatment of urinary tract infections and shigellosis.

FLUOROQUINOLONES

Quinolones are synthetic fluorinated analogs of nalidixic acid, that nucleic acid synthesis. Ofloxacin and ciprofloxacin inhibit gram-negative cocci and bacilli, including Enterobacteriaceae, Pseudomonas, Neisseria, Haemophilus, and Campylobacter. Many staphylococci also are sensitive these drugs. Intracellular pathogens such as Legionella, Chlamydia, M tuberculosis and M avium complex, are inhibited by fluoroquinolones.

Pharmacokinetics: After oral administration, the fluoroquinolones are well absorbed and distributed widely in body fluids and tissues. Oral absorption is impaired by divalent cations, including those in antacids. The fluoroquinolones are excreted mainly by tubular secretion and by glomerular filtration. All fluoroquinolones accumulate in renal failure.

Clinical Uses:

- Fluoroquinolones are effective in urinary tract infections even when caused by multidrug-resistant bacteria, eg, Pseudomonas. Norfloxacin 400 mg, ciprofloxacin 500 mg, and ofloxacin 400 mg given orally twice daily and all are effective.
- These agents are also effective for bacterial diarrhea caused by Shigella, Salmonella, toxigenic E coli, or Campylobacter.
- Fluoroquinolones (except norfloxacin) have been employed in infections of soft tissues, bones, and joints and in intraabdominal and respiratory tract infections, including those caused by multidrug-resistant organisms such as Pseudomonas and Enterobacter.
- Ciprofloxacin and ofloxacin are effective for gonococcal infection, including disseminated disease, and ofloxacin is effective for chlamydial urethritis or cervicitis.

Adverse Effects:

The most common effects are **nausea, vomiting, and diarrhea.**

Fluoroquinolones may damage growing cartilage and cause an arthropathy. Thus, they are not routinely recommended for use in patients under 18 years of age. Since fluoroquinolones are excreted in breast milk, they are contraindicated for nursing mothers.

USES AND ADVERSE EFFECTS OF SULPHONAMIDES

Clinical Uses

Oral Absorbable Agents:

- Sulfisoxazole and sulfamethoxazole are short- to medium-acting agents that are used to treat **urinary tract infections**, **respiratory tract infections, sinusitis, bronchitis, pneumonia, otitis media, and dysentery.**
- Sulfadiazine in combination with pyrimethamine is first-line therapy for treatment of **acute toxoplasmosis**.
- Sulfadoxine, longacting sulfonamide, in combination with pyrimethamine used as a second-line agent in treatment for **malaria.**

Oral Nonabsorbable Agents:

- Sulfasalazine is widely used in ulcerative colitis, enteritis, and other inflammatory bowel disease.
- Sulfasalazine is split by intestinal microflora to yield sulfapyridine and 5-aminosalicylate.
- Salicylate released in the colon in high concentration is responsible for an antiinflammatory effect.

Topical Agents:

- Sodium sulfacetamide ophthalmic solution or ointment is effective treatment for bacterial conjunctivitis and as adjunctive therapy for trachoma.
- Silver sulfadiazine is a much less toxic topical sulfonamide and is preferred to mafenide for prevention of infection of burn wounds.

Adverse Reactions:

- The most common adverse effects are fever, skin rashes, exfoliative dermatitis, photosensitivity, urticaria, nausea, vomiting, and diarrhea.
- Stevens-Johnson syndrome, crystalluria, hematuria, hemolytic or aplastic anemia, granulocytopenia, and thrombocytopenia occur less frequently.
- Sulfonamides taken near the end of pregnancy increase the risk of kernicterus in newborns.

TRIMETHOPRIM

MOA: Trimethoprim **inhibits bacterial dihydrofolic acid reductase**. Dihydrofolic acid reductases convert dihydrofolic acid to tetrahydrofolic acid, a stage leading to the synthesis of purines and ultimately to DNA.

Pharmacokinetics: Trimethoprim is usually given orally.

It is absorbed well from the gut and distributed widely in body fluids and tissues, including cerebrospinal fluid. Trimethoprim concentrates in prostatic fluid and in vaginal fluid, which are more acid than plasma.

Therefore, it has more antibacterial activity in prostatic and vaginal fluids than many other antimicrobial drugs.

Uses: Trimethoprim can be given alone in acute urinary tract infections, because most communityacquired organisms tend to be susceptible to the high concentrations.

Adverse effect: Trimethoprim produces the predictable adverse effects of an antifolate drug, especially megaloblastic anemia, leukopenia, and granulocytopenia. This can be prevented by the simultaneous administration of **folinic acid,** 6-8 mg/d.

JUSTIFICATION OF TRIMETHOPRIM-SULFAMETHOXAZOLE COMBINATION (COTRIMOXAZOLE)

The half-life of trimethoprim and sulfamethoxazole is similar. Trimethoprim, given together with sulfamethoxazole, produces sequential blocking in this metabolic sequence, resulting in marked enhancement of the activity of both drugs. The combination often is bactericidal, compared to the bacteriostatic activity of a sulfonamide alone.

Clinical uses: Trimethoprim-sulfamethoxazole is effective treatment for Pneumocystis carinii pneumonia, shigellosis, systemic Salmonella infections, urinary tract infections, and prostatitis. It is active against many respiratory tract pathogens; Pneumococcus, Haemophilus species, Moraxella catarrhalis, and Klebsiella pneumoniae.

PHARMACOLOGY OF ISONIAZID

INH is the most active drug for the treatment of tuberculosis caused by susceptible strains. It is structurally similar to pyridoxine. It is bactericidal for actively growing tubercle bacilli. INH is able to penetrate into phagocytic cells and thus is active against both extracellular and intracellular organisms.

INH inhibits synthesis of mycolic acids, which are essential components of mycobacterial cell walls.

INH is readily absorbed from the gastrointestinal tract, and it diffuses readily into all body fluids and tissues. Metabolism of INH, especially acetylation by liver N-acetyltransferase, is genetically determined. INH metabolites and a small amount of unchanged drug are excreted mainly in the urine. The dose need be adjusted in severe hepatic insufficiency.

Clinical Uses: Used in the treatment and prevention of tuberculosis.

Adverse Reactions:

- **INH-induced hepatitis** is the most frequent major toxic effect and the risk of hepatitis greater in old age, alcoholics and possibly during pregnancy and the post-partum period.
- **Peripheral neuropathy**is more likely to occur in slow acetylators and patients with predisposing conditions such as malnutrition, alcoholism, diabetes, AIDS, and uremia.
- **CNS system toxicity**, which is less common, includes memory loss, psychosis, and seizures, and may also respond to pyridoxine.

CHEMOTHERAPY OF TUBERCULOSIS

This is caused by Mycobacterium tuberculous bacteria. Often it lies dormant for years until the body‘s immunity is suppressed, whereupon it spreads again to cause the disease. In children the disease can manifest soon after infection. It usually affects the lungs but it may affect almost any other organ. Untreated it is fatal.

Clinical features

For Pulmonary Tuberculosis

Main Clinical features

- Cough and expectoration lasting for more than two weeks.
- Intermittent fever with evening rise in temperature and associated with sweating— for over two weeks.
- Loss of weight and appetite.
- Haemoptysis

Supportive clinical features

- Pleuritic - Chest pain
- Close contact with Tuberculosis patient (specially children)
- Past history of Tuberculosis

Diagnosis

Pulmonary Tuberculosis

- Any patient with sputum for AFB is positive irrespective of what abovementioned symptoms he has.
- Any patient with clinical features given above and who has an X-rayappearance suggestive of tuberculosis even if he is sputum AFB negative.

- Any child who has one or more of the symptoms of tuberculosis as givenabove on whom a PPD skin test (montoux) is positive – even if it is sputumnegative.
- In cases where X-ray cannot be organised and sputum is negative a clinicalexamination by a qualified doctor can be done and the doctor can decideon empirical treatment with ATT and given for 2 months. If clinical symptomsimprove then treatment can be continued till full course of treatment isgiven. If there is no improvement patient must be referred to a highercentre for reassessment.

Extra-pulmonary tuberculosis

Diagnosis based on clinical picture

Confirmation

- By examination and culture of body fluid showing AFB or growing AFB on culture (pleural fluid, cerebrospinal fluid, ascites, etc.)
- Or mantoux positive in young child
- Tissue biopsy showing typical granuloma or AFB.

Treatment

Treatment depends on categorization

Category	**Treatment of TB**
Category: I	New Sputum smear positive

	Seriously ill sputum smear-negative Seriously ill extra-pulmonary*
Category:II	Sputum smear positive relapse** Sputum smear positive failure** Sputum smear positive treatment after default
Category:III	Sputum smear negative, not seriously ill Extra pulmonary, not seriously ill

*Examples of seriously ill extra pulmonary T.B cases are meningitisdisseminated T.B.,Tuberculous pericarditis, peritonitis, bilateral or extensive pleurisy, spinal T.B. with neurological complications and intestinal and genito-urinary T.B.

**In rare and exceptional cases patient are sputum smear negative or who have extra pulmonary disease can have relapse or failure. This diagnosis in all cases should always be made by an MO and should be support of histological evidence of current, active tuberculosis. In these

cases the patient should be categorized as other and given category two treatment.

Relapse:

A patient declared cured of TB by a physician, but who reports back to the healthservice and is found to be bacteriologically positive.

Failure

A smear-positive patient who is smear positive at 5 months or more after startingtreatment. Failure also includes a patient who was initially smear-negative but whobecomes smear-positive during treatment.

Default: A patient who, at any time after registration, has not taken anti-TB drugs for 2months or more consecutively.

Drugs used for treatment

Medicines	**Denoted by**	**Dose (thrice a week)**	**Dose/Kg BW**
Isoniazid	H	600mg	10-15mg/kg
Rifampicin	R	450mg	10mg/kg
Pyrazinamide	Z	1500mg	35mg/kg
Ethambutol	E	1200mg	30mg/kg
Streptomycin	S	0.7gm/day	15mg/kg

Drug regimen

Category	**Intensive phase**	**Continuation phase**
Category: I	2 months	4 months

	HRZE Thrice a week 8 Weeks -24 doses	HR thrice a week 18 Weeks- 54 doses
Category:II	2 months + 1 month HRZES + RHZE thrice a week 12 Weeks-36 doses	5 months HRE thrice a week 22 weeks -66 doses
Category:III	2 months HRZ thrice a week 8 Weeks-24 doses	4 months HR thrice a week 18 Weeks-54 doses

SOME DRUGS USED IN LEPROSY

This is an infectious disease caused by Mycobacterium leprae that affects the skin, mucous membranes and peripheral nerves. Man is the only significant reservoir of infection and transmission often occurs through household contacts.

Drugs include:

- Dapsone

- Rifampin
- Clofazamine
- Minocycline
- Ofloxacin

TREATMENTS OF LEPROSY

Treatments

Leprosy is a curable disease using the highly effective MDT (multidrug therapy).

Pauci-bacillary leprosy: It is the form of leprosy in which five or less skin lesions are present. The treatment is 600mg once monthly supervised dose of rifampicin and 100mg daily dose of dapsone for 6 months.

Multi-bacillary leprosy: It includes leprosy with more than five skin lesions or smear positive cases even if the lesions are less than fve. BB, BL and LL leprosy are multi bacillary. The treatment is 600mg rifampicin + 300mg clofazimine (once monthly supervised dose) and 100mg dapsone and 50mg clofazimine once daily for one year.

ANTIAMOEBIC DRUGS

- Nitroimidazoles: Metronidazole, Tinidazole, Secnidazole, Ornidazole
- Alkaloids: Emetine, Dehydroemetine

- Amide: Diloxanide furoate, Nitazoxanide
- 8-Hydroxyquinolines: Quiniodochlor, Diiodohydroxyquin
- Antibiotics: Tetracyclines, Paromomycin

PHARMACOLOGY OF ANTIAMOEBIC DRUGS

- **Metronidazole:** It is highly active amoebicide having broad-spectrum activity against anaerobic protozoa, including Giardia lamblia. Metronidazole is selectively toxic to anaerobic microorganisms. After entering the cell by diffusion, its nitro group is reduced by certain redox proteins which exert cytotoxicity. Metronidazole also inhibits cell mediated immunity. **Side effects:** Anorexia, nausea, metallic taste and abdominal cramps are the most common.
- **Emetine:** Emetine is a potent and directly acting amoebicide, kills trophozoites but has no effect on cysts. It acts by inhibiting protein synthesis in amoebae by arresting intraribosomal translocation of tRNAamino acid complex. It is administered by s.c. or i.m. injection: 60 mg OD. **Side effects:** Nausea, vomiting, abdominal cramps, diarrhoea, weakness, stiffness of muscles, myositis, hypotension etc.
- **Diloxanide Furoate:** It is a highly effective luminal amoebicide which directly kills trophozoites responsible for production of cysts.
- **8-Hydroxyquinolines:** They kill the cyst forming amoebic trophozoites in the intestine, but do not have tissue amoebicidal action. They areused for the prophylaxis and treatment of nonspecific diarrhoeas, traveller's diarrhoea, etc. **Side effects:**

nausea, transient loose and green stools, pruritus, etc. but carry toxic potential if improperly used.

- **Antibiotics:** Tetracyclines reduce proliferation of entamoebae in the colon.

TREATMENT OF AMOEBIASIS

Acute amoebic dysentery:

- Metronidazole or tinidazole is the drugs of choice.
- Secnidazole, ornidazole, are the alternatives.
- Tetracycline can be used as third drug.

Mild intestinal amoebiasis/asymptomatic cyst passers

- Nitroimidazoles are the first line drugs.
- Diloxanide furoate can be used concurrently.
- A tetracycline may be given along with the luminal amoebicide in severe cases.

Amoebic liver abscess

- Metronidazole or tinidazole are the first choice drugs.
- i.v. metronidazole is initially used, followed by oral dosing.
- Dehydroemetine is used when metronidazole doesn't produce desired effect.

PHARMACOTHERAPY OF GIARDIASIS

Giardia lamblia infects children and adults by oro-faecal contamination and mostly lives in the intestine. It causes acute watery short duration diarrhea with foul smellling stools, gas and abdominal cramps. If untreated, it may pass on to chronic diarrhoea with greasy or frothy stools but no blood or mucus.

Drugs:

Metronidazole 400 mg TDS (children 15 mg/kg/day) for 5–7 days or 2 g daily for 3 days Or tinidazole **0.6 g daily** for 7 days or 2 g single dose Or

Secnidazole 2 g single dose. Nitazoxanide is used for the treatment of diarrhea and dysentery caused by Cryptosporidium parvum, Giardia lamblia, E. histolytica. 500 mg (children 7.5 mg/kg) twice daily for 3 days is recommended dose.

Quiniodochlor 250 mg TDS for 7 days is a somewhat less effective alternative. **Paromomycin in a dose of 500 mg TDS for 5–7 days,** is less effective than metronidazole, but is free of systemic side effects and can be used during pregnancy.

DRUGS USED FOR TRICHOMONIASIS

Trichomonas vaginalis causes vulvovaginitis. It is a common sexually transmitted disease affecting some sexually active women.

Oral Drugs

Metronidazole 400 mg TDS for 7 days or 2 g single dose, or

Tinidazole 600 mg daily for 7 days or 2 g single dose or

Secnidazole 2 g single dose, are the drugs of choice.

Intravaginal Drugs

Diiodohydroxyquin 200 mg is inserted intravaginally at bed time for 2 weeks.

Quiniodochlor 200 mg is inserted in the vagina every night for 1–3 weeks.

Povidone-iodine 400 mg is inserted in the vagina daily at night for 2 weeks.

ANTHELMINTICS

Anthelmintics are drugs that either kill (**vermicide**) or expel (**vermifuge**) infesting helminths.

Classification of Drugs

For Round worm: Mebendazole, Albendazole, pyrantel

For Hookworm: Mebendazole, Albendazole, pyrantel

For Pin worm: Mebendazole, Albendazole, pyrantel

For Thread Worm: Ivermectin

For Whipworm: Mebendazole

For Filaria: Diethyl carbamazine**,** Ivermectin

For Guineaworm: Metronidazole

For Tapeworms: Praziquantel, Niclosamide

PHARMACOLOGY OF ANTHELMINTICS

- **Mebendazole:** It has produced around 100% cure rate in roundworm, hook worm. The site of action of mebendazole is microtubular protein 'β-tubulin' of the parasite. It binds to β-tubulin of susceptible worms with high affinity and inhibits its polymerization.
- **Albendazole:** It has broad-spectrum activity, excellent tolerability and has the advantage of single dose administration. One dose treatment has produced cure rates in ascariasis, hookworm and enterobiasis which are comparable to 3 day treatment with mebendazole.
- **Pyrantel Pamoate:** It is used for roundworm and hookworm infections. It is used against Ascaris, Enterobius and Ancylostoma. Pyrantel causes activation of nicotinic cholinergic receptors in the worms resulting in persistent depolarization. As a result contracture and spastic paralysis takes place. Worms are then expelled.
- **Diethylcarbamazine Citrate (Dec):** It is the first drug for filariasis caused by the nematodes Wuchereria bancrofti and Brugia malayi. A dose of 2 mg/kg TDS clears Mf of W. bancrofti and B. malayi from peripheral blood in 7 days. The most important action of DEC is alteration of organelle membranes of the Mf promoting cell death.
- **Ivermectin:** Ivermectin is the drug of choice for single dose treatment of onchocerciasis and strongyloidosis.
- **Niclosamide:** Niclosamide is a highly effective drug against Taenia saginata, T. solium, and Hymenolepis nana, and pin worm. It acts by

inhibiting oxidative phosphorylation in mitochondria and interfering with anaerobic generation of ATP by the tapeworm.

- **Praziquantel:** It is active against Schistosomes, other trematodes, cestodes. It causes leakage of intracellular calcium from the membranes, so paralysis occurs.

ANTIFUNGAL DRUGS

- **Antibiotics:**Amphotericin B (AMB), Nystatin, Hamycin, Griseofulvin
- **Antimetabolite:**Flucytosine (5-FC)
- **Azoles**: Clotrimazole, Econazole, Miconazole, Oxiconazole, Ketoconazole, Fluconazole, Itraconazole
- **Allylamine:**Terbinafine
- **Other topical agents:**Tolnaftate, Undecylenic acid, Benzoic acid, Quiniodochlor, Sodium thiosulfate

PHARMACOLOGY OF ANTIFUNGAL DRUGS

- **Amphotericin B:** It is obtained from Streptomyces nodosus.It has high affinity for ergosterol present in fungal cell membrane. It combines irreversibly with ergosterol, gets inserted into the membrane forming a micropore and disrupts the membrane integrity and ultimately cell death.Adverse effects include pain,

swelling at site of injection, Nausea, vomiting, diarrhea, upset stomach, loss of appetite, weight loss, muscle or joint aches, headache, warmth, redness, or tingly feeling under skin, skin itching or mild rash.

- **Griseofulvin:** It was one of the early antibiotics extracted from Penicillium griseofulvum. It inhibits fungal cell mitosis and nuclear acid synthesis. Adverse effects include Headache, G.i.t. disturbances, Rashes, Photoallergy, Gynaecomastia.
- **Flucytosine (5-FC):** Flucytosine acts against Candida and Cryptococcus. It enters the fungal cell, and then is metabolized to 5-fluorouracil. The 5-fluorouracil is inhibits synthesis of both DNA and RNA. The result is death of the fungal organism. Adverse effects include bone marrow depression, enteritis, diarrhea, liver dysfunction.
- **Clotrimazole:** It is effective in the topical treatment of tinea infections like ringworm. It inhibits the fungal cytochrome P450 enzyme 'lanosterol 14-demethylase' and thus impairs ergosterol synthesis leading to a cascade of membrane abnormalities in the fungus.
- **Terbinafine:** It is active against dermatophytes and Candida. It interferes with fungal membrane function and cell wall synthesis. In Candida albicans, growth inhibition with terbinafine occurs due to ergosterol deficiency. Topical terbinafine can cause itching, dryness, irritation, urticaria and rashes.

- **Benzoic acid:** It has antifungal and antibacterial. Removal of the fungus needs prolonged application till infected keratin is totally shed.

SOME IMPORTANT QUESTIONS

1. Write a note on historical landmarks in Pharmacology.
2. Write a note on scope of Pharmacology.
3. What are different nomenclatures of drugs?
4. What are different sources of drugs?
5. Describe new drug development processes.

6. Write Steps involved in Clinical trial.
7. Write various routes of drug administration.
8. Write advantages of oral route.
9. Write disadvantages of oral route.
10. Write advantages of IV route.
11. Write disadvantages of IV route.
12. Write advantages of IM route.
13. Write disadvantages of IM route.
14. Write advantages and disadvantages of rectal route.
15. Write advantages and disadvantages of sublingual/buccal route.
16. Intrathecal route
17. Inhalation route
18. Intraperitonial route
19. Intra-articular route
20. Intradermal
21. Subcutaneous
22. Transdermal patches
23. Conjunctival
24. Vaginal and Urethral
25. Inunction (Rubbing
26. What are different mechanisms of drug absorption?
27. Define absorption of drug. Name the factors affecting it.
28. Define distribution. Mention the factors affecting distribution.
29. What is drug biotransformation/metabolism?
30. Which enzymes are responsible for drug metabolism?
31. Elaborate different drug biotransformation reactions.
32. What are different classes of prodrugs?
33. Write about the factors these affect drug metabolism.
34. What are first pass effect. which route avoid it.
35. What are the drugs which undergo extensive first pass metabolism?
36. Define excretion. Write different route of drug elimination.

37. What is plasma half-life/biological half-life/terminal half-life or $t_{1/2}$? Why determination of plasma half life is impoertant?
38. What is first order kinetics of drug elimination?
39. What is zero order kinetics?
40. What is mixed order kinetics / nonlinear kinetics / Michelis-menten equation?
41. What are the differences between first order and zero order kinetics?
42. What is Therapeutic Drug Monitoring (TDM)?
43. Write the principles of drug action.
44. Write the mechanisms of drug action.
45. What is antagonism? Write different drug antagonisms.
46. What are different types of dose responses of drugs?
47. Write in detail regarding receptor mediated drug action.
48. What is non-receptor mediated drug action?
49. What are the factors those modify drug actions?
50. What are different adverse drug effects/ adverse drug reactions?
51. Write a note on drug allergy.
52. Write the differences between tolerance and tachyphylaxis.
53. Write a note on anaphylaxis.
54. Write about some important receptors, their agonists and antagonists.
55. Write enzyme inhibiting drugs with examples.
56. Enlist some drugs which are excreted unchanged in urine.
57. Enlist different ion channels and their stimulators and blockers.
58. How to calculate child dose (up to 8 years) of a drug from adult dose.
59. What is Autonomic nervous system? What are its main divisions?
60. What is Cholinomimetic (cholinergic) and Sympathomimetic (adrenergic) drugs?
61. Write the synthesis, storage, release and degradation of Acetylcholine.

62. What are cholinestarases and anticholinesterases?
63. Write different cholinergic receptors and their locations.
64. Elaborate muscarinic receptors and their associated functions?
65. Elaborate nicotinic receptors and their associated functions.
66. Classify parasympathomimetics (cholinergic agonists, Cholinomimetic).
67. Write the pharmacological actions and uses of Acetylcholine?
68. Write a note on Carbachol.
69. Write in brief about Pilocarpine.
70. Write in brief about Physostigmine.
71. Write in short about Neostigmine.
72. Write a note on organophosphates.
73. What are the uses of parasympathomimetics?
74. What are the therapeutic uses of anticholinesterase agents?
75. What are the contraindications to the use of choline esters?
76. What is Organophosphorous poisoning? Write its management.
77. Name parasympatholytics/ Atropinic/ Anticholinergic drugs.
78. Write therapeutic classification of anticholinergic drugs.
79. Write the pharmacological actions of Atropine?
80. Write in short about Hyoscine (Scopolamine).
81. Write in brief about synthetic atropine derivatives.
82. What are the uses of parasympatholytics?
83. What is belladonna poisoning? Write its management.
84. What are the drugs used for myasthenia gravis?
85. Write therapeutic uses of ergot alkaloids.
86. Write examples of endogenous catecholamines.
87. What are different adrenergic receptors/ adrenoceptors?
88. Write adrenoceptor subtypes and their actions.
89. Clasify Sympathomimetic drugs according to their MOA.
90. Classify Sympathomimetic drugs according to their therapeutic uses.
91. What are the important pharmacological actions of Adrenaline?
92. Write Pharmacology of adrenaline.
93. Write pharmacology of Noradrenaline.

94. Write Pharmacology of Ephedrine in detail.
95. Classify α -adrenergic antagonists.
96. Write pharmacology of Prazosin.
97. What are the important uses of Alpha-blockers?
98. Classify β-adrenergic antagonists.
99. What are the important uses of β-adrenergic antagonist?
100. Write Pharmacology of Propranolol.
101. Write in brief the management of glaucoma.
102. Biphasic response, Dale's reversal phenomenon?
103. Define and classify hypertension.
104. What are non-pharmacological therapies of hypertension?
105. Classify antihypertensive drugs.
106. Justify the use of Diuretics in hypertension.
107. In which hypertensive patients, diuretics are used
108. Justify the use of (ACEIs) in hypertension.
109. Write adverse effects of Captopril.
110. Justify the use of ARBs in hypertension.
111. Justify the use of methyldopa in hypertension.
112. Write adverse effect of methyldopa.
113. Justify the use of α blockers in hypertension.
114. Justify the use of both α and β blockers in hypertension.
115. Justify the use of nitroprusside in hypertension.
116. Justify the use of calcium channel blockers in hypertension.
117. What are the adverse effects of Calcium channel blockers?
118. What are the contraindications of ACEIs?
119. Name 4 drugs to treat hypertension with renal failure.
120. Name 4 drugs to treat hypertensive urgencies.
121. Name 5 drugs which can cause hypertension.
122. Mention the lines of treatment of primary hypertension.
123. Classify antianginal drugs.
124. Justify the use of organic nitrates in angina pectoris.
125. Justify the role of ca2 blocker in angina pectoris.
126. Justify the role of beta blockers in angina pectoris.
127. Classify coagulants.

128. Write Mechanism of coagulant action.
129. Write therapeutic uses of Vitamin K.
130. Classify anticoagulants.
131. Write a note on heparin.
132. Write a note on low molecular weight heparin.
133. Enumerate Synthetic Heparin Derivatives.
134. Write a note on Miscellaneous Parenteral Anticoagulants.
135. What are the differences between Heparin & Warfarin?
136. Write adverse effects of warfarin.
137. Write adverse effects of heparin.
138. What are the therapeutic uses of Anticoagulants?
139. Classify antiplatelet agents.
140. Write mechanism of action of aspirin.
141. Write mechanism of action of dipyridamole.
142. Define thromolytics/ fibrinolytics. Write their MOA.
143. Classify drugs used for Congestive Heart Failure.
144. Write pharmacology of drugs used for CH failure.
145. Write management of digoxin toxicity.
146. Classify drugs used for acute MI.
147. Write pharmacotherapy of cardiac arrhythmia.
148. Write a note on diuretics.
149. Classify lipid lowering agents
150. Define sedative and hypnotic.
151. Classify sedatives and hypnotics.
152. Write mechanism of action and uses of Barbiturates.
153. Write a note on acute barbiturate poisoning.
154. Write MOA and adverse effects of Benzodiazepines.
155. Write examples of Narrow & Broad-spectrum AEDs.
156. What are general mechanisms of action of antiepileptic drugs?
157. Write a note on phenytoin.
158. Write a note on Carbamazepine.
159. Write a note on Sodium valproate.
160. Write a note on Ethosuximide.

161. Write a note on Clonazepam.
162. What are gabapentin and pregabalin?
163. Write a note on topiramate.
164. Which antiepileptics are relatively safe during pregnancy?
165. Write the management of status epilepticus.
166. Give examples of drugs which can cause seizures.
167. Write the Drug of Choice of different epileptic syndromes.
168. Why benzodiazepines are preferred over barbiturates?
169. What is a local anaesthetic?
170. Classify local anaesthetics according to their chemistry.
171. Classify local anaesthetics as per duration of action.
172. What is the mechanism of action of Local Anaesthetics?
173. How to prolong the actions of local anaesthetics?
174. What are the major side effects of local anaesthetics?
175. What are the various uses of local anaesthetics?
176. What is Parkinsonism?
177. List the drugs used in the treatment of Parkinsonism.
178. Anticholinergic drugs used for the treatment of drug induced Parkinsonism.
179. What is the role of Levodopa + Carbidopa in Parkinsonism?
180. What is bromocriptine and write its uses?
181. What is the role of COMT inhibitors in Parkinsonism?
182. What is the role of MAO-B inhibitor/ selegiline in Parkinsonism?
183. What is the role of benztropine in Parkinsonism?
184. What are opioids?
185. Classify opioids.
186. Write a note on morphine.
187. Write a note on acute morphine poisoning.
188. Write a note on Codeine.
189. What are the clinical uses of morphine?
190. Write a note on tramadol.
191. Write a note on pure opioid antagonists.
192. What are the chemical mediators of inflammation?

193. Classify NSAIDs.
194. Write mechanism of action of NSAIDs.
195. Write a note on aspirin.
196. Write a short note on paracetamol.
197. Write a note on diclofenac.
198. Write in brief on Sulindac.
199. Write in short about ibuprofen.
200. Write in short about indomethacin.
201. Write 4 NSAIDs available as gel for topical application.
202. What are the signs, symptoms and pathogenesis of depression?
203. Classify antidepressants.
204. Enumerate pharmacology of all antidepressants.
205. What are the therapeutic effects of Antidepressants?
206. What are mood stabilizers?
207. What is anxiety? Classify anxiolytics.
208. Write the pharmacotherapy of Anxiety disorders.
209. Classify antipsychotics/ Neuroleptics.
210. Write mechanism of actions of all antipsychotics
211. What are the drugs those cause extrapyramidal side effects.
212. Write signs, symptoms & pharmacotherapy of migraine.
213. Define chemotherapy.
214. Classify antimicrobial agents according to their structure.
215. Classify antimicrobial agents according to their mechanism of action.
216. Classify antimicrobial agents according to their type of action.
217. Classify antimicrobial agents according to type of organisms they affect.
218. Classify cephalosporin antibiotics and write their mechanism of action.
219. What are the uses of cephalosporins?
220. Classify penicillin antibiotics & write their Mechanism of action.

221. Write a note on penicillin G.
222. What are the uses of Ampicillin?
223. Name 8 Aminoglycosides & write their Mechanism of action.
224. Write major toxicities & contraindications of Aminoglycosides?
225. Write a note on streptomycin.
226. Write a note on gentamicin.
227. Write a note on Amikacin.
228. Name 4 Macrolides and write their Mechanism of action.
229. Write a note on erythromycin.
230. Write the uses of Erythromycin.
231. Write a note on clarithromycin.
232. Write a note on Azithromycin.
233. Write a note on clindamycin.
234. Name 4 tetracyclins and write their Mechanism of action.
235. Write therapeutic uses of tetracycline.
236. Classify Sulfonamide antibiotics. Write MOA.
237. Write a note on vancomycin.
238. Write about Bacitracin.
239. Write a note on cycloserine.
240. Write in brief about Chloramphenicol.
241. Classify anti tubercular drugs.
242. Write pharmacology of Antitubercular drugs.
243. Write pharmacology of Rifampin.
244. Write about Nalidixic acid.
245. Write in detail on fluoroquinolones.
246. Write uses and adverse effects of sulphonamides.
247. Write a note on Trimethoprim.
248. Justify Trimethoprim-Sulfamethoxazole combination.
249. Write pharmacology of Isoniazid.
250. Write chemotherapy of tuberculosis.
251. Name some drugs used in leprosy.
252. Write the treatments for leprosy.
253. Classify antiamoebic drugs.

254. Write pharmacology of antiamoebic drugs.
255. Write a note on the treatment of amoebiasis.
256. Write pharmacotherapy of Giardiasis.
257. Write about drugs used for trichomoniasis.
258. Classify Anthelmintics.
259. Write Pharmacology of Anthelmintics.
260. Classify antifungal drugs.
261. Write pharmacology of Antifungal drugs.
262. What are the different functions of hormones?
263. Classify hormones according to their location.
264. What are the sites and mode of actions of hormones?
265. Classify different corticosteroids.
266. What are the pharmacological actions of Glucocorticoids?
267. What are the different uses of Glucocorticoids?
268. What are the contraindications of Glucocorticoids?
269. What are different types of diabetes mellitus?
270. Write actions of Insulin.
271. Write a note on Different insulin Preparations.
272. What are the uses of insulin?
273. What are the side effects of insulin?
274. Write a note on oral hypoglycemic agents.
275. What are Gonadal Hormones? Write their actions.
276. What are the uses of estrogen and progestrerone?
277. Write a note on Oral contraceptives.
278. Write a note on testosterone.
279. Write a note on antiandrogens.
280. Write a note on Thyroid hormones.
281. Write a note on thyroid inhibitors.
282. Write about uterine stimulants (oxytocics, abortifacients).
283. Write a note on uterine relaxants (tocolytics).
284. Name the common drugs of abuse.
285. Describe symptoms & management of alcohol withdrawal.
286. Write symptoms & management of nicotine withdrawal.
287. Classify the Drugs Used In Asthma.

288. Write pharmacology of drugs used for bronchial asthma.
289. Write a note on H1 antihistaminics.
290. Classify autacoids.
291. Classify drugs acting on uterus. Write on uterine stimulant.
292. Classify thyroid inhibitors. Write on radioactive iodine.
293. Classify antiemetics. Describe prokinetic drugs.
294. Write a note on antitussives.
295. Write a note on nasal decongestant.
296. Write A Note On Gout Management.
297. What are the Commonest Side Effects of drugs?
298. Mechanism of action of some important drugs.
299. Write a note on parenteral iron preparation.
300. Write in detail about Histamine.
301. Write a note on H1 Receptor Antagonists.
302. Write a note on serotonin and serotonin agonists.
303. Write a note on serotonin antagonists.
304. Write in detail regarding Prostaglandins.
305. Write a note on anti tussives.
306. Write Pharmacology of drugs used for acid peptic disease.
307. Write pharmacology of Laxatives and cathartics