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UNIT-I

GENERAL PHARMACOLOGY

1 - INTRODUCTION

Pharmacology is the science that deals with the study of drugs and their interaction with the living systems. The word pharmacology is derived from Greek- 'pharmacon' means drug and 'logos' means study.

DEFINATIONS (Terminology used)

Drug (As per WHO): A 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 recipient.

Pharmacokinetics is the branch of science which deals with the absorption, distribution, metabolism and excretion of drugs, i.e. what the body does to the drug.

Pharmacodynamics is the branch of science which deals with the mechanism of action and pharmacological action of drug, i.e. what the drug does to the body.

Therapeutics Index (TI) is the ratio of median lethal dose and effective dose.

$$\text{Therapeutic index} = \frac{LD_{50}}{ED_{50}}$$

Median lethal dose or LD_{50} is the dose which kills half the population of the animal tested.
Median effective dose or ED_{50} is the dose which produces the desire response in the half the animal population tested.
The therapeutics index provides an idea about the safety of the drug.

Pharmacotherapeutics : It is the application of pharmacological information together with knowledge of the disease for its prevention, mitigation or cure

Therapeutics is the branch of science deals with cure or treatment of disease.

Toxicology is the branch of science deals with the poisonous effects of drugs, its detection, diagnosis and treatment.

Chemotherapy deals with the use of chemical substances in the treatment of infectious disease.

2- SOURCES OF DRUGS

The sources of drugs could be natural or synthetic.

Natural sources

1. Plants: e.g. morphine, atropine, digoxin, quinine
2. Animals: e.g. Insulin, heparin, thyroid extract
3. Minerals: e.g. kaolin, iron, sulphur, radioactive isotopes
4. Marine: e.g. shark liver oil, cod liver oil
5. Microorganism: e.g. penicillins, streptomycin
6. Human: e.g. immunoglobulins, growth hormone, chorionic gonadotrophins

Synthetics Most drugs are now synthesized e.g. omeprazole, paracetamol, asprin. Many drugs are obtained by **cell cultures** e.g. urokinase. Some are now produced by **recombinant DNA technology** e.g. insulin

NATURE OF DRUGS

1. Alkaloidal : atropine quinine morphine
2. Glycocidal: Digoxin, sennoside
3. Resins: oleo-gum resins
4. Tannins: catechu, tannic acid
5. Fixed oils: castor oil, shark liver oil
6. Volatile oil: Clove oil, eucalyptus oil
7. Gums: agar, acacia, tragacanth

3- ROUTES OF DRUG ADMINISTRATION

The routes can be broadly divided into

1. Topical route
2. Oral route
3. Parenteral route
4. Transmucosal route
5. Novel drug delivery system

TOPICAL ROUTE

Drugs may be used for local applications in the form of dusting powder, lotion, paste, ointments, plasters etc.

Drugs are commonly applied on skin, eye, nose, ear, throat, rectum, vagina.

Merits/Advantages

- Easiest route of drug administration
- Prolonged effect of drug

Demirits/Disadvantages

- Watery soluble drug sometimes absorbed in blood which may lead to an undesirable toxic effect.
- Drugs for corneal application may penetrate and produce irritation, e.g. cocaine

ORAL ROUTE

Drugs are administered in the form of tablets, capsule, and liquid orals with the help of fluids i.e. water or milk.

Advantages

- Oldest and safest route
- Most convenient
- Most economical
- Self medication is possible
- Withdrawal of drug is possible

Disadvantages

- Onset of action is slow
- Bio-avaibility is not 100%
- Required high dose
- Accuracy of dose is not possible
- Not suitable for uncooperative and unconscious patients
- Irritant and unpalatable drug cannot be administered
- Not suitable in emergency cases

PARANTERAL ROUTE

A. **INJECTIONS:** Drugs are administered by injection which takes the drug directly into the tissue fluid or blood without having to cross the intestinal mucosa.

Advantages

- Onset of action is very quick
- Bioavaibility is 100%
- Low dose are effective
- Accuracy of dose is possible.
- Suitable for uncooperative and unconscious patients
- Irritant and unpalatable drugs can be given by this route.
- Suitable for emergency case

Disadvantages

- Risky route
- Inconvenient
- Costly route
- Self medication is not possible
- Withdrawal of drug is not possible
- Aseptic technique is to be followed to avoid possibility of infection

TYPES OF INJECTION

a) **Intradermal:** Drug is injected in the layer of skin. Only a small quantity can be administered by this route and are made for local effects.

Applications

- Diagnosis of shick test, tuberculosis test
- Introduction of vaccine like BCG
- Hypersensitivity test may be carried out by this route.

b) **Intramascular:** The drug is injected in the layer of muscle tissue. Muscle layer is more muscular and less sensitive so irritant drug is given by this route. IM is suitable for administration of solutions and suspensions

Applications

- Administration of sex hormones, steroids, penicillins etc

c) **Intravenous:** Drug is injected directly into the vein. Large volume parenteral are given by this route. E.g. Dextrose injection, saline injection

d) **Subcutaneous:** Drug is injected at subcutaneous region, lipid soluble drug are injected by this route. Only upto 2ml of drug can be injected by this route. Drugs like adrenaline, morphine, insulin are given through this route.
e) **Intra-arterial:** Drug is injected into an artery. Anticancer drugs are sometimes administered by this route
f) **Intra-thecal:** Drug is administered in the subarachnoid space. E.g. spinal anesthetics.
g) **Intra-peritoneal:** Drug is injected into the peritoneal cavity, by this route fluids like glucose and saline can be given to the children
h) **Intra-medullary:** The drug is directly injected into the bone marrow. This route is useful when veins are not available due to circulatory collapse or thrombosis. In adult sternum is chosen and in children tibia or femur is chosen for injection

B. **INHALATIONS:** Gases, volatile liquids, aerosols and vapors are giving through inhalation.

Advantages

- Rapid onset of action
- The systemic concentration of volatile liquid such as anesthetics can be effectively controlled.

Disadvantages

- Accuracy of dose is not possible
- Local irritation of the respiratory tract, may increase secretions.

TRANS MUCOSAL ROUTE

A. **SUBLINGUAL ROUTE:** Drug is kept below the tongue, allowed to dissolve. Drug mix with saliva and directly inters to the systemic circulation. E.g. Nitroglycerine for Angina pectoris.

Advantages

- Onset of action is very quick
- Bioavailability is 100%

B. **TRANS-NASAL ROUTE:** Drug is used in the form of snuff or nasal spray. The drug is readily absorbed through the mucous membrane of nose.
C. **TRANS-RECTAL ROUTE:** Drugs can be absorbed through the rectum for producing systemic effects. E.g. Diazepam for status epileptics

Advantages

- Gastric irritation is avoided
- Useful in old and terminally ill patients

NOVEL DRUG DELIVERY SYSTEM

A. **OCCUSERT:** Drugs are placed directly under the eyelid. It can release the drugs like pilocarpine for prolonged periods.
B. **PROGESTASERT:** It is an intrauterine contraceptive device. It produces controlled release of progesterone within the uterus for a year.
C. **JET INJECTION:** By using a gun like instrument, the drug solutions are projected as a high velocity jet (dermo jet). The drug solution passes through superficial layer of the skin and gets deposited in the subcutaneous layer.
D. **PRODRUG:** it is an inactive drug which after administration is metabolized into an active drug.

For example, L-dopa after metabolism converted into active Dopamine which is effective in parkinsonism

L-Dopa ⟶ Dopamine

(Inactive) (Active)

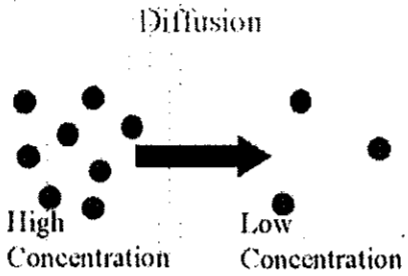
4 - PHARMACOKINETICS

Pharmacokinetics is the branch of science which deals with the absorption, distribution, metabolism and excretion of drug.

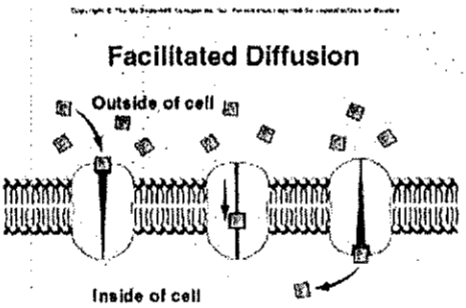
ABSORPTION

Absorption of a drug involves passage of drug across the cell membrane. Absorption involve three process.

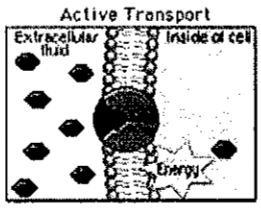
A) **PASSIVE TRANSPORT** The drug moves across the cell membrane without losing energy. They are of two types:
   a) **Diffussion**
      - Diffusion through lipid e.g. lipid soluble drug.
      - Diffusion through aqueous channel e.g. water soluble drug.



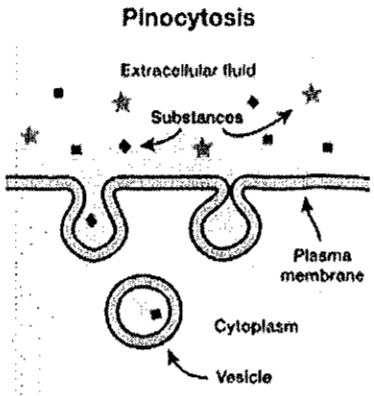
b) **Faciliated transport** Some high molecular drug unable to diffuse through semipermeable membrane like glucose, amino acids. Such substances are attracted by carrier proteins which binds with the drug to be transported. Carrier protein change its shape and deposit the substances to other side.



B) **ACTIVE TRANSPORT** The drug moves across the cell membrane by utilizing energy and sometimes it also required carrier proteins. Only drugs related to natural metabolites are transported by this process, e.g. iron, amino acids, levodopa



C) **PINOCYTOSIS** The transport of the drugs by formation of vesicles. The protein and macromolecules are transported by this process



FACTORS MODIFYING DRUG ABSORPTION

A) **Physical state:** Drugs in the form of liquids are well absorbed than solids. Crystalloids are more readily absorbed than colloids.
B) **Particle size:** Smaller the particle size better is the absorption.
C) **Concentration:** Higher concentrated form of drugs are quickly absorbed than dilute solutions
D) **Solubility:** Lipid soluble drugs are easily absorbed in compared to water soluble drugs.
E) **Absorbing surface:** Drugs can be better absorbed from the small intestine than from the stomach because of large surface area.
F) **P_H of drug:** Acidic drugs are better absorbed from the stomach, e.g. salicylates. Basic drugs are better absorbed from the intestine, e.g. ephedrine.
G) **Ionization:** Unionized drugs are lipid soluble and are well absorbed than ionized drugs
H) **Formulation:** Diluents used in the formulation of drugs may sometimes interfere with absorption, e.g. calcium and magnesium reduce the absorption of tetracycline when used as a diluents.
I) **Diseases:** Disease of guts like malabsorption, diarrhea reduced the absorption of drug.
J) **Presence of other agents:** Vitamin C enhance the absorption of iron, Liquid paraffin reduces the absorption of fat soluble vitamins A, D, E, K.

DISTRIBUTION

After a drug is absorbed, it is distributed to various body tissues and fluids. Drugs which easily pass through cell membrane achieve wide distribution while the drugs which do not easily pass through the cell membrane are limited in their distribution.

After a drug reaches to the systemic circulation, most drug bind to plasma proteins (albumin, alpha-acid glycoprotein) and prolong the duration of action. The free or unbound fraction of drug is only available for action, metabolism and excretion, while the protein bound form serves as a reservoir.

There are some areas in our body where only limited entries for most of the drugs, such areas are

A) **Entry into central nervous system:** Entry of the drug to CNS is limited by **Blood Brain barrier (BBB).** It exist between plasma and extracellular surface of the brain. The barrier is constituted by glial cells and tight junction of capillary endothelium in the brain. Only highly lipid soluble drugs readily pass through this barrier.
B) **Entry into fetal circulation:** Entry of drugs into fetal circulation is restricted by **Blood Placental barrier,**exist between maternal and fetal circulation. It permits only the entry of highly lipid soluble form of drugs.

STORAGE DEPOTS

Some drugs after distribution, get stored in different areas of the body such areas is known as storage depots. Tissue binding delays the excretion and thus prolongs the duration of action of the drug.

TISSUE (STORAGE DEPOTS)	BINDING DRUG
Adipose tissue	Thiopentone sodium, benzodiazepines
Muscles	Emetine
Bone	Tetracycline, heavy metals
retina	Chloroquine
Thyroid	Iodine

METABOLISM

Metabolism or biotransformation is the process of biochemical alteration of the drug in the body. These process convert the lipid soluble drug to water soluble compounds so that they are easily excreted trough the kidneys.
The most important organ of biotransformation is the liver. But drug are also metabolized by the kidney, lungs, blood, skin etc

RESULTS OF BIOTRANSFORMATION

Biotransformation generally inactivates the drugs, but some drugs may be converted to active or more active metabolites as follows:

A) **Active to inactive**

Most of the drugs are active and the metabolite is inactive form

E.g. Phenytoin ⟶ Sulphoxide formation

B) **Active metabolite from active drug**

E.g. Diazepam ⟶ Oxazepam

C) **Active metabolite from inactive drug (prodrug)**

E.g. Levo dopa ⟶ Dopamine

D) **Toxic metabolite from active drug**

E.g. Halothane ⟶ Trifluroacetic acid

METHODS OF BIOTRANSFORMATION

The pathways of drug metabolism can be divided into:

- phase I (Non synthetic reaction)
- phase II (synthetic reaction)

Phase I Includes Simple oxidative, reductive, and hydrolytic reactions.

a) **Oxidation** are the most important metabolizing reactions, occur mainly in liver, and mostly catalysed by mono amino oxygenase present in the liver.

Ethyl alcohol ⟶ Acetaldehyde ⟶ Acetyl CoA

b) **Reduction** is the less common process,drugs like chloramphenicol, halothane are metabolized by reduction.

c) **Hydrolysis** drugs like procaine, acetylcholine are metabolized by hydrolysis.

If the metabolite is not sufficiently water soluble to be excreted, it undergoes Phase II reaction.

Phase II reactions involve covalent attachment of small polar endogenous molecule such as glucuronic acid, sulfate, or glycine to form water-soluble compounds. This is also known as a ***conjugation reaction***.

FACTOR MODIFYING BIOTRANSFORMATION

A) **Inhibitors:** Drug metabolizing enzyme can be inhibited by certain other drugs like omeprazole, ciprofloxacin, leads to the increase in the duration of action.
B) **Stimulators:** Drug metabolizing enzymes can be more activated by certain drugs like phenobarbitone and rifampicin, leads to increase the metabolism of drugs like Phenytoin and warfarin.
C) **Age:** metabolism is poor in young children because of poor development of drug metabolizing enzymes.
D) **Genetic:** Primaquine produces hemolysis in genetic deficiency of enzyme glucose-6-phosphate dehydrogenase (G-6-PD)
E) **Body temperature:** Increase in body temperature increases drug metabolism, where as decrease in body temperature has the opposite effect.

EXCRETION

Excretion is a process by which inactive metabolite are excreted from the body. The major organs of drug excretion are the Kidney, Skin, Lungs, Saliva, Milk etc

Kidney is the most important organ of drug excretion. E.g. morphine, paracetamol, salisylates, penicillin

Lungs: drugs like general anaesthetics, alcohol are excreted through lungs.

Skin: Heavy metals like arsenic, mercury are excreted through lungs.

Saliva: Drugs like iodides, metallic salts are excreted through saliva.

Milk: Drugs like pethidine are excreted through milk

5 - PHARMACODYNAMICS

Pharmacodynamics deals with the study of actions of the drugs on the body and their mechanism of action. Drugs produce their effects by interacting with the physiological system of the organism and perform various actions such as,

Stimulation: Increases the activity of the specialized cells, e.g adrenaline stimulate heart.

Depression: Decrease the activity of specialized cells, e.g. barbiturates depress the CNS

Replacement: Drugs may be used for the replacement when there is a deficiency of natural substances, e.g. iron in anemia.

Anti-infective: Drugs may be act by destroying infective organisms, e.g. antibiotics

Cytotoxic: Drugs damage the cells, e.g. anticancer drugs

Modification of immune system: vaccine and sera act by improving immune system

SITES AND MECHANISM OF ACTIONS

Drugs may produce localized effects on certain cells, tissues, organs etc or systemic effects on most cells of the body. Drugs may act by one of the following mechanism:

Through receptors: Rantidine, cimitidine block H2 receptors and inhibit the gastric acid secretions.

Through pumps: Drugs like omeprazole, esinoprazole inhibit the proton pump which is the final step in gastric acid secretion.

Through enzymes: Drugs like acetazolamide inhibit the enzyme carbonic anhydrase.

Through ion channels: Calcium channel blockers like nifidipine, amlodipine, verpamil, diltiazem are used in the management of cardio-vascular disorders.

Physical actions: Action of a drug could result from its physical properties.

- Adsorption - activated charcoal in poisoning
- Mass of the drug - laxatives like ispaghula

Chemical interaction: drug may act by chemical reaction.

- Antacids – neutralize gastric acids
- Chelating agents – Bind with heavy metals

Altering metabolic process: Sulphaonamides interfere with bacterial folic acid synthesis.

6 - FACTORS MODIFYING THE ACTION OF DRUGS

The various factors which modify the response to a drug are as follows:

Age: In newborn, the liver and kidneys are not fully developed, so the pharmacokinetics and Pharmacodynamics of many drugs may be changed resulting in altered response. Hence calculation of the appropriate dose, depending on the body weight is important to avoid toxicity.

Young's formula

$$\text{Child's dose} = \frac{\text{Age (yrs)}}{\text{Age} + 12} \times \text{Adult dose}$$

In the elderly, the capacity of the liver and kidney to handle the drug is reduce, hence lower doses are recommended.

Body weight: The normal dose is calculated for medium healthy built person, for the obese and underweight persons the dose has to be calculated individually.

Clark's formula

$$\text{Dose} = \frac{\text{Body wt (kg)}}{70} \times \text{average adult dose}$$

Sex: Due to hormonal effects and smaller body configuration the drug response may influence in women and also special care must take while prescribing for pregnant and lactating women.

Route of administration: Route of drug administration may modify the drug response, e.g. magnesium sulphate given orally is purgative. But when given I.V. it causes CNS depression and has anticonvulsant activity.

Time of administration: Drugs which produce nausea, vomiting and irritation should be taken after meal. Sedative and hypnotic drugs are more active at night in compare to day time.

Diet: Food interfere with the absorption of many drugs, e.g. tetracycline form complexes with calcium present in food and are poorly absorbed.

Genetic factors: The effect of drugs may vary due to genetic factors, e.g. Primaquine produces hemolysis in individual with a deficiency of Glucose-6-phosphate dehydrogenase.

Cumulation: Drugs like Digoxin are excreted slowly. So repeated administration leads to accumulation of a drug in the body resulting in toxicity. This phenomenon is called as Cumulation.

Tolerance: It is the unusual resistance to the normal therapeutics dose of the drug. So large dose is required to produce same effects. Tolerance may be **natural** or **acquired**

- **Natural tolerance:** Some species/race shows less sensitivity to the drug, e.g. rabbit show tolerance to atropine, Black race are tolerant to mydriatics.
- **Acquired tolerance:** It develops on repeated administration of a drug, e.g. barbiturates, morphine.

Tachyphylaxis: It is the rapid development of tolerance when some drugs are administered repeatedly at short intervals, e.g. ephedrine, amphetamine

Drug Interaction: When two or more drugs are given concurrently the effects may be additive, synergistic or antagonistic.

- **Additive effect:** the total pharmacological response produce by two drugs is equal to the sum of the individual effects. E.g. ephedrine with theophylline in asthma.
- **Synergism:** When the action of one drug is enhanced by another drug, the combination is synergistic. E.g. levodopa with carbidopa
- **Antagonism:** One drug opposing or inhibiting the action of another drug. Antagonism can be :-
  - **Chemical antagonism:** occurs as a result of chemical interaction between two drugs e.g. BAL in arsenic poisoning
  - **Competitive or reversible antagonism:** Occurs due to competition between two drugs for the same receptor. E.g. acetylcholine and atropine compete at muscranic receptor.
  - **Non-competitive or irreversible antagonism:** Occurs due to the inactivation of receptor by the antagonist. E.g. antagonism of acetylcholine by decamethonium.
  - **Physiological antagonism:** Two drugs act at a different sites to produce opposing effects. For example histamine act on H2 receptor to produce bronchospasm and hypotension while adrenaline reverses these effect by acting on adrenergic receptor

UNIT-II

DRUG ACTING ON CENTRAL NERVOUS SYSTEM

7 - SEDATIVES AND HYPNOTICS

Sedative: these are the drugs which reduce excitement without producing sleep
Hypnotics: are the drugs which produces sleep resembling natural sleep
Sedative act as hypnotic and vice-versa the main difference is in the dose about 1/3 dose of a hypnotics will acts as sedatives

Normal sleeps are of two types:

- Non rapid eye moment (NREM): The eyeballs are motionless.
- Rapid eye moments (REM): the eye show rapid moment person awakened during this phase say that they were dreaming.

A normal sleep begins with NREM(about 90mints) and then passed to a short duration of REM sleep (about 20mnts) after making with NREM sleep and this cycle goes on both NREM and REM are essential for normal sleep.

CLASSIFICATION:

1) **Barbiturates :**
   a. Long action barbiturates (duration of action in 8hrs or more)
      Ex: barbitone, Phenobarbitone.
   b. Intermediate acting barbitone (4 hrs or more)
      Ex: amylobarbitone, cyclobarbitione
   c. Short acting barbitone (less than 4 hrs)
      Ex: hexobarbitone, secobarbitone.
   d. Ultra short acting barbiturates. (less than 1 hrs)
      Ex: thiopentone, methohexitone.
2) **Non- barbiturates :**
   a. Benzodiazepines
      Ex: diazepam, nitrazepam, alprazolam.
   b. Alcohol
      Ex: chlorhydrate
   c. Aldehydes
      Ex: paraldehyde

Barbiturates:

Barbiturates are the derivative of barbituric acid act as general depressant. They are not prefers now a days as sedatives and hypnotics because of development of relatively safer benzodiazepines.

PHARMACOLOGICAL ACTIONS:

1) **C.N.S :** barbiturates produces C.N.S depression such that from mild sedation to even coma.
2) **Sleep :** barbiturates induces sleep resemble natural sleep but it decrease the time spent on REM sleep.
3) **C.V.S:** they depress cardiac activity and in higher dose cause fall in b.p
4) **Respiratory system :** in higher dose they depress respiratory centre in brain and may produces death.
5) **Kidneys :** large dose decrease urinary output due to decrease in glomerular filteration and release of ADH (anti diuretics hormone)
6) **Liver :** large dose may produce hepatic dysfunction.

Mechanisum of action:

Barbiturates have Gaba Amino Butyric Acid (GABA) like action or enhance the effect of GABA which is an inhibitory neuro transmitter.

Barbiturates may also inhibit the neuronal uptake of GABA or may stimulate its release.

PHARMACOKINETICS

Barbiturates are rapidly absorbed after oral as well as Parentral administration, they are widely distributed in the body. They mainly metabolized in their liver and to a small extent in kidney and brain excretion is through urine.

ADVERSE EFFECTS

- **Tolerance :** with duration of treatment tolerance develops and it requires to increase the dose to produce same effect.
- **Drug dependence :** repeated use develop both pscychological and physical dependence
- **Intolerance :** excitement, vomiting, nausea, headache, diarrhea.
- **Drug automatism:** sometimes an individual takes repeated dose of barbiturates without remembering that earlier as dose has been taken
- **Respiratory depressant:** foetal respiratory depressant if administered during labour.

ACUTE BARBITURATE POISONING:

Acute barbiturate poisoning occurs due to accidental overdose or consumption with suicidal intention, leads to hypotension, respiratory depression, and coma. If not treated properly death result due to respiratory arrest

USES

- As a sedative and hypnotics
- Anaesthesia : ultra short acting barbiturates like thiopentone
- Preanaesthetic medication
- Anticonvulsant (specially long acting barbiturates)

1) Non barbiturates

Benzodiazepines: These classes of drugs are safer and also possess better sedative hypnotics anti- anxiety activity.

PHARMACOLOGICAL ACTIONS

1) **C.N.S :** benzodiazepines causes sedation, hypnotics, muscle relaxant and anticonvulsant
2) **Respiratory system:** Hypnotic does not affect the respiration in normal person but higher doses cause respiratory depression.
3) **C.V.S**: toxic dose may produce fall in b.p
4) **Pharmacodynamic :** benzodiazepines facilitate the action of GABA in C.N.S
5) **Pharmacokinetics :** given orally but IV or IM . can also be used . They are widely distributed in the body . They can cross placental and secreted in the milk . They are metabolized and in liver and excreted in urine.

ADVERSE EFFECTS

- Drug dependence
- Fatigue, memory loss
- Blurring of vision
- Benzodiazepines are contraindicated in respiratory depression , hepatic impairment also sleep apnea syndrome

USES

It is used as sedative, hypnotic, anti-anxiety muscle relaxant, anticonvulsant.

8 - NARCOTIC ANALGESIC AND ITS ANTAGONIST

Analgesics are the drugs which relive pain without causing loss of consciousness.

Analgesics can be classified as:

1) Narcotic analgesics
2) Non-narcotic analgesics(NSAID)/non steroidal anti-inflammatory drugs

1. Narcotic analgesic or opoid analgesics:

This consists of opium alkaloid and their derivatives. They act on CNS and are used as to relive moderate to severe pain.To produce analgesic effect and other pharmacological action opium alkaloids and their derivatives has to bind with opium receptors. Opoid receptors are of many types such as mu, kappa, delta, sigma, which are located within the CNS.

CLASSIFICATION

1) **Natural opium alkaloids**
   a) Phenanthrene derivatives
      Ex: morphine, thebaine, codeine
   b) **Benzyl isoquinoline derivatives**
      Ex: papaverine, noscapine
2) **Semi synthetic derivatives of opium alkaloids**
   Ex: heroin, apomorphine, dihydromorphine
3) **Synthetic derivatives**
   Ex: pethidine, pentazocine, methadone, nalbuphine

MORPHINE

Morphine is a natural opium alkaloids obtain from the unripe capsule of the poppy plant, papaver somniferum used as a powerful analgesic.

PHARMACOLOGICAL ACTIONS

1) Analgesic action: morphine is a potent analgesic and relieves pain without loss of consciousness.

2) Action of CNS: morphine produces euphoria in the presence of pain, but in the absence of pain, and in increased dose it produce sleep.

3) Respiratory action: morphine produces depression of respiration by directly depress the respiratory centre in the brain

4) Pupils: morphine produces constriction of the pupil and higher dosage it characterized by pin point pupil.

5) Emetics action: in small dose morphine produce vomiting due to stimulation of CTZ (chemo receptor trigger zone) but in higher dose it depress the vomiting center and hence there is no vomiting in poisoning.

6) Antitussive effect: morphine suppresses cough of depressing the cough center

7) ADH secretion: morphine produce release of ADH this result in decrease of urine output.

8) GIT effect: morphine decrease the mortality of the gout and produces constriction of intestinal smooth muscle and increase absorption of water and it all leads to constipation

9) CVS effect: normal dose of morphine produce no effect on heart or circulation but hypotension may be produced at toxic dose.

PHARMACOKINETICS

Given orally, absorption of morphine is slow an incomplete and undergoes extensive first pass metabolism. Quick effect is produce on subcutaneous injection. It is metabolized in liver and excreted through urine and bile.

ADVERSE EFFECTS

Acute morphine poisoning: It cause due to accidental overdose and suicidal intention, characterized by respiratory depressant, pin point pupil, hypotension, hypothermia, cyanosis, coma and death.

Treatment

- Positive pressure respiration
- Maintenance of blood pressure
- Gastric lavage with kmo_4 to remove unabsorbed drug
- Specific antidote, naloxone 0.4 to 0.8 mg i.v repeated every 10 to 15min
- Tolerance and drug dependence
- GIT effect: nausea, vomiting, constipation,
- CNS : diasphoria, mental changes
- Intolerance : skin rashes, tremors, delirium

USES

1) As an analgesic for relief of severe pain
2) Treatment diarrhoea
3) As an Antitussive

CODEINE

It is a naturally opium alkaloids codeine depress the cough centre in a low dose . it is less potent than morphine as an analgesic . it produce less respiratory depression and less constipation and less chance of addiction

It is well absorbed when given orally compared to morphine constipation is the most common side effect.

USES: It is used as antitussive.

9 - OPOID ANTAGONIST

These are the drugs which antagonized the effect of morphine and other opioid analgesic.
Ex: naloxane, naltrexone

NALOXONE

It is pure opioid antagonist. These group agents are used to antagonized the respiratory depressant sedative effect and other untoward effect and morphine like drugs.

USES

- It is used as antagonist in opioid poisoning and drug of choice for morphine overdose
- It is used to reverse neonatal asphyxia due to opioid used in labor

NALTREXONE

It is pure opoid antagonist which can be given orally it is twice as active as naloxone with three times its duration of action.

USES

- It is a drug of choice for deaddiction in patient addicted to heroin like opioids

10 - ANTI-CONVULSANTS/ANTI-EPILEPTIC DRUGS

Epilepsy is a group of neurological disorders characterized by Loss or disturbance or consciousness, characteristic body movements (usually but not always), autonomic hyperactivity. The attack called as epileptic seizures are initiated by abnormal and irregular discharges of electricity from millions of neurons in the brain depending on the area of the brain involved

epilepsy is classified into following classes

- Grandmal epilepsy
- Temporal epilepsy
- Petitmal epilepsy
- Myclonic epilepsy
- Focal epilepsy

PHARMACODYNAMIC/MECHANISM OF ACTIONS

Glutamate is the excitatory neurotransmitter and alpha-amino butyric acid (GABA) is the inhibitory neurotransmitter in the C.N.S most of the antiepileptic drugs act by inhibiting GABA transaminases and the excessive release of the excitatory neurotransmitter, glutamate

CLASSIFICATION

A) Hydrations:
   Ex: phenytoin
B) Barbiturates
   Ex: Phenobarbitone, primidone
C) Iminostilbenes
   Ex: carbamazepine
D) Succinimides:
   Ex: ethosuximides
E) Aliphatic carboxylic acids
   Ex: sodium valporate
F) Benzodiazepines:
   Ex: clonazepam, diazepam
G) Newer antiepileptic
   Ex: lamotrigine, gabapentine
H) Miscellaneous:
   Ex: trimethadione, Acetazolamide

PHENYTOIN

Phenytoin has good anticonvulsant activity and useful in generalized and partial seizers. It acts by blocking the sodium channels in the neuron of the brain.

It is well absorbed after oral administration. The onset of action is slow, but duration of action is long. It's metabolized in liver and metabolite are almost completely excreted in urine within 40 hrs.

ADVERESE EFFECTS

Giddiness, tremors, headache, insomnia, nausea, vomiting, anoxia, skin rashes

On long term use swelling of gums, bleeding, gingivitis. When used in pregnancy it causes cleft palate, hair lips and microcephaly in the foetus.

USES

In grand malepilepsy , psychomotor epilepsy

CARBAMAZEPINE

Carbamazepine has a good anticonvulsant activity and are of the most commonly used and more effective in temporal lobe epilepsy and grandmal epilepsy. It is slowly absorbed on oral administration. But overall bioavailability is 90%

ADVERSE EFFECTS

Like nausea vomiting giddiness, skin rashes , blurred vision.

USES: Temporal lobe epilepsy, grandmal epilepsy, chronic neuropathic pain and in bipolar mood disorder.

SODIUM VALPORATE

It is highly effective in petitmal epilepsy. It acts by inhibition of gamma amino butyrate transaminases and potentiate the post synaptic GABA activity. It is completely absorbed after oral administration and metabolized in liver. It can cause nausea, vomiting, hepatic damage, sedation, ataxia and allergic reaction.

USES

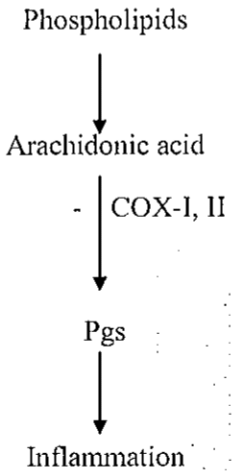
In petitmal epilepsy

11 - ANALGESIC ANTIPYRETICS/NON-OPOID ANALGESIC/NSAIDS

These are the drugs produce relief of pain and elevated body temperature. As these drugs also produce anti-inflammatory effects they are known as NSAIDS. As these drugs act without interacting with opioid receptors they are also called as non opioid analgesic.

Thus this group of drugs having 3 main actions analgesic, anti-inflammatory and antipyretics

Mechanism of action



NSAIDS act by suppressing the formation of PGs (prostaglandins) and other mediators of inflammation helps of enzymes **cyclo-oxygenase (COX)**. This arachidonic acid is liberated from damage cells during on inflammation. The prostaglandins formed are responsible for many of the features of inflammation (i.e. sweating, redness and pain)

The NSAIDS blocks the action of enzymes cox and thus prevent or reduce the production of PGS and other mediation of inflammation

CLASSIFICATION

A) NON-SELECTIVE COX-I INHIBITORS

1. SALICYLATES AND CONGENERS

   Ex: salicylates , aspirin, salicyclic acid, sodium salicylate

2. PARA-AMINO PHENOL DERIVATIVES

   Ex: paracetmol

3. PYRAZOLON DERIVATIVES

   Ex: aminopyrine, antipyrine, phenylbutazone

4. MISCELLANEOUS

   Ex: Indomethacin, ibuprofen, Diclofenac, nimusulide

B) SELECTIVE COX-II INHIBITORS:

Ex: celecoxib, rofecoxib, valdecoxib

SALICYLATES

PHARMACOLOGICAL ACTIONS :

1) Analgesic: aspirin is a good analgesic and effective only in dull achieving pain of low intensity.

2) Antipyretics: In fever salicylate bring down the temperature to normal level. But in normal individual there is a no change in temperature

3) Respiration: salicylate stimulate respiration indirectly and directly and increase respiration rate and volume and may lead respiratory alkalosis.

4) G.I.T: aspirin causes gastric irritation and produces pain, nausea, vomitting, salicylates also causes gastric ulceration and haemorrhage.

5) Anti-inflammatory action: at higher dose of 4-6gm/day aspirin act as anti-inflammatory agents and suppressed the sign of swelling erythema and pain.

6) Kidneys: in low dose it depresses uric acid excretion where as in high dose it enhance uric acid excretion.

7) C.V.S: No effects at normal dose, toxic doses produce paralysis of vasomotor centers.

8) Blood: salicylate lower erythrocytic sedimentation rate (ESR). They also increases Prothrombin level of plasma prolong bleeding time.

9) Endocrines: salicylate stimulates the release of adrenaline, adrenal medulla ACTH. They interference with the binding of thyroxine depresses the secretion of thyroid stimulating hormones.

10) Local action: salicylate having antiseptic, fungi statics and karatolytic affects

PHARMACOKINETICS

It will absorbed orally and distributed through out the body.it can cross blood brain barrier and placenta. They are metabolized in liver and excreted through urine.

ADVERSE EFFECTS:

- **SALICYLISM:** higher dose causes salicylism characterized by nausea, vomiting, dizziness, hyperventilation, drowsiness, confusion, deafness, tremors, convulsions, coma, death due to respiratory failure and C.V collapse
- **GIT disturbance:** nausea, vomiting , diarrhea, ulceration, perforation, and haemorrhage
- Prolong use can cause hepatotoxicity, intolerance leading to skin rashes

USES:

- As an analgesic and antipyretic
- As an anti rheumatic
- For local application as keratolytic , fungistatic and antiseptic

PARACETMOL

It is a para amino phenol derivative. It has analgesic and antipyretic effects but not having anti-inflammatory and uricosuric effect and also not produces gastrointestinal irritation. Paracetmol is well absorbed orally and metabolized in liver and excreted in urine.

Selective Cox-II inhibitors:

Celecoxib and rofecoxib both are highly selective cox-II inhibitors. They have good analgesic antipyretic and anti-inflammatory action. Both celecoxib and rofecoxib can cause salt and water retention leading to hypertension and edema.

They can be used in acute painful conditions like post-operative pain, dental pain, in osteo-arthritis and ruhematoided arthritis.

12 - DRUG DEPENDENCE (drug addiction and drug abuse)

Drug addiction is a state in which an individual is incapable of maintaining normal physical and mental functions without the presence of drug.

Characteristic of drug dependence are:

- An overpowering desire to take the drug
- A tendency to obtain the drug by any means.
- A tendency to increase the dose physical and psychological dependence on the body
- Harmful effect to the individual and society.

Examples:

- **opium alkaloids:**
  Ex: morphine, heroin, pethidine
- **cannabis indica**
  Ex:cocaine
- **others:**
  Ex: lysergic acid diethyl amine, barbiturates, alcohol etc

DRUG ABUSE

Drug abuse refers to the use of drug for the purposes other than approved medicinal and social use.

Ex: narcotics like morphine, pethidine, barbiturates

DRUG HABITUATION

Drug habituation is a condition which occurs due to repeated administration of drug . It is characterize by:

- Desire to take the drug.
- No tendency to increase the dose.
- Only psychic but not physical dependence on the drug
- A harmful effect if only to the individual and not to the society

13 - GENERAL ANESTHETICS

General anesthetics are the agents which produce reversible loss of sensation and consciousness.

Stages of general anaesthetics:

During the administration of general anesthetics it is necessary to control the depth of anesthetics which is related to dose. The progress of anesthesia divided into four stages.

1. **Stage of analgesia**: this stage extent from the beginning of inhalation of anesthetics up to loss of consciousness. There is a gradual depression of cortical centre and caused sensation of falling, suffocation and visual and auditory disturbance. Minor surgical operation such as dental extraction can be carried out during this stage, with continued administration of anesthetics the patient passes into the second stage.
2. **Stages of delirium or excitement:** this stage extends from loss of consciousness to the beginning of surgical anesthesia. This stage may be associated with marked excitement with increased in muscular activity and vomiting.
3. **Stages of surgical anaesthesia:**
   It has divided into four phases
   a) **Phase 1:** the pupils are constricted and eye balls are moving. The blood pressure and pulse rate are normal.
   b) **Phase 2:** the eyes balls are fixed the pupil begin dilating. There is a loss of cornea reflexes and skeletal muscular relax.
   c) **Phase 3:** pupils are dilated and light reflex lost, the B.P begins to falls. There is a marked muscle relaxant.
   d) **Phase 4:** the pupil or widely dilated, there in a shallow abdominal respiration, B.P is low.
4. **Stages of medullary paralysis :**
   It is seen only with overdose. It is the stage of medullary depression. Less action of breathing, circulation failure and death may follow.

CLASSIFICATION OF GENERAL ANAESTHETICS

a. **Inhalation anesthetics**
   Volatile liquids Ex: ether, halothane, enflurane, isoflurane
   Gases Ex: nitrous oxide, Cyclopropane

b. **Intravenous anaesthetic**
   Ex: thiopentone, propofol (non-volatile anesthetics), Ketamine, benzodiazepines.

Pre-anesthetics medication

Before the administration of anaesthetic certain drug are administrated in order to make anaesthetics safer and more pleasant and is known as pre-anaesthetic medication. It is given in order to:

a) Decrease anxiety
b) Provide amnesia for the pre-operative period.
c) Relieve pre-operative pain.
d) Reduces side effect of anaesthetics.
e) Make anaesthetic safer.
f) Reduces gastric acidity.

Drugs used are

I. **Sedative and hypnotic:**
Benzodiazepines reduce anxiety and produce sedation. Diazepam 5-10mg given orally. It also produces amnesia.

II. **Antihistamines :**
Like promethazine have sedative, antiemetic, and anti-cholinergic properties

III. **Anti emetics :**
Metoclopromide and non-steroidal are used to prevent post-operative nausea and vomiting.

IV. **Anticholinergic:** like atropine, scopolamine are used to decrease bronchial and salivary secretions

V. **Drugs that reduce acidity :** Ex: ranitidine, cimitidine

VI. **Opioids:** Ex: like morphine and pethidin provide analgesia and reduces pain and also decreases the amount of general anaesthetic required.

UNIT-III

LOCAL ANAESTHETICS

14 - LOCAL ANAESTHETICS

Local anaesthetics are drugs which block conduction of impulses in nerves, when applied locally and produce loss of sensation of pain from localized area.

CLASSIFICATION

1) **Injections**
   - Low potency
     Ex: procaine, chlorprocaine.
   - Intermediate potency
     Ex: Lignocaine, prilocaine
   - High potency
     Ex: tetracaine, bupivacaine, dibucaine
2) **Surface anaesthetics**
   Ex: cocaine, lignocaine, tetracaine

MECHANISM OF ACTION/PHARMACODYNAMIC

Local anaesthetics prevent the generation and conduction of impulses in the nerve by blocking voltage dependent sodium channels which prevents depolarization.

PHARMACOLOGICAL ACTIONS

1. **Effect on sensations:** Local anaesthetics block the sensation of pain, temperature, touch, and pressure
2. **Effect on C.N.S.:** Local anaesthetics produce stimulation of CNS which causes euphoria, restlessness and tremors
3. **Effect on CNS:** All local anaesthetics produces vasodilation, except cocaine

ADVERSE EFFECTS: Restlessness, Tremors, Hypotension, Dermatitis, Vasodilation, Euphoria

USES

- **Surface anaesthesia:** for pain due to burns, ulcers.
- **Infiltration anaesthesia :** to anaesthetize nerve ending by subcutaneous in filtration
- **Nerve block anaesthesia:** anaesthetize nerve when injected dose to specific nerve.
- **Spinal anaesthesia:** use in the case of spinal surgery.

UNIT - IV

CHEMOTHERAPHY

15 - ANTIBIOTICS

These are the chemical substance produce by microorganism having the property of inhibit the growth or destroying other microorganism.

CLASSIFICATION

1. **Antibiotics effective against gram positive bacteria:**
   Ex: penicillin, erythromycin, cephalosporins
2. **Antibiotics effective against gram negative bacteria:**
   Ex: streptomycin, Gentamycin, kanamycin
3. **Broad spectrum antibiotics (effective against both gram -ve and gram +ve bacteria)**
   Ex: tetracycline, Chloramphenicol
4. **Antibiotics effective against acid resistance bacilli**
   Ex: Rifampicin, streptomycin
5. **Antibiotics effect against cancer**
   Ex: Actinomycin-D, Mitomycin

PENICILLIN

Penicillin is the most important and oldest antibiotics. It was first extracted from penicillin notatum.

CLASSIFICATION

1) **Natural penicillin**
   Ex: penicillin -G, procaine penicillin
2) **Semi-synthetic penicillin**
   a) Acid resistance penicillin: Ex: Phenoxy methyl penicillin, Phenoxy ethyl penicillin
   b) Penicillinase resistance: Oxacillin, Cloxacillin
   c) Effective against gram +ve and gram –ve: Ex: ampicillin, amoxicillin,

PENICILLIN - G

It is also known as benzyl penicillin

PHARMACOLOGICAL ACTIONS

Antibacterial activity: penicillin is effective against gram positive cocci like streptococci, staphylococci, gonococci, and effective against gram negative like bacillus anthrus, diphtheria, and clostridium tetanus.

PHARMACODYNAMIC/MECHANISM OF ACTIONS

Penicillin interferes with the synthesis of cell wall mucopeptide of gram positive cocci. These make cell membrane of the organism susceptible to damage by solutes in the surrounding medium. Penicillin dose not interfare with the tissue cell wall synthesis in human and higher animals, so it is non-toxic to human being in higher dose also.

ADVERSE EFFECTS

Nausea, vomiting, allergic reaction, renal disturbances, haemopoitic disturbances.

USES

- Treatment of bacterial infections, meningococcal infections, streptococcal infections.
- In treatment of diptherial and tetanus.
- treatment of veneral disease like syphilis gonerrhoea

Semi synthetic penicillin

AMPICILLIN

It is effective against gram positive and gram negative organism. The anti-bacterial activity is similar to benzyl penicillin but it is more useful for gram negative bacteria.

Mechanism of action :(phramacodynamics)

Similar to that of benzyl penicillin

Adverse effect: similar to that of benzyl penicillin

Uses:

- Treatment of urinary tract infections. Biliary and intestinal infection.
- Treatment of meningitis.

Amoxicillin and clavulanic acid combination:

Clavulanic acid is a beta-lactum inhibitor which prevents the damage of beta-lactum ring of amoxicillin by beta-lactamase enzyme produced by microorganism. It also prevent bacterial resistance with amoxicillin.

Erythromycin

It is produced by fermentation product of the fungus streptomycin erythrus. Its antibacterial activity is similar to penicillin. It is also effective against penicillin resistance organism

Mechanism of action

It acts by inhibiting protein synthesis by acting on bacterial ribosome.

Adverse effects

Dermatitis, nausea, vomiting, epigastric pain

Uses

It is useful against infection caused by pencillin organism.

Streptomycin

It is obtain from streptomyces griseus. It is active against gram negative bacteria.

Pharmacological actions

Antibacterial activity: streptomycin is bacteriostatics in low concentration and bacterial activity in high concentration. The organisms which are sensitive to streptomycin are mycobacterium tuberculosis, E-coli, H-influenza, shigella, the drug is more effective at alkaline pH

Mechanism of action

Streptomycin combines with bacterial ribosome and entre in protein synthesis

Adverse effects

Local irritation: nausea vomiting, intolerance like skin rashes, dermatitis 8th cranial nerve damaged (auditory nerve)

Uses

- Treatment of tuberculosis combination with other drug.
- Urinary tract infections treatment
- Treatment of respiratory tract infection
- Treatment of acute bacillary infection.

Tetracycline

Chemically these are naphthalene derivative. The various tetracyclines are differing only slightly in structure. Ex: oxytetracycline, chlortetracycline.

Pharmacological actions

Antibacterial activity: these drugs are essentially bacteriostatics and along with Chloramphenicol act as broad spectrum antibiotics. They are effective against gram positive and gram negatives, certain fungi, rickettsia organisms.

Pharmacodynamics (mechanism of action)

Tetracycline act by different ways:

- Tetracycline inhibits certain essential enzymes required for bacterial cell wall formation.
- It inhibit bacterial protein synthesis by acting on ribosome
- Tetracycline chelate (make complex) with certain cation like calcium, magnesium which are essential for functional activity of various enzymes system of the bacteria.

Adverse effects

Skin rashes, dermatitis, nausea, vomiting, and diarrhoea

Contraindications

1) **Tetracycline is contraindicated with milk:** tetracycline make complex with calcium and magnesium present in milk which inhibit the absorption of tetracycline through intestine.

2) **Tetracycline is contraindicated during pregnancy:** it interferes with calcification in bones and teeth of fetus and administration during pregnancy.

Uses

- Use in urinary tract infection (U.T.I)
- Treatment of bacillary dysentery.
- Treatment of acne vulguris.

CHLORAMPHENICOL

It is a broad spectrum antibiotic and entirely synthetic

Pharmacological actions

Antibacterial activity: it is effective against gram positive and gram negative organism like S.typhi, E.coli, and H.influenza. It is less effective against gram positive strains of streptococci.

Mechanism of action

Chloramphenicol act by interfering with the synthesis of bacterial protein by inhibiting ribosome

Adverse effects

- Intolerance: skin rashes, dermatitis
- Bone marrow: depression charcterised by anemia aplastic anaemia, thrombocytopenia.
- **Gray baby syndrome:** it is observed in infants characterized by vomiting, anorexia, abdominal disturbances and irregular respiration.This may leads to hypothermia , cyanosis, shock and death

Uses

In typhoid fever, Treatment of U.T.I, Meningitis, whooping cough

16 - SULPHONAMIDES

Antibacterial compounds containing SO_2NH_2 (sulphanilamide) group in their side chain are called as sulphonamide.

Classification

1. used for treating systemic infections

- short acting sulphonamides
  Ex: sulphadaizine, suphafurazole, sulphadimidine
- intermediate acting sulphonamides
  Ex: Sulphamethoxazole, sulphaphenazole
- long acting sulphonamides
  Ex: sulphamethoxy pyridazine, sulphadimethoxine

2. used for gastrointestinal Succinyl sulphathiazole

Ex: sulphaguanidine, succinly sulphathiazole.

Pharmacological actions

Antibacterial activity: they are effective against variety of gram positive and gram negative organism such as streptococci, gonococci, staphylococci, meningococci, clostridium, E.coli, bacillus anthrus.

Mechanism of action

Sulphonamide had structural similarly to PABA. Folic acid derived from PABA is important in bacterial nucleoside formation.

Sulphonamide inhibits the enzyme folic acid synthetase, which is useful for the conversion of PABA to folic acid. This cause deficiency of folic acid resulting in injury to the bacterial cell wall.

Adverse effect

Intolerance, skin rashes, dermatitis, toxic hepatitis, toxic nephrititis, renal irritation, aplastic anemia.

17 - ANTI-TUBERCULAR DRUG

Tuberculosis or T.B. (Tubercle bacillus) is an infectious disease caused by various strains of mycobacterium usually mycobacterium tuberculosis. Tuberculosis usually attacks the lungs but can also affect other parts of the body. The classic symptoms are a chronic cough with blood-hinged sputum, fever, night-sweats and weight loss. The drug used for the treatment of tuberculosis is called as anti-tubercular drugs. Treatment is difficult and requires long courses of multiple antibiotics. Social contacts are also screened.

CLASSIFICATION

First line drugs

Ex: streptomycin, Isoniazid, Rifampicin, Ethambutal, Pyrazinamide

Second line drugs

Ex: Ethionamide, kanamycin, cyclocerine, para-amino salicylic acid

Isoniazid (INH)

This is the most effective against mycobacterium. This drug act only on organisms in active state of division. It inhibits phospholipids formation and damaged the cellmembrane of tubercular bacteria. It also inhibits the formation of DNA.

Adverse Effect: Intolerance (like skin rashes, fever), convulsion, loss of memory, loss of self control, peripheral neuritis, dryness of mouth

Uses: Treatment of tuberculosis in combination of other drugs.

Rifampicin

It is the one of the most effective against mycobacterium tuberculosis. It inhibit phospholipid formation and demage the cell membrane of tubercular bacteria.

Adverse effect: Skin rashes, diarrhoea, dizziness, orange red colour to urine, sweating.

Uses: Treatment of tuberculosis in combination with the other drugs.

Ethambutol

It is effective against mycobacterium resistant to Isoniazid and streptomycin.
This drug act only on organisms in active state of division. It inhibits phospholipids formation and damaged the cell membrane of tubercular bacteria. It also inhibits the formation of DNA.

Adverse Effect: Intolerance (like skin rashes, fever), convulsion, loss of memory, loss of self control, peripheral neuritis, dryness of mouth
Uses: Treatment of tuberculosis in combination of other drugs.

18 - ANTI-LEPROTICS DRUGS

Leprosy is a chronic infectious disease caused by **mycobacterium leprae**. The disease mainly affects the skin, the peripheral nerves, mucosa of upper respiratory tract and also the eyes. It multiply very slowly, symptoms can take as long as twenty years to appear. Untreated leprosy can cause progressive and permanent damage to skin, nerves limbs & eyes. The drug used for the treatment of leprosy is called as anti leprotic drugs.

CLASSIFICATION

1) Sulphones
Ex: Dapsone, Solapsone
2) Phenazine
Ex: Clofazimine
3) Antituberclosis drugs
Ex: Rifampicin , Ethionamide
4) Other antibiotics
Ex: Ofloxacin , Clarithromycin

Sulphones is a drug of choice in the case of leprosy. Dapsones are the derivative of 4-4, diamino diphenyl sulphone (DDS)

Mechanism of action:

Sulphones had structural similarly to PABA. Folic acid derived from PABA is important in bacterial nucleoside formation.
Sulphones inhibits the enzyme folic acid synthetase, which is useful for the conversion of PABA to folic acid. This cause deficiency of folic acid resulting in injury to the bacterial cell wall.

Adverse effect: Dermatitis, skin rashes, liver damage, hematurea, anorexia, vomiting

Uses: Treatment of leprosy

19 - ANTI-FUNGAL DRUGS

Disease caused by fungus is known as **mycosis**. Mycoses are common and a variety of environmental and physiological conditions can contribute to the development of fungal diseases. People are at risk of fungal infections when they are taking strong antibiotics for a long period of time because antibiotics kill not only damaging bacteria, but healthy bacteria as well. This alters the balance of microorganisms in the mouth, vagina, intestines and other places in the body, and results in an overgrowth of fungus.
Individual with weakened immune systems are also at risk of developing fungal infections. This is the case of people with HIV/AIDS, people under steroid treatments, and people taking chemotherapy. People with diabetes also tend to develop fungal infections.
Mycoses are classified according to the tissue levels initially colonized
1 Superficial mycoses:- Superficial mycoses are limited to the outermost layers of the skin and hair
2 Subcutaneous mycoses:- Subcutaneous mycoses involve the dermis, subcutaneous tissues, muscle and fascia.
3 Cutaneous mycoses:-Cutaneous mycoses extend deeper into the epidermis, and also include invasive hair and nail diseases.
4 Systemic mycoses due to primary pathogens:- Systemic mycoses due to primary pathogens originate primarily in the lungs and may spread to many organ systems
5 Systemic mycoses due to opportunistic pathogens:-Systemic mycoses due to opportunistic pathogens are infections of patients with immune deficiencies, who would otherwise not be infected. Examples of immunocompromised conditions include AIDS, alteration of normal flora by antibiotics, immunosuppressive therapy, and metastatic cancer.

Anti fungal agents are used to treat variety of fungal infections. Some of antifungal agents are active orally while others are mostly applied in the form of ointments, creams, liniments, lotions, suspension etc

CLASSIFICATION OF ANTI-FUNGAL DRUGS

1 **Topical antifungal agent** ------- Ex: Nyastatin, Hamycin, Tolnaftate
2 **Systemic antifungal agents** ------ Ex: Griseofulvin, Amphotericin-B
3 **Official fatty acid** ---------- Ex: Undecylenic acid

Nyastatin

It is **a polyene antibiotics** obtain **from streptomyces noursi**. It is effective against local fungal infections.

Mechanism of action

It binds with cell membrane producing changes in permeability and loss of cations.
Uses: Local fungal infections of mouth, skin and vagina.

Griseofulvin

It is obtain from **penicillium Griseofulvin**. It is effective against dermatophytic infection of the skin, nails and hairs
Adverse effect: Avoided in liver diseases and in pregnancy
Uses: Treatment of ring worm infection of hand, scalp, feet and body

20 – ANTI MALARIAL DRUGS

Malaria is disease caused by parasitic protozoa which belongs to the genus plasmodium transmitted through the bite of female anopheles mosquito.
The symptoms of malaria are fever with chill. The drug which are used for the treatment of malaria is known as antimalarial drugs
The four species of malaria parasite include:
Plasmodium vivax: less sever malaria
Plasmodium ovale: mild severe
Plasmodium malaria: mild severe
Life cycle of malaria parasite:
Life cycle of malaria parasite can be classified into two types
Asexual cycle: This occurs in the infected host
Sexual cycle: This occurs in the mosquito.
Asexual cycle
When female anopheles mosquitos bite a normal individual, it induces sporozites into circulation.The sporozites are immediately carried to the liver. They grow and sporulate in the liver.Developed sporozites know as merozoites are released from the liver. These merozoites enter the red blood cells and multiply there. The rupture of red blood cells releases more merozoites . These merozoites attack fresh red blood cells and multiply there fever and chill of malaria is due to the rupture of red blood cells .
Some of the merozoites differentiate into male and female gametocytes.

- **Sexual cycle**

When a mosquito bite an infected individual there gametocytes are sucked along with blood
In the gut wall of mosquito the male and female gametocytes unites to form a zygote
Zygote later developed in to ookinate and oocyst. From the oocyst sperozoites are release. The seprozoites are introduced when the mosquito bites another individual. Then asexual cycle now continues in host

Classifications

1. **Cinchona alkaloids:** quinine
2. **4-aminoquinolines:** chloroquine, hydroxy chloroquine
3. **8-aminoquinolines:** pamaquine, primaquine
4. **Acridines:** mepacrine
5. **Biguanides:** progunail, cycloguanil
6. **Diamidopyrimidines:** pyrimethamine
7. **Miscellaneous:** mefloquine, halofantrine.

Quinine

Quinine is an alkaloids obtained from cinchona bark. It is the oldest antimalarial drug still in use

Pharmacological actions

1. **Antimalarial action:** quinine suppresses the symptoms of malaria like fever with chill.

2. **Local anaesthetic effect:** quinidine on topical application produces local anaesthetics.

3. **G.I.T effect:** quinine causes GIT irritation and produces nausea and vomiting like symptoms

4. **C.V.S effect:** Quinine decreases the cardiac output which causes hypotension .

5. **Oxytocis effect:** quinine causes contration of uterus and contraindicated during pregnancy

Pharmacokinetics

Quinine is well absorbed through oral administration distributed throughout the body fluids and cross the placental barrier. Quinine is metabolized in liver and excreted through urine.

Uses: Treatment of malaria.

Adverse reactions:

Intolerance like skin rashes, thrombocytopenia, aplastic anemia.
Cinchonism characterized by nausea, headach , ringing in the ears, defness, blurred vision, colourvision, photophobia.

21 - ANTI-NEOPLASTIC AGENTS/ANTI-CANCER DRUGS/ ANTI-TUMOUR DRUGS

Neoplasms are the medical term for cancer or tumour. Cancer is defined as a rapid proliferation of abnormal cell of any tissue, leading to the dearrangment of normal body functions. Cancer is not a disease but a group of diseases affecting different organs and system of the body.
A cancer cell arises from mesodermal cells (which form bone, muscles, cartilages and tissues) is called sarcoma, and if it arises from endoderm cells (which form intesti8nal system and its associated organs) and ectoderm cells (which form skin, and appendages and nerve tissue) is called carcinoma. Leukemia and polycythemia are the types of blood cancer.
The agent which causes cancer is known as carcinogenic agents.
Cancer is more difficult to cure than bacterial infections. The drugs which are used in the treatment of cancer is known as anticancer drugs. The therapy which is utilized today is use of ionizing radiation, surgery and use of chemotherapeutic agents.

Classification:

A) Alkylating agents:

- nitrogen mustards:
  Ex: Melphalan, cyclophosphamide, Chlorambucil
- ethylenimines:
  Ex: triethylene melamine, triethylene triphosphamide
- alkyl sulfonates:
  Ex: Busulfan

B) Antimetabolite:

- folic acid antagonist
  Ex: methotrexate
- purine antagonist:
  Ex: 6-mercaptopurine
- pyrimidine antagonist:
  Ex: 5-flurouracil

C) Radioactive isotops:

Ex: radio gold, radio iodine, radio phosphorus

D) Miscellaneous:

- natural alkaloids:
  Ex: vincristine, vinblastine
- antibiotics:
  Ex: actinomycin-D, mitomycin-C
- hormones:
  Ex: androgens, progestins, corticosteroids
- others:
  Ex: procarbazine, L-asperginase, asplatin, oxiplatins.

ALKYLATING AGENTS

Mechanism of actions (pharmacodynamics):

Alkylating agents ionise to form cations. These cations transfer the alkyl group to the cell constituents such as amino, carboxyl or phosphate group.
Alkylating agents also react with nucleic acid bases and inhibit the synthesis of D.N.A. This interfere with cell division and growth.

PHARMACOLOGICAL ACTIONS:

1. Cytotoxic effect: these drugs affect rapidly normal growing cell and produce the following effects.

2. Bone marrow depression: leading to leucopenia, anemia amd thrombocytopenia.

3. Damage of intestinal mucosa: leading to ulceration, perforation and hemorrhage

4. Damage of hair follicles causing alopecia.

5. Damage of gonads: causing inhibition of spermatogenesis in male

6. Emetic effect: Alkylating agnts produce nausea and vomiting

7. Radiomimetic effect: alkylating agents produce radiomimetic effect like bone marrow depression, ulceration, foetal abnormalities, genetic changes and inhibition of antibody production

8. Immunosuppressant effect: alkylating agents suppress immune response by bloking antibody formation.

Pharmacokinetics

All Alkylating agents administered orally and quickly distributed throughout the body metabolized in the liver excreted through urine.

Uses:

Treatment of cancer such as hodgkins disease, leukemia, ovarian cancer.

22 - ANTHELMINTICS

These are drugs that expel parasitic worms from the body, by either stunning or killing them. This includes both flat worms, e.g. Flukes and tapeworms and round worms, e.g.: Nematodes. They may also be called as vermifuges and vermicides. The drug used for the treatment of worm infection are mebendazole, Albendazole, pyrantel etc

Mebendazole: It is a broad spectrum Anthelmintics and effective against round worm, hook worm, tape worm and thread worm. Mebendazole blocks the utilization of glucose uptake, leads to death of the worm and expelled from the git.

It is the safe drug and does not shows any toxicity. It is administered orally and generally available as 100mg chewable tablets

Uses: treatment of worm infection.

23 - ANTI-AMOEBIASIS

Amoebiasis is a protozoal disease caused by **Entamoeba histolytica**. Amoebiasis is due to poor hygienic conditions and is transmitted by the faecal-oral route and symptoms can range from mild diarrhea to dysentery with blood and mucosa in stool. Drugs used for the treatment of amoebiasis are metronidazole, tinidazole, Diloxanide furate, and tetracycline.

Metronidazole: Metronidazole is effective in intestinal amoebiasis. It is administered orally and completely absorbed from intestine. It is excreted through urine

UNIT - V

DRUG ACTING ON G.I SYSTEM

24 - PEPTIC ULCER

Peptic ulcer is a sour on the lining of the stomach or deudenum. Peptic ulcer in the stomach is called as gastric ulcer and that occurs in deudenum is called as deudenal ulcer.

Peptic ulcer are caused by H.Pylori and the use of Non-Steroidal Anti-inflammatory Drugs (NSAIDs) like asprin and ibuprofen. Smoking and drinking alcohol also worsen ulcer and prevent healing.

Symptoms of peptic ulcer-Feels like a dull or burning pain,occurs when the stomach is empty(between meals or during the night)

Classifications

1	**Drugs That Neutralis Gastric Acid**	
	a)Antacids	Aluminium hydroxide gel, Magnesium carbonate, magnesium trisilicate, Sodium bi carbonate
2	**Drugs That Reduces gastric Acid Secretion**	
	a) H_2 Receptor blockers	Cimetidine, Ranitidine, Famotidine, Roxatidine
	b) Proton pump inhibitors	Omeprazole, Pantoprazole, rabeprazole, Esinoprazole
	c) Muscarinic Antagonist	Pirenzipine
3	**Ulcer Protective**	Sucralfate, Bismuth Compound
4	**Ulcer Healing Agents**	Carbenoxolone, Cisapride, Prostaglandins

ANTACIDS

Antacids are the basic substance, when given orally they neutralizes the gastric acids and raise the P_H of the gastric contents. Antacids are of two types-

Systemic Antacids, when administered get absorbed into systemic circulation and may cause systemic alkalosis, e.g. sodium bicarbonate.

Non-Systemic Antacids, when administered form insoluble complex in small intestine. These are usually insoluble, very poorly absorbed, longer acting and most suitable antacids, e.g. aluminium hydroxide, magnesium trisilicate, calcium carbonate.

USES

Antacids are used in hyperacidity,peptic ulcer and reflux oesophagitis. **Digene, Gelusil, Ulcigel, gastromax** are the some antacid commercial preparations available.

H_2 RECEPTOR BLOCKERS

H_2 blockers like ranatidine, cimetidine prevent the action of histamine by acting on H2 histaminic receptor in the stomach wall and reduce gastric secretions. They can cause 90% reduction in gastric secretion by a single dose,because of these effect healing of peptic ulcer is faster.

USES

H_2 blockers are used in the treatment of peptic ulcer, gastritis, reflux-oesophagitis.

DOSE

Cimitidine: 400mg twice daily orally for 6 weeks
Ranitidine: It is more potent than cimetidine
150mg twice daily orally for 6 weeks
Famotidine: It is even more potent than ranitidine
40 mg once a day at bedtime orally for 6 weeks (or) 20mg twice daily

ADVERSE EFFECTS

Cimitidine has antiandrogenic action and can cause loss of libido, impotence and gynaecomastia in males.
Cimitidine prolongs the action of warfarin, beta blockers, phenytoin, morphine etc

PROTON PUMP INHIBITORS

The parietal cells of the stomach secrete H^+ with the help of an enzyme H^+K^+ ATPase(proton pump). This is the final step in gastric acid secretion. Proton pump inhibitors like omeprazole, Pantaprazole specifically inhibit this enzyme and there by inhibit gastric secretion.
Omeprazole is a prodrug and gets activated in the acidic environment

USES

In peptic ulcer & in severe gastroesophageal reflux

ADVERSE EFFECTS
Nausea, vomitting, G.I. disturbance

ULCER PROTECTIVE
In acidic medium (PH<4), sucralfate forms a stick, viscid gel which firmly adheres to the base of the ulcers. It remains there for over 6 hrs acting as a physical barrier and prevents contact with acid and pepsin.
One tablet is given 1hr before each meal and one at bed time for 4-8 weeks.

NURSING POINTS
- ❖ NSAIDs make ulcer bleeding and perforation more likely,particularly in elderly. Steroids in high doses may cause ulcers to develop and make their complication more dangerous. Both drugs should be avoided if possible in patients with history of peptic ulcers.
- ❖ Patient should be advised to avoid irritating foods, alcohol and stop smoking

25 - EMETICS

Emetics are drug which are used to induce vomiting and are generally used in the case of poisonings. Emetics drug show its action either by stimulating chemoreceptor trigger zone (CTZ) or by irritating the gastric mucosa.

CLASSIFICATION
A) Centrally acting – Morphine, Apomorphine
B) Peripherally acting – Musturd, Nacl solution
C) Both peripherally & centrally acting – Ipecacuanha

Apomorphine is a derivative of morphine. Given 2 to 8mg SC/IM, it produces vomiting in 5-10 min. It act by stimulating CTZ.

Ipecacuanha contains an alkalod emetine. Given 15-20ml as a syrup, it produce vomitting in 15 min. It is safe even in children.

Musturd liberates a volatile oil in the gastrointestinal tract which produces irritation and induce vomitting. Given 1 teaspoonful with water.

USES
Emetics are advised in certain cases of poisonings.

26 - ANTI-EMETICS

Anti-emetics are the drugs which are used to prevent or relieve from nausea and vomiting.

Anti-emetics show its action by acting on following mechanism:

- Acting directly on vomiting centre
- By acting on CTZ, or
- Acting peripherally.

CLASSIFICTION

Anti-cholinergics	Hyoscine, Scopolamine
Antihistamines	Cyclizine, Diphenhydramine
Neuroleptics	Chlorpromazine
Prokinetics	Domeperidone, Metoclopramide
$5HT_3$ Antagonist	Ondansetron, Granisetron

ANTI-CHOLINERGICS

Hyoscine, is very effective in motion sickness. Motion sickness or travelling sickness is due to over stimulation of the vestibular appartus, along with psychological and environmental factors. Taken 30 minutes before journey, hyoscine (0.4 - 0.6 mg) act for 6 hrs and the dose should be repeated, if the journey is longer than that.

A transdermal patch releases hyoscine, constantly over 3 days and is to be applied behind the ear. Sedation and dry of the mouth are common side effects.

PROKINETICS

Prokinetics are drugs which promote gastrointestinal motility and quicken gastric emptying. Example: Metoclopramide, domeperidone.

Metoclopramide blocks the dopamineD_2 receptor. It increases the tone of lower oesophagel sphincter and promotes gastric emptying

$5HT_3$ Antagonist

5-Hydroxy tryptamine released in the gut ia an important transmitter of emesis (vomitting). A drug like ondansetron blocks 5HT3 receptor and prevents vomitting.

It is a power full anti-emetic and can be given orally or intravenously. It especially usefull to controll vomitting induced by anti-cancer drugs or radiotherapy. It is also usefull in post-operative vomitting.

DOSE

Ondansetron: 8mg orally 0r 8mg slow i.v. over 15min. ½ to 1 hr before chemotherapy.

Granisetron is more power full than ondansetron.

27 - PURGATIVES

Purgatives are the drugs that promotes defecation (passage of stool). These drugs are used to overcome the constipation and proper evacuation of bowels.

They are also called as **laxatives** and **cathartics**. Laxative have milder action while cathartics or purgatives are more powerful drugs.

CLASSIFICATION

A) Bulk purgatives – bran, plantago seeds, agar, methyl cellulose
B) Foecal softners – liquid paraffin
C) Osmotic purgatives – magnesium sulphate, magnesium hydroxide, lactulose
D) Stimulant purgatives – bisacodyl, castor oil, senna

BULK PURGATIVES

These purgative include various natural or synthetic polysaccharide and cellulose derivatives. These substance are not absorable from gastrointestinal tract. They absorb water and swell,that increases the volume of stool, forming a large, soft and solid stool.

FOECAL SOFTNERS

Liquid parrafin is a chemically inert mineral oil. It lubricate and softens faeces. It may leak out of the anus causing discomfort, hence not preffered.

OSMOTIC PURGATIVE

Certain salts like **magnesium sulphate, magnesium hydroxide** are not absorbed in the intestine, osmotically retain water and increase the bulk of intestinal contents. They increase peristalsis to evacuate a fluid stool. They are used to prepare the bowel before surgery and in food poisoning.

STIMULANT PURGATIVE

Stimulant purgatives like **castor oil, senna** produces irritation to the gastrointestinal tract which causes increase in peristalsis movements which allow easy evacuation of bowel.

28 - ANTI- DIARRHOEALS

These are the drugs used in the treatment of **diarrhoea.** Most of the anti-diarrhoeal drugs act by diminishing the intestinal motility or by absorbing excess water from the gut, thus making the faeces more solid.

Anti-diarrhoeal drugs provide only symptomatic relief and not cure the cause. Therefore these should be used only in non-infective diarrhoea and after anal surgery..

CLASSIFICATION

A) Protective and adsorbents – light kaolin, activated charcoal, pectin
B) Astringents – tannic acids, bismuth salts
C) Miscellaneous – opium alkaloids, loperamide

PROTECTIVES AND ADSORBENTS

Protectives and adsorbents act by producing a protective coating on the gastrointestinal mucosa and prevent irritation. They also adsorb noxious substances like gases, bacteria and bacterial toxins responsible for diarrhoea.

ASTRINGENTS

Astringents are the agents which precipitate the superficial proteins and form a protective layer. This prevents irritation of the gastrointestinal tract.

OPIUM ALKALOIDS- Codeine an opium alkaloid stimulates the opioid receptor on the gastrointestinal smooth muscles to reduce peristalsis. This delays the passage of intestinal contents. Codeine phosphate 30-60mg 3-4 times a day orally.

APPETIZERS- Appetizers (stomachics): These are the drugs used for the treatment of anorexia (loss of appetite). The appetizers induce appetite by increasing gastric secretion. The agents used in the treatment of anorexia are;
Bitters: chirata, quassia
Alcohol

CARMINATIVES - These are the drugs which help in the expulsion of gases from the stomach and intestine. They are used in the treatment of flatulence and also in colics. Examples cardamom, Ginger, Asafoetida, Dimethylpolysiloxane

ANOREXIANTS: - Anorexiants are the drugs which suppress appetite. These drugs are used for the treatment of obesity. Examples Amphetamine, Methyl cellulose, biguanides

SIALOGOGUES
Sialogogues are drugs which increase salivary secretions. Sialogogues are used in dry mouth caused by fever and also to control side effects of anti-parkinsonism drugs. Examples flavored sweets, lemon drops

UNIT -VI

HISTAMINE AND ANTI-HISTAMINE

29 - HISTAMINE AND ANTI-HISTAMINE

Histamine is biological amines. It is formed by decarboxylation of histidine. It is mainly formed in biological fluids, platelets, leucocytes, basophils, mast cell of lungs, GI mucosa. Histamine after release act on two types of histamine receptor (H_1 and H_2) in our body. As such histamine has no diagnostic and therapeutic uses, it has only experimental uses.

Pharmacological actions

Blood vessels: In human it will produce vasodilation but in small species like rabbit and rat it will produce vasoconstriction.

Blood pressure: Histamine produces fall in blood pressure in human. This effect is due to vasodilation and venous polling of blood.

Triple response: On intradermal or subcutaneous, it will produce triple response:-

a) Local redness (Flush) due to dilation of capillaries and venules.
b) Local arteriolar dilation (Flare)
c) Local edema (Wheal) due to escape of fluid from the capillaries

Smooth muscle: Histamine produce constriction of smooth muscle such as intestine, bronchioles and uterus

Secretions: Histamine is a powerful inducing gastric secretions rich in acid and pepsin.

Pharmacokinetics

Histamine is well absorbed by subcutaneous and intramuscular but its absorption is very poor on oral administration. It is metabolized by methylation by monoanino oxygenase and oxidation by diamine oxidase.

Adverse effect: hypotension, redness, headache, visual disturbance, diarrhoea

Uses: Histamine does not have any therapeutics use, but it mainly used for diagnostic purpose like study of gastric secretions, diagnosis of leprosy where triple response is absent.

ANTI-HISTAMINE

Antihistamines are the drug which blocks the action of histamine, which liberate in the body. Antihistamine mainly blocks the action of histamine on H_1 receptor.

Classification

A. First generation

1. Low sedative: Ex:- Mepyramine, Triprolidine, Cyclizine
2. Moderately sedative: Ex:- Pheniramine, Meclizine, Buclizine
3. Highly sedative: Ex:- Diphenhydramine, Promethazine, Hydroxyzine

B. Second generation

Ex:- Cetrizine, Loratadine, Azelastine, Mizolastine, Astimizole

H_1 Receptor antagonists (H_1 antihistamines)

Pharmacological actions

1. Sedation: All antihistamine produces wide range of sedation. So skilled work is not advisable after taking antihistamines.

2. Autonomic nervous system: Most of the antihistamines exhibit anticholinergic effects. As a result, they produce dryness of mouth. Some antihistamines exhibit an adrenergic blocking effect.

3. Local anaesthesia: Most antihistamines posses a local anaesthetic effects.

4. Suppression of motion sickness: The antihistamines suppress motion sickness caused by vestibular disturbances. They also prevent vomiting due to labyrinthine disturbances.

5. Depressant effect on heart: Some antihistamines have a quinidine like effect on the heart. So they are useful in controlling fibrillation of the heart.

6. Drying of secretions: Antihistamines produce dryness of mouth. They also produce drying of nasal secretions and hence the use as 'cold cures'

Pharmacokinetics

Well absorbed through oral and Parentral administration. It is widely distributed throughout the body mainly in spleen, kidney, liver and excreted through urine.

Adverse effects

- Gastrointestinal disturbances like nausea, anorexia and epigastric pain.
- Cardiovascular symptoms like hypotension and palpitation.
- Blood dyscrasias like agranulocytosis, leucopenia and hemolytic anemia
- Dryness of mouth and eyes
- Sedation and drowness
- Allergy

Uses:

- Treatment of allergic disorders
- In the management of vomiting due to motion sickness
- In common cold, to inhibit nasal discharge

UNIT- VII

CARDIOVASCULAR DRUGS

30 - CARDIAC GLYCOSIDES

Cardiac glycosides are the group of chemically related drugs which having specific action on the heart. Cardiac glycosides are used for the treatment of congestive heart failure. Cardiac glycoside mainly obtained from:

1. **Digitalis:** containing cardiac glycoside digitoxin and gitoxin
2. **Stropanthus:** Containing cardiac glycosides G-stropanthus and A-stropanthus
3. **Squills:** Containing cardiac glycoside proscillaridine
4. **Toad:** only the animal source containing cardiac glycoside bufotoxin.

Cardiac glycoside containing **sugar (glycone)** and **non sugar (aglycone)** portion. Aglycone portion is responsible for the pharmacological action on the heart. The sugar portion helps in the permeability of cardiac glycosides on the myocardium.

DIGITALIS

Pharmacological action of digitalis

A) Cardiac actions

1. **Cardiac contractility:** Digitalis increases the force of systolic contraction of the heart muscle. Also it decreases the duration of systole. So in limited time, the heart contracts powerfully leading to complete ventricular emptying.
2. **Heart rate:** In individual with congestive cardiac failure (CCF), digitalis reduce the heart rate. Small dosage of digitalis produce a decrease in heart rate by stimulation of the vagus nerve.
3. **Blood pressure:** The effect depends on the initial state of the circulation. If it is low, it is returned to normal and it is not raised beyond normal.
4. **Cardiac size:** Digitalis decreases the size of both normal and failing heart, which causes reduce in cardiac output.
5. **Cardiac output:** Digitalis decreases cardiac output in normal heart and this effect is due to reduction in size. In failing heart, digitalis increases cardiac output. This effect is produced due to return of heart to normal size, increased force of contraction and complete cardiac emptying.
6. **Conduction system:** Digitalis depresses the conduction system directly. Also, the refractory is increased and the conduction rate is slowed.

B) Extra cardiac actions

1. **Kidney:** The first prominent manifestation of the effect of digitalis in edema is dieresis. This is due to:
   - Decrease in venous pressure which shifts the edema fluid into circulation.
   - Direct renal action, inhibiting the reabsorption of sodium.
2. **Gastrointestinal tract:** In toxic doses, digitalis produces nausea, vomiting and diarrhoea

Pharmacokinetics

Digitalis is adequately absorbed from the intestine. Subcutaneous or intramuscular injection is unreliable and it may produce local irritation, swelling and abscess. In blood, it is bound to plasma albumin. High concentration is found in the heart. It is eliminated very slowly through the kidney. So it is likely to produce cumulative toxicity.

Adverse effect

1. **Gastrointestinal tract:** Digitalis produce nausea, vomiting and diarrhoea.
2. **Cardiac toxicity:** Digitalis produces all types of cardiac arrhythmias like atrial tachycardia, atrial fluter, atrial fibrillation, ventricular tachycardia, ventricular flutter and ventricular fibrillation.
3. **Blood coagulation:** Digitalis increases the coagulabilty of blood.
4. **Vision:** Digitalis produces visual defects like blurred vision and colour defects.
5. **Neurological symptoms:** They are headache, fatigue, drowsiness and mental symptoms.

Uses: For the treatment of congestive heart failure**,** to control arrhythmias

31 - ANTI-ARRHYTHMATIC DRUGS

Cardiac arrhythmia is a disease characterized by disturbance in cardiac rhythm caused due to effective impulse formation or defective impulse conduction. Anti-arrhythmic are the drugs used to correct cardiac arrhythmias.

Classification

1. **Myocardial depressants:** Ex:- Quinidine, Procainamide, Lignocaine, phenytoin
2. **Sympathetic blockers:** Ex:- Propranolol
3. **Calcium channel blockers:** Ex:- Verapamil
4. **Miscellaneous:** Ex:- Potassium, Amiodorone

QUINIDINE

Quinidine is a natural alkaloid obtain from cinchona bark.

Pharmacological actions

A. Cardiac effects

1. **Depolarisation:** Quinidine slows the rate of depolarization. This is produced by depressing the entry of sodium ions into the cell. So quinidine prolongs the depolarization-repolarisation cycle.
2. **Impulse formation**: Quinidine slows the production of impulse from the SA node.
3. Excitability: Quinidine decreases the excitability of cardiac muscle. So AV impulse becomes ineffective.
4. **Refractory period:** Quinidine increases the refractory period. During refractory period the heart does not respond to weak and premature stimuli.
5. **Conduction velocity:** Quinidine slows the rate of conduction in the heart muscle. This along with decrease excitability and increased refractory period brings down the heart rate
6. **Cardiac contractility:** Cardiac contractility is decreased by decreasing the entry of calcium into cardiac muscle cells.

B. Extra cardiac effects

1. Quinidine produces a fall in blood pressure on oral or Parentral administration.
2. Quinidine produces a relaxant effect on skeletal muscles.
3. Quinidine also having Antimalarial, antipyretics and oxytocic actions.

Pharmacokinetics

Quinidine is well absorbed from GIT tract and also after intramuscular injection. In plasma it is partially bound to albumin. It is metabolized in the liver and excreted through urine.

Adverse effects

1. **GIT effects:** Nausea, vomiting and diarrhoea
2. **Cinchonism:** Characterised by giddiness, light-headedness, tinnitus, impaired hearing and blurred vision.
3. **Cerebral:** Convulsions due to effects on CNS
4. **Hypotension**

Uses: Treatment of cardiac arrhythmias.

32 - ANTI-ANGINAL DRUGS (Vasodilators)

Angina pectoris is a condition in which there is a compressing type of pain occurs in the chest. Angina pectoris may occurs due to occlusion of coronary vessels due to thrombosis or due to anaemic conditions. The coronary vasodilators are useful in the treatment of angina pectoris.

Classification of anti-anginal drugs

(Coronary vasodilators)

1. **Nitrites and nitrates:** Ex:- Amyl nitrite, Glyceryl trinitrate, Isosorbide dinitrate
2. **Beta adrenergic blockers:** Ex:- Propranolol
3. **Calcium channel blockers:** Ex:- Verapamil, Nifidipine, Diltiazem
4. **Potassium channel openers:** ex:- Nicorandil

Nitrites and nitrates

Pharmacological actions

1. **Blood vessels:** These compounds produce direct relaxant effect on arteries, veins and capillaries. All blood vessels are not equally affected. Vasodilatation is marked in coronary, cerebral and Cutaneous vessels.
2. **Smooth muscles:** Nitrites and nitrates produce relaxation of smooth muscles like intestine, biliary tract, ureter and uterus.
3. **Eye:** These drugs dilate intraocular blood vessels. So intraocular pressure may be increased.
4. **Methemoglobin formation:** Nitrites convert hemoglobin to methemoglobin. Methemoglobin combines with cyanides to form non-toxic cyanmethemoglobin. So nitrites are useful in the treatment of cyanide poisoning.

Adverse effects: Headache, flushing of face, hypotension.

Uses: Treatment of angina pectoris.

33 - ANTI-HYPERTENSIVE DRUGS

Hypertension is blood pressure elevated enough to perfuse tissues and organs. Elevated systemic blood pressure is usually defined as a systolic reading greater than or equal to **140 mm Hg** and a diastolic reading greater than or equal to **90 mm Hg** (≥140/90).

Hypertension is the most common cardiovascular disorder. Hypertensions are of two types:

1. **Primary (or essential) hypertension**, in which no specific cause can be identified, constitutes more than 90% of all cases of systemic hypertension.
2. **Secondary hypertension**, resulting from an identifiable cause, such as renal disease or adrenal hyper functions.

The drug used for the treatment of hypertension is known as anti-hypertensive drugs.

Classification of anti-hypertensive drugs

1. **ACE inhibitors:** Ex:- Captopril, Enalapril, Lisinopril, Ramipril
2. **Angiotensin antagonist**: Ex:- Candesartan, losartan, Telmisartan, Valsartan
3. **Calcium channel blockers:** Ex:- Diltiazem, Verapamil, Amlodipine, Felodipine, Nicardipine
4. **Diuretics**: Ex:- Chlorothiazide, Hydrochlorthiazide, Frusemide, Amiloride, Spironalactone
5. **Beta adrenergic blockers:** Ex:- Propranolol, Metoprolol, Atenolol
6. **Alpha adrenergic blockers:** Ex:- Prazocin, Terazocin, Phentolamine
7. **Central Sympatholytics:** Ex:- Clonidine, Methyldopa
8. **Vasodilators:** Ex:- Diazoxide, Hydralazine, Minoxidil, Nitroprusside

Angiotensin Converting Enzymes (ACE) Inhibitors: ACE inhibitors prevents the conversion *of Angiotensin I* to *Angiotensin II*, responsible for vasoconstrictions and increased B.P. ACE inhibitors effective in all types of hypertension.

Calcium Channel Blockers: The contractility of cardiac and vascular smooth muscles is dependent on extra cellular calcium concentration. The calcium channel blockers interfere with the entry of calcium into myocardial and vascular smooth muscles to produce dilation of arterioles to reduce blood pressure.

Diuretics: Diuretics enhance salt and water excretion and helps in reducing blood pressure. Thiazide diuretics (Chlorothiazide, Hydrochlorthiazide) are the first line drugs in mild to moderate hypertension. And they also potentiate the effect of other antihypertensive drugs.

34 - DRUGS USED IN ATHEROSCLEROSIS (Lipid Lowering Agents)

Atherosclerosis is a disease characterized by narrowing of blood vessels. Atherosclerosis is associated with increase level of plasma lipids like *cholesterol* and *triglycerides*.

Classification

1. **Drugs lowering triglyceride:** Ex:- Clofibrate, Gemfibrozil
2. **Drugs lowering cholesterol:** Ex:- Cholestyramine, Dextrothyroxine, Probucol
3. **Drugs lowering triglyceride and cholesterol:** Ex:- Nicotinic acid

CLOFIBRATE

Clofibrate lower the plasma level of triglyceride by two ways:

1. Inhibiting synthesis of cholesterol in liver
2. Inhibiting the transfer of triglyceride from liver to plasma.

Clofibrate orally administered and well absorbed from GIT, metabolized in liver and excreted through urine.

Adverse effects: Nausea, vomiting, diarrhoea, allergy and fluid retention

Uses: Management of atherosclerosis.

UNIT - VIII

DRUGS ACTING ON BLOOD AND BLOOD FORMING ORGANS

35 - COAGULANTS

Coagulants: These are the substances which promote coagulation and are indicated in the treatment of severe hemorrhagic conditions.

CLASSIFICATION

1. **Vitamin K**
   a) K1 (from plants): Ex:- Phytonadione
   b) K2 (from bacteria): Ex:- Menaquinone
   c) K3 (synthetic): Ex:- Menadione
2. **Miscellaneous:** Ex:- Thrombin, Fibrinogen, Tissue extract

THROMBIN

It is a sterile protein substances prepared from human plasma and is freeze dried. Thrombin is affected by air heat and light. Hence it is a stored in the atmosphere of nitrogen in glass container which is sealed so as to prevent from micro organisms and moisture. The container kept at a temperature2 – 8^{O}C and protected from light.

Uses : It is used as an coagulant:

a) **Topically** to control mirror bleeding , due to superficial cut and injuries.
b) **Orally** to prevent gastro intestinal bleeding.

36 - ANTICOAGULANT

Anticoagulants are the drugs used to reduce the coagulation of blood. Anticoagulant agents are usually administered patient with acute myocardial infarction and the one undergoing treatment of pulmonary and venous thrombosis.

CLASSIFICATION

a) **Parentral anticoagulant**
   Ex: Heparin
b) **Oral anticoagulant**
   Ex: warfarin sodium, phenindione.

HEPARIN is a mixture of mucopolysaccharides of molecular weight ranging from 3000 to 40000.
Source: Lung of intestinal mucosa of ox, pig or sheep.
Uses: To prevent post operative deep venous thrombosis.
To prevent clotting during open heart surgery.

WARFARIN SODIUM: is a oral anticoagulant. It was originally used as rat poison. It acts by interfering with synthesis of vitamin K dependent clotting factors in liver. It is well soluble and so can be administered by all routes. Haemorrhage is the main toxicity and it can be controlled by vitamin K.
Uses: To prevent post operative venous thrombosis.
To prevent myocardial infractions.
Used as rodenticides.

Haemostatics

These are the substances used to stop bleeding from a local approachable sites. They are most effective on oozing surface like tooth shocket, open wounds. Examples:

1. Absorbable gelatin sponge
2. Oxidized cellulose
3. Astringents (tannic acid)

Plasma Expanders

Plasma expanders are the high molecular weight substances which exert colloidal osmotic pressure when infused intravenously and maintain the plasma level when there is a loss of blood due to haemorrhage.

Examples:

Blood products: Whole blood, Plasma, Plasma proteins

Colloidal plasma substitute: Dextrans, Gelatin

Fluid plasma substitute: Normal saline, dextrose solution

UNIT - IX

DRUGS ACTING ON KIDNEY

37 - DIURETICS

Diuretics are the drugs which increase the rate of urine output.
They are useful to treat:

a) Different types of edema like cardiac edema, edema of pregnancy, renal edema.
b) Hypertension along with antihypertensive drugs.
c) To reduce intraocular pressure.

CLASSIFICATION

Based on mechanism of actions			Based on potency		
1	Promoters of glomerular blood flow	Xanthines	1	Weak diuretics	Osmotic diuretics Xanthine diuretics Carbonic anhydrase inhibitors
2	Inhibitors of tubular reabsorption	Thazides Acetazolamide	2	Moderately potent diuretics	Thiazides
3	Antagonist of aldosterone	Spirnolactone	3	Very potent diuretics (High ceiling diuretics)	Frusemide Bumetanide Ethyacrynic acid
4	Osmotic diuretics	Mannintol Glycerol Isosorbide	4	Potassium retaining diuretics	Triamterene Amiloride
5	Potassium retaining diuretics	Triamterene Amiloride			
6	Loop of henle diuretics	Frusemide Ethacrynic acid			

Thiazide diuretics: These drugs act by inhibiting the reabsorption of salt (including Na, Cl, k) and water from the kidney tubules. Thus more fluid and salts pass out of the tubules and causes a dieresis. The exact site of action is distal tubule part of the kidney tubules.

Adverse effects: Hyperglycemia, Hypokalaemia (potassium has to be supplemented along with them), Increased uric acid level.

Uses:

1. To relieve edema caused by congestive cardiac failure, and renal disease
2. The first line drugs in mild to moderate hypertension

Loop diuretics: These drugs also inhibit reabsorption of Na+, K+, Cl- from the kidney tubules. They act at a different site in the kidney tubules and are more powerful than the thiazides. The exact site of action is loop of Henle part of the kidney tubules.

Uses: Congestive cardiac failure, left ventricular failure with lung edema, nephritic syndrome, and developing renal failure

Carbonic anhydrase inhibitors: These drugs (Acetazolamide) inhibit the activity of the enzyme carbonic anhydrase which present in the renal tubules, gastric mucosa, pancreas, eyes and RBCs. This enzymes catalyses the reaction

$$H_2O + CO_2 \xrightarrow{\text{Carbonic anhydrase}} H_2CO_3$$

$$H_2CO_3 \longrightarrow H^+ + HCO^-_3$$

In kidney this H^+ is secreted in exchange of Na^+. Inhibition of carbonic anhydrase causes less production of H^+ ⟶ less exchange of Na^+ ⟶ more excretion of Na+ and water.

In eyes its inhibition causes reduced formation of aqueous humour. Thus can be used in glaucoma to lower intraocular pressure.

Osmotic diuretics: These drugs (mannitol, urea) increase the concentration of the fluid (urine) within the tubules thus exerting an osmotic effect in the renal tubules. This prevents the reabsorption of salt and water from the tubule and causes dieresis.

They are mild diuretics and are less used in treating edema but they are useful in reducing cerebral edema.

UNIT - X

DRUGS USED IN RHEUMATIC DISORDERS AND GOUT

38- DRUGS USED IN RHEUMATIC DISORDERS AND GOUT

Rheumatic disorders are inflammatory or degenerative disorders that affect mainly the musculoskeletal system i.e. joints, muscles, ligaments, tendons and bursae. These are basically chronic autoimmune disorders like rheumatoid-arthritis, osteoarthritis, ankylosing spondylitis, myositis etc.

Drugs used in rheumatic disorders are:

1. NSAIDs like asprin, Indo-methacin, ibuprofen
2. Corticosteroids
3. Cytotoxic drugs like azathioprine, Chlorambucil, Methotrexate
4. Anti-malarials like Chloroquine, hydroxy Chloroquine

Gout is a painful inflammatory condition that is characterized biochemically as a disorder of **uric acid metabolism** and clinically by hyperuricaemia and recurrent attacks of acute arthritis.

If the condition remains untreated over a period of years, deposition of sodium urate crystals may occour in joints (gouty arthritis), subcutaneous tissue (tophi), and renal parenchyma (gouty nephropathy).

Drug treatment in gout is used for two purpose:

1. To relieve an acute attack e.g.
    - Colchine
    - NSAIDs
    - Corticosteroids
2. To decrease the amount of uric acid in the body by :
    - Increasing excretion of uric acid by using uricosuric agents like probenecid, sulfinpyrazone
    - Inhibiting the synthesis of uric acid e.g. allopurinol

UNIT - XI

HORMONES AND HORMONES ANTAGONIST

39 - INSULIN AND GLUCAGON

The pancreas synthesizes and secretes two hormones **insulin** and **glucagon**. Both are mainly concerned with carbohydrates metabolism and blood sugar level. Insulin tends to lower the blood sugar level whereas glucagon tends to raise the blood sugar level.

INSULIN

Insulin is a hormone produced by beta cells of islets of **langrehans**. It is a polypeptide containing 51 amino acids arranged in 2 chains namely A & B having 21 & 31 amino acids connected each other by two disulphide bridge. It lowers the concentration of glucose in the blood by:

- Stimulating the uptake and utilization of glucose by the peripheral tissues (e.g. skeletal muscles).
- Stimulating conversion of glucose to glycogen in the liver and muscle.
- Increasing the production and decreasing the breakdown of fats and proteins.

Secretion of insulin from β cells is mainly controlled by blood glucose level. A high blood glucose level stimulates β-cells to secrete insulin and vice-versa.

Insulin deficiency leads to a disease condition known as diabetes mellitus, characterized by hyperglycemia, glycosuria, hyperlipemia and –ve nitrogen balance.

There are two types of diabetes mellitus

Type-I or insulin-dependent diabetes mellitus (IDDM)

Type-II or Non- insulin-dependent diabetes mellitus (NIDDM)

Source of insulin

Insulin is available in many preparations which vary in both in their duration of action and their purity. Although insulin can be prepared synthetically, commercially insulin is obtained from pork or beef pancreas. Because of their non-human origin they can produce allergic reactions. Purification of this insulin can reduce the chance of allergic reactions. Now highly purified insulin are available, which are less allergic than previous insulins.

Preparations of insulin

Preparation of Insulin	Onset of action	Duration of action	Group
Soluble (acidic) insulin	1 hr.	8-12 hrs	Short acting insulins.
Soluble (neutral) insulin	1 hr.	8-12 hrs.	
Insulin zinc suspension (amorphous)	1 hr.	12 hrs.	
Isophan insulin (Insulin+protamine)	2 hrs.	24 hrs.	Intermediate acting insulins.
Biphasic insulin (Beef insulin + pork insulin)	2 hrs.	24 hrs.	
Insulin zinc suspension (mixed) (30% amorphous+70% crystalline)	2 hrs.	24 hrs.	
Insulin zinc suspension (crystalline)	6 hrs.	36 hrs.	Long acting insulins
Protamine zinc insulin	6 hrs.	36 hrs.	

Adverse effects: hypoglycemia, allergic reactions

Uses: Insulin is used to control blood glucose level in diabetes mellitus

40 - ORAL HYPOGLYCAEMIC AGENTS (ORAL ANTIDIABETIC DRUGS)

These are the drugs administered orally for the treatment of Type-II diabetes. These agents lower blood glucose level on oral administration.

Classification

1. **Sulfonylureas**
   - 1st generation: Ex:- Tolbutamide, Chlorpropamide, Tolazamide
   - 2nd generation: Ex:- Glibenclamide, Glipizide, Gliclazide, Glimepride
2. **Biguanides:** Ex:- Phenformin, Metformin
3. **Meglitinides:** Ex:- Repaglinide, Nateglinide
4. **Thiazolidinedidones:** Ex:- Troglitazone, Rosiglitazone, Pioglitazone
5. **Aplha glucosidase inhibitors:** Ex:- Acarbose, Miglitol

Sulfonylureas

Sulfonyureas are compound chemically related to sulphonamide. Sulfonyl urea orally effective in presence of functional pancreas. These drug lower blood sugar level on oral and parenteral administration.

Mechanism of action

Sufonylureas reduce the blood glucose level by:

1. Stimulating the release of insulin from the pancreatic β cells
2. Increasing the sensitivity of peripheral tissues to insulin.
3. Increasing the number of insulin receptors.
4. Suppressing gluconeogenesis in the liver.

Pharmacokinetics

Rapidly absorbed from oral administration, well distributed , metabolized in the liver and excreted through urine.

- **Adverse dffects**
- Bitter and unpleasant taste
- Nausea, vomiting, diarrhoea, muscle weakness
- Decreased in body weight.

Biguanides

Biguanides lower blood glucose level by insulin like effects on the tissues. Mechanism of action is not clear. They-

- Suppress hepatic gluconeogenesis.
- Inhibit glucose absorption from the intestines.
- Stimulates peripheral uptake of glucose in tissues in the presence of insulin.

Phenformin is not used because it causes lactic acidosis. Metformin is safer with lower incidence of lactic acidosis. It does not cause hypoglycaemia since it is an **euglycaemic** agent and does not reduce the blood glucose level below normal.

Adverse effects: Nausea, diarrhoea, and metallic taste. Anorexia is the advantageous as it helps in reducing body weight.

Glucagon

It is a hormone produced by the α-cells of the islets of langrehans of pancreas. It tends to raise blood sugar level by causing the liver to release glucose.

Uses:

- Severe hypoglycaemia: glucagon can be used in the emergency treatment of severe hypoglycaemia due to insulin.
- Diagnostic uses: for diagnosis of IDDM
- Before radiology of the bowel: as glucagon relaxes intestines.

41 – SEX HORMONES AND ORAL CONTRACEPTIVES

The **gonads** produce hormones which are known as sex hormones.
Male sex hormones are called androgens. Most important androgen is **testosterone**
Female sex hormones are **estrogens** and **progesterone**.

Androgens

These are the substances which are responsible for the development of secondary sexual character in male. Most potent androgen is testosterone which is produced by the interstitial cells of the testis.

Testosterone actions

Testosterone is required for normal spermatogenesis and maturation of spermatozoa. It is also responsible for the development of secondary sex character in males including distribution of hair, deepening of the voice, muscularity, and enlargement of penis and seminal vesicles. They also have an anabolic effect on protein metabolism, promoting muscle development, skeletal growth, and prevent osteoporosis.

Uses

- Testosterone is used in the treatment of testicular hormone deficiency.
- Some time used in breast cancer as antiestrogen

Androgen Antagonist

Cyproterone : It blocks the action of male hormones, thus act as a potent antiandrogen. It is used in the treatment of female hirustism and hypersexuality in the male.

Estrogen

These are the female sex hormones, mainly secreted from the graffian follicle of the ovary, in the influence of follicular stimulating hormone(FSH) from the anterior pituitary.

Actions: Estrogens have number of actions

- Responsible for development of female secondary sex characters
- Proliferation of the endometrium
- Sensitization of uterine muscle for various stimulating agents
- Increase in duct tissue of breast
- Inhibition of production of prolactin by the pituitary

Uses

- Used as replacement therapy in some dysmenorrhoea and menstrual disturbances in combination with a progestogen.
- As a replacement therapy in peri- and post menopausal women to relieve sign/ symptoms of menopause e.g. hot flushes, emotional disturbance, dyspareunia, and osteoporosis.
- Used in contraceptive pills along with progesterone.
- Can be used in prostatic carcinoma and breast carcinoma.
- Applied locally in senile vaginitis and vulvitis.

Progesterone

It is a female sex hormone, secreted by the **corpous leuteum** in the later half of menstrual cycle, under the influence of **leutinizing hormone (LH).** If pregnancy occours corpous leuteum remains functional and secretes progesterone during early pregnancy (1st trimester). In 2^{nd} and last trimester of pregnancy progesterone is produced by placenta.

Action

- It causes further thickening of endometrium which is already sensitized by estrogens, to facilitate the implantation of the fertilized ovum
- Development of secondary phase in endometrium (later half of menstrual cycle)
- Reduces excitability and motility of uterus.
- If fertilization occours then maintenance of the fetus in the uterus during pregnancy.
- Proliferation of acini in the breast, along with estrogens it prepares breast for lactation.

Uses:

- Most commonly used in contraceptive pills with or without estrogens. Sometimes also incorporated in intra-uterine contraceptive devices (progestasert)
- Sometimes used in uterine (endometrial) carcinoma.

Oral Contraceptives

Contraceptive drugs are substances which prevent conception. Most oral contraceptives in use are a combination of an estrogen and progesterone. Rarely only progesterone can be used. Oral contraceptive prevents conception by:

- Somehow inhibiting ovulation.
- Making the endometrium unsuitable for implantation of ovum.
- Changing the character of cervical mucus- this reduces sperm motility.

The usual estrogen in this combination is Ethinyl Oestradiol and the commonest progesterone is norethisterone or levonorgestrel.

Only **progesterone** containing pills can also be used but they are less effective contraceptive as compared to combination pills.

Different preparations of oral contraceptives contain:-

1. **Progestogen only**
   Norethisterone 350µmgs
   Levonnorgestrel 30 µmgs
2. **Combined preparations**
   Ethinyloestradiol : 20-35 µmgs + Norethisterone 500-1000 µmgs
   Ethinyloestradiol : 30-50 µmgs + Levonnorgestrel 50-200 µmgs
   Ethinyloestradiol : 30-50 µmgs + Norgestrel 300-500 µmgs

   Most of the oral contraceptives are taken for 21 days, starting on the fifth day of the normal cycle. This is followed by a seven days interval, during which withdrawal bleeding occurs, before starting the next course.

UNIT - XII

AUTONOMIC NERVOUS SYSTEM

42 - INTRODUCTION

The autonomic nervous system **(ANS)** is a part of nervous system which supplies the viscera of the body e.g., respiratory system, cardiovascular system, G.IT, various smooth muscles and secretory glands.

The **ANS** consists of two major subdivisions

- The sympathetic
- The parasympathetic.

The sympathetic and parasympathetic mostly exhibit mutual antagonism.

Neurotransmitter in case of sympathetic system is non-adrenalin. So, it is also known as adrenergic system. While in case of parasympathetic nervous system neurotransmitter is acetylcholine so, it is also known as cholinergic system.

Adrenergic receptors:

- They are stimulated by non-adrenaline and are of two types α_1 and α_2 and β
- The α-receptors are mainly excitatory in nature(except in the intestine where they are inhibitory).
- The β-receptors are mainly inhibitory in nature (except in the heart where they are excitatory).
- These are two types β_1 and β_2.
- β_1 receptor (excitatory) located mainly in heart.
- β_2 receptor(inhibitory) located mainly in the bronchial, vascular and uterine smooth muscles.

Cholinergic receptors:

- They are stimulated by acetylcholine and are also of two types.
- Muscarinic receptors: they are mainly present at parasympathetic neuroeffector junction.

Nicotinic receptors: they are mainly present in autonomic ganglia, adrenal medulla, CNS, and skeletal neuromuscular junction.

43 - PARASYMPATHOMIMETIC OR CHOLINERGIC DRUGS

Parasympathomimetic are the agents which produce effects similar to that of parasympathetic nerve stimulation. They act at the same sites as the acetylcholine (i.e. muscranic receptors and nicotinic receptors). Thus they stimulate the parasympathetic system and mimic the actions acetylcholine.

It is an acetic acid ester of choline and is the physiological stimulant of both muscarinic and nicotinic receptors. It is synthesized within the cholinergic neurons.

Acetyl CoA + choline → Acetylcholine + CoA

It is destored by enzyme cholinesterases, into acetic acid and choline.

CLASSIFICATION:

1. Ester of choline

EX: acetylcholine, methacholine, carbachol

2. Cholinomimetic alkaloids:

Ex: pilocarpine, muscarine.

3. Anticholinesterases:

a) Reversible: physostigmine, Neostigmine

b) Irreversible: di-isopropyl flurophohate, tetraethyl pyrophosphate.

Pharmacological actions:

Muscarinic actions: They are present at postganglionic parasympathetic nerve endings. The three subtypes of muscarinic receptors are M_1, M_2, M_3,

- Increased secreations (e.g., sweat, intestinal, pancreas etc)
- Smooth muscle contraction (eg: bronci, GIT, bladder)
- Decreases heart rate (bradycardia) and contractility.
- Constriction of pupil(i.e miosis)

Nicotinic actions:

- Both sympathetic and parasympathetic ganglia (N_N, N_M receptor)
- Contraction of skeletal muscles.
- Stimulation of sympathetic and parasympathetic ganglia and stimulation of the adrenal medulla.

Uses

It is not used therapeutically, because:

- Of its widespread action throughout the body.
- of its short duration of action , as it is rapidly destroyed by enzyme cholinesterase.
- Its oral administration is totally ineffective.

Anticholinesterase drugs

These drugs inhibit the action of enzyme cholinesterase, and thus prevent the breakdown of acetylcholine. Thus they potentiate the effects of acetylcholine. Thus they potentiate the effects of acetylcholine.

Classification of anticholinesterases:

1) Reversible anticholinesterases:

Ex: physostigmine, Neostigmine, pyriodstigmine, edrophonium, benzypyrinium.

2) Irreversible anticholinestearases:

Ex: diisopropylflurophosphate, tetraethyl pryrophosphate, parathion, Malathion.

1) Reversible anticholinesterases:

All the reversible anticholinestreases except physostigmine are synthetic compounds.

Pharmacological actions:

- **Eye:** on eye the anticholinesterase agents produce miosis, spasm accommodation abd decrease in intraocular tension.
- **Gastrointestinal tract:** the effect of anticholinesterases on G.I tract are identical . they produce increase in motility and also secreations of G.I tracts.
- **Skeletal muscle:** these drugs produce stimulation followed by depression.
- **Secreations**: bronchial, lacrimal, slivary, gastric and prancreatic secretions are increased.

Therapeutic uses:

- For reducing intraocular tension in glaucoma.
- For diagnosis and treatment of myasthenia gravis.
- For atropine poisoning.

2) Irreversible anticholinesterases :(organo phosphorous compounds)

These compounds have prolonged action and high toxicity. So they have limited use

ORGANO PHOSPHOROUS COMPOUNDS POISONING

As organophosphates are used as agricultural and domestic insecticides, poisoning by them is quite common. Poisoning may be occupational (as while spraying insecticides), accidental, or due to suicidal intention. Symptoms result from vomiting, abdominal cramps, diarrhoea, miosis, sweating, increased salivary, tracheobronchial, and gastric secretions and bronchospasm, hypotension, muscular twitching, weakness, convulsions and coma. Death is due to respiratory paralysis.

44 - PARASYMPATHOLYTICS DRUGS OR CHOLINERGIC BLOCKING AGENTS

These drugs block the muscarinic effect of acetylcholine (hence also known as antimuscranic drugs) all antimuscranic drugs are competitive antagonists(they compete with acetylcholine for muscarinic receptors).

Atropine is a protype of this group of drugs. The pharmacological effects of all other antimuscarinic drugs are very much similar to that of atropine.

Classification of drugs:

i) Belladonna alkaloids:

Ex: atropine, scopolamine (hyosine)

ii) Semi synthetic substitutes of belladonna alkaloids:

Ex: homatropine, atropine methylnirate, scopolamine methylbromide,

iii) Synthetic substitutes of belladonna alkaloids:

Ex: methantheline, Propantheline, oxyphenonium

ATROPINE

It is obtained from atropa belladonna and datura stromonium. It is reversibly blocks the muscarinic receptor. Acetylcholine cannot stimulate these blocked receptors. Thus it blocks all the muscarinic actions of acetylcholine.

PHARMACOLOGICAL ACTIONS

1) Antisecretory action: it inhibits secretions from glands of respiratory tract, GIT, sweat glands and lacrimal glands. So it is used in ulcers.
2) Vagolytic action: it inhibits vagal tone and increases heart rate. So it can be used in

vasovagal syncope, bradycardia, and partial heart block.

3) It blocks the actions of acetylcholine in CNS. So it can be used in Parkinsonism and motion sickness.
4) Its antisecretory action and bronchodilator actions are useful in bronchial asthma.
5) It decreases tone, motility and secretion of GIT. So can be used in several diarrhoea.
6) It causes dilatation of pupil (i.e. mydriasis) and paralysis of accommodation (i.e. cycloplegia) So can be used to dilate pupil during testing errors of refraction.
7) Its antispasmodic action can be used to relieve intestinal biliary or urinary colic.
8) It can be used as an **antidote in Anticholinesterases** (organ phosphorous) and mushroom poisoning.

PHARMACOKINETICS

The belladonna alkaloids are well absorbed on oral and Parentral administration. Atropine crosses the placental barrier and also is secreted in milk. It is partly excreted unchanged by kidneys.

ADVERSE EFFECTS

Dry mouth, Tachycardia, Flushing, Constipation, Increase in body temperature, ataxia, delirium .

USES

- In peptic ulcers to decrease the secretion of acid
- In organophosphorous poisoning
- As pre-anaesthetic medication.

45 - SYMPATHOMIMETICS DRUGS

These are the drugs having actions similar to that of adrenaline or sympathetic stimulation.
There are three important endogenous catecholamine's namely:Noradrenalin, adrenaline, and dopamine.
They are synthesized in the body from phenylalanine

CLASSIFICATION

1) Catecholamine's

Ex: adrenaline, noradrenalin, dopamine , isoprenaline

2) Non-catacholamines

Ex: ephedrine, amphetamine, methylamphetamine, hydroxyamphetamine.

Adrenaline (epinephrine)

Adrenaline is found in nervous tissue, adrenal medulla and chromaffin cell scattered throughout the body. It is a protype sympathomimetics agents, it stimulate both α, β receptors.

Pharmacological actions

Its most important actions are on cardiovascular system, respiratory system and metabolism.

1) Cardiovascular system:

- because of it's α, β actions adrenaline increases heart rate and force of contraction.
- Increases in cardiac output
- Increased systolic blood pressure.
- Adrenaline also causes vasodilation
- Diastolic pressure falls.

For these actions adrenaline is used in syncope and cardiac arrest.

- Because of its cutaneous vasoconstrictor effect it can be used to stop bleeding in case of bleeding gums. This action is also used to prolong the absorption of local anaesthetic agents.

2) Respiratory system: it's α actions causes decreased bronchial secretions and its β_2 action causes bronchodilatation. These two effects reduce bronchial resistance. For this reason adrenaline is drug of choice in bronchial asthma.

3) Metabolism: adrenaline overall increases catabolism and causes hyperglycaemia, hyperlactacidemia and rise in body temperature.

4) Eyes: adrenaline causes mydriasis and decreases intraocular tension

5) Skeletal muscles: it facilitates neuromuscular transmission i.e. anti-fatigue action

6) Glands: secretions from most of glands is inhibited by adrenaline

Because of all the above actions (specially CVS and respiratory system) adrenaline is first drug of choice in allergic emergencies like serum sickness, oedema, anaphylactic shock etc)

Uses

- in the syncopal attacks of stokes
- In allergic disorders
- In bronchial asthma.

46 - SYMPATHETIC BLOCKING DRUGS

Sympathetic blocking agents (adrenergic blocking agents) inhibit the response to sympathetic nerve stimulation

Classification:

Alpha adrenergic blocking agents

1) **Both α_1, α_2 blockers:** phenoxybenzamine, phentolamine, ergot alkaloids.
2) **α_1 blocker:** prazosine.
3) **α_2 blocker:** yohimbine.

Beta adrenergic blocking agents

1) Both β_1 and β_2 blockers: propranolol, sotolol, nodolol, timolol.
2) β_1 blockers : atenolol, metaprolol
3) β_2 blockers: butoxamine.

PHARMACOLOGICAL ACTION OF BETA ADRENERGIC BLOCKING AGENTS (Propranolol)

1. C.V.S: Beta blockers decrease heart rate, force of contraction and cardiac output. Blood pressure falls

2. RESPIRATORY TRACT: Blockade of β_2 receptors in bronchial smooth muscle causes increase I airway resistance-may precipitate acute attack in asthmatics.

3. EYE: Many β blockers reduce intraocular pressure by decreased secretion of aqueous humour

ADVERSE REACTIONS

- Sudden hypotension, bradycardia
- Nausea, vomiting, constipation, bronchospasm
- Allergic reactions
- Prolonged used of Propranolol may produce fatigue, muscle cramps, lethargy, hallucinations, and mental depression.

USES

- Angina pectoris
- Cardiac arrhythmias
- Myocardial infraction
- Hypertension
- Thyrotoxicosis
- Pheochromocytoma
- Chronic open-angle glaucoma