

1. General Pharmacology

a. Introduction and definitions—Health, Drug, Pharmacology, Pharmacokinetics and Pharmacodynamics, Sources of drugs.

Health- As defined by World Health Organization (WHO), it is a “State of complete physical, mental, and social well being, and not merely the absence of disease or infirmity”.

Pharmacology- Pharmacology is derived from two Greek words- Pharmacon (drug), logos (a discourse or treatise) - It is a science that deals with drugs. It includes a detailed study of the history, properties, physiological effects, mechanism of action, absorption, distribution, metabolism, excretion and uses of a drug.

Drug- The word drug derived from French word- *Drogue* (a dry herb). A drug is defined as any substance which is used to cure, diagnose or prevent a disease.

Divisions of Pharmacology-

a. Materia Medica- It is the study of preparation, properties, uses and effects of a drug. It is an old branch of Pharmacology.

b. Pharmacokinetics- (What the body does to a drug). It is the study of absorption, distribution, metabolism and elimination (ADME) of drugs.

c. Pharmacodynamics- (What a drug does to the body?) It is the study of the biochemical and physiological effects of drugs and their mechanisms of action.

d. Neuropharmacology- It is the study of the effects of drugs on CNS and ANS functioning.

e. Psychopharmacology- It is the study of the effects of drugs on mood, sensation, thinking and behavior.

f. Pharmacogenetics- It is the study of unusual effects of drug produced in individuals with gene defect.

g. Pharmacogenomics - It is the study of the role of genetics in drug response.

h. Pharmacoepidemiology- It is the study of the effects of drugs in large number of people.

i. Dental Pharmacology- It is the study of drugs commonly used in the treatment of dental disease.

j. Posology- It is the study of dosages of drugs.

k. Clinical Pharmacology- It is the scientific study of drugs in man. The efficacy and safety of a drug is studied in patients and healthy volunteers.

l. Chemotherapy- It deals with the effects of drugs on micro-organisms and parasites which occur in a living organism. It also includes the treatment of cancer.

m. Toxicology- It deals with poisonous effects of drugs, detection of poison and its treatment.

Sources and active ingredients of drugs-

a. Plant drugs - The following is the list of plant drugs and sources.

Quinine- Cinchona bark

Vincristine- Vinca plant

Digoxin, digitoxin- Digitalis purpurea

Morphine- *Papaver somnifera*

Atropine- *Atropa belladonna*

Nicotine- Tobacco

Caffeine- Coffee, tea

b. Drugs from microorganisms- Many life-saving drugs are obtained from fungi, moulds and bacteria e.g. penicillin from *Penicillium notatum*, chloramphenicol from *Streptomyces venezuelae*, griseofulvin (an anti-fungal drug) from *Penicillium griseofulvum*, neomycin from *Streptomyces fradiae* and streptomycin from *Streptomyces griseus*.

b. Animal drugs- Some drugs are still obtained from animal source. For example: Insulin, extracted from pork and beef pancreas, is used for the treatment of diabetes mellitus. Thyroid powder is used for treating hypothyroidism. Heparin is used as an anticoagulant. Hormones are used as replacement therapy. Vaccines (cholera, T.B., smallpox, polio) and sera (antidiphtheria and antitetanus) are used for prophylaxis/treatment.

c. Mineral drugs- Minerals (naturally occurring inorganic solid substances with chemical formula) or their salts are useful therapeutic agents. For example: Ferrous sulphate is used in iron deficiency anaemia. Magnesium sulphate is employed as purgative. Magnesium trisilicate, aluminium hydroxide and sodium bicarbonate are used as antacids for hyperacidity and peptic ulcer. Kaolin (aluminium silicate) is used to treat diarrhoea. Radioactive isotopes of iodine, phosphorus, gold are employed for the diagnosis/ treatment of diseases particularly malignant conditions.

d. Synthetic drugs- At present majority of drugs used are prepared synthetically, such as aspirin, oral anti-diabetics, antihistamines, amphetamine, chloroquine, chlorpromazine, general and local anaesthetics, paracetamol, phenytoin, synthetic corticosteroids, sulphonamides and thiazide diuretics. Advantages of synthetic drugs are: They are chemically pure. The process of preparing them is easier and cheaper. Control on the quality of the drug is excellent.

e. Drugs from DNA recombinant technology- Hepatitis vaccine, human insulin. The following are the various active ingredients of drugs.

a. Alkaloids- Alkaloids are a group of naturally occurring chemical compounds that contain mostly basic nitrogen atoms. Eg.Caffeine, atropine, morphine, quinine. Alkaloids are basic substances, and combine with an acid to form salt. These salts are soluble in water and are used in medicine. Eg Caffeine citrate, morphine sulphate, atropine sulphate, quinine sulphate.

b. Glycosides- Glycosides are a class of molecules in which, a sugar molecule (glycon) is bonded (ether linkage) to a “non-sugar” (aglycone/genin) molecule. The glycone part is essential for the pharmacokinetic aspect of aglycone. The aglycone part is responsible for the pharmacological effect. Eg. Digitoxin, digoxin, sennoside A, quabain.

c. Oils –Oil is a non-polar neutral viscous liquid. In plants oils are present in the following forms-

Volatile oil (essential oil)- Volatile oil is a concentrated hydrophobic liquid containing volatile aroma compounds from plants. Eg-Peppermint oil, clove oil, ginger oil, eucalyptus oil.

Fixed oil- These are the glycerides of oleic acid, palmitic acid and stearic acid. Eg. Olive oil, castor oil, cotton seed oil. Fixed oils from animal source are cod liver oil, shark liver oil, butter.

Waxes- Waxes are composed of fatty acids combined with monohydric alcohol. Eg. Wax, beeswax.

Mineral Oil- These are mixture of hydrocarbons obtained by fractional distillation. Eg. Hard, soft and liquid paraffin.

d.Tannins- These are non-nitrogenous plant constituents, and have an astringent action. Eg- Pyrogallol tannins (occur in oak apple), pyrocatechol tannins (occur in eucalyptus).

e.Gums- They are exudates of plants. Chemically they are polysaccharides, and on hydrolysis yield simple sugars. Eg- Agar, tragacanth.

f. Resins- Resins are produced by oxidation and polymerization of volatile oils. Eg. Oleoresin, gum - resin (asafoetida), myrrh, balsams (benzoin).

b. Routes of drug administration (1h)

A route of administration in Pharmacology and Toxicology is the path by which drugs, fluid, poison, and other substance is taken into the body.

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

I. Local routes-The drugs are applied locally for local effects. Systemic absorption of the drug from these routes is minimal or absent. Hence systemic side effects or toxicity are absent or minimal.

1. Topical- This refers to external application of the drug to the surface for localized effect.

a. Skin- Drug is applied as ointment, cream, lotion, paste, powder, spray, etc.

b. Mucous membrane-

Mouth and pharynx- As paint (Mandle's paint), lozenges (strepsils), mouth washes and gargles (povidone iodine gargle).

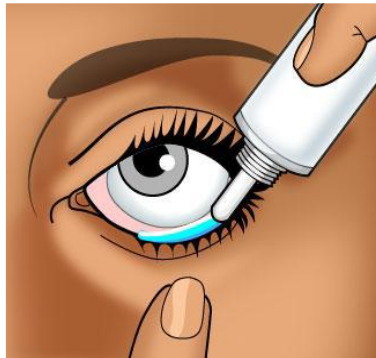


DEFINITION :

Gargles are aqueous and hydro alcoholic solution which is used to treat or prevent throat infection.



Eyes, ear and nose- As drops, ointments, irrigation, nasal spray, Otrivin nasal spray to reduce nasal congestion. chlopamphenicol eye ointment.

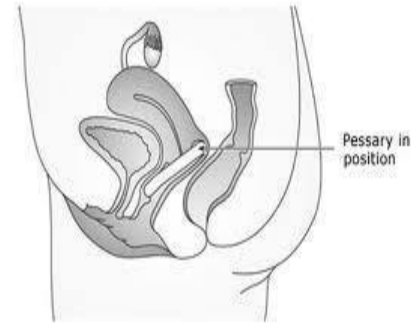
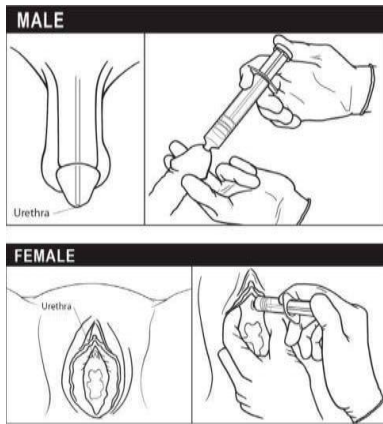


Gastrointestinal tracts- Non absorbable drugs are given orally. Magnesium hydroxide, sucralfate, neomycin.

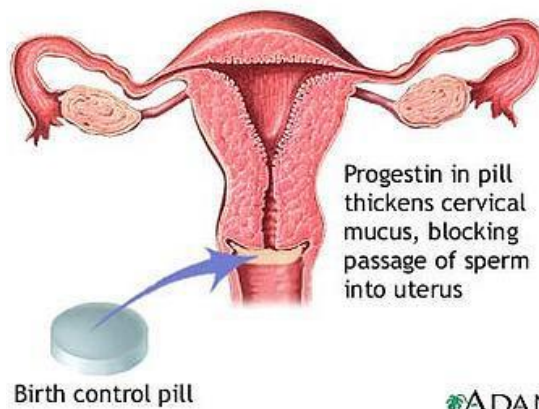
Bronchi and lungs- As inhalations, aerosols- e.g. salbutamol, cromolyn sodium.



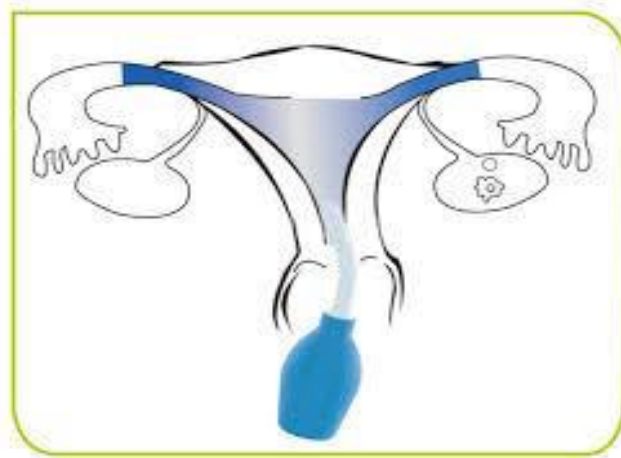
Urethra- As jellies E.g. Lidocaine (xylocaine)- For the surface anaesthesia of male or female urethra.



Vagina- As pessaries-(clotrimazole vaginal pessaries), vaginal tablets (estrogens vaginal tablets), vaginal inserts (spermicide), vaginal creams (ovestin), vaginal douches (betadine vagina douche).



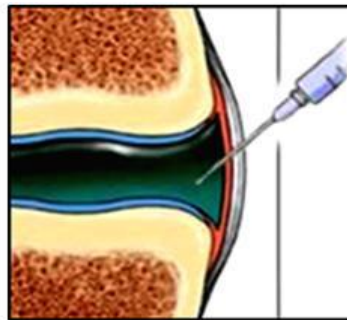
ADAM.



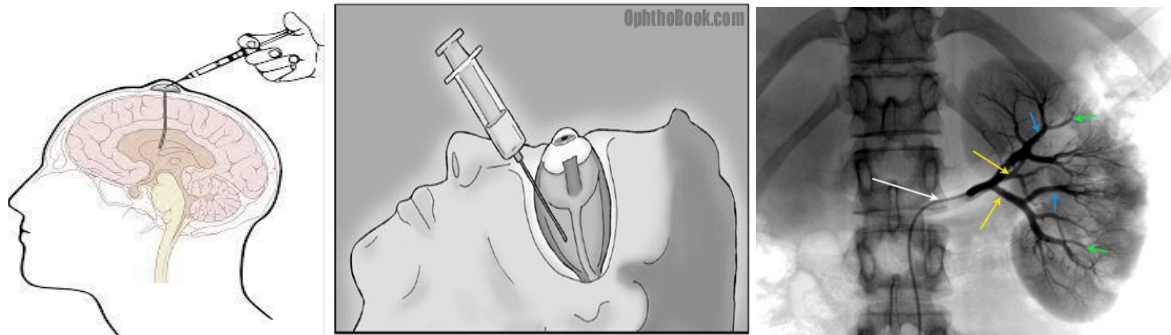
Anal canal- Ointments, suppositories- (hydrocortisone suppositories).

2. Deeper tissues- Using syringe and needle drug is administered to deeper tissues, but the drug is not absorbed into systemic blood circulation.

Intra-articular injections- Intra-articular hydrocortisone injection in osteoarthritis.



Intrathecal injection- Intrathecal administration of vincristine in cancer chemotherapy.



Retrobulbar injection- Injection in to the space behind the globe of eye balls. Ocular anaesthesia for cataract surgery.

3. Arterial supply- Intra-arterial route is used in angiography- Angiography is the x-ray (radiographic) study of the blood vessels. An angiogram uses a radio-opaque substance, or contrast medium, to make the blood vessels visible under X ray- cerebral, pulmonary, coronary, renal angiography.

II Systemic routes-

1. Oral Route: - In this route the drug is placed in the mouth and swallowed. It is also called per oral (p.o.). The solid dosage forms- tablets, capsules, powders, spansules, moulded tablets and liquid dosage forms- syrups, mixtures, elixirs, emulsions, etc can be given orally.

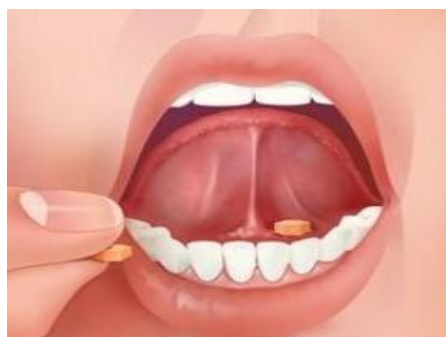
Advantages of oral route

- Convenient - Can be self administered, pain free, easy to take
- Absorption - Takes place along the whole length of the gastro intestinal tract.
- Cheap - Compared to most other par-enteral routes

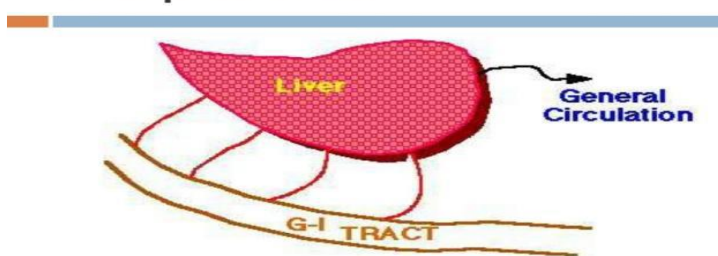
Disadvantages of oral route

- Action is slower and thus not suitable for emergencies.
- Unpalatable drugs-e.g. paraldehyde are difficult to administer.
- May cause nausea and vomiting.(e.g. emetine)
- Not suitable for uncooperative/un-conscious/vomiting patients.
- Some drugs are destroyed by gastric juice- e.g. insulin, vasopressin.
- Sometimes inefficient - only part of the drug may be absorbed
- First-pass effect- drugs absorbed in to the liver by portal circulation and get metabolized before entering into the systemic circulation.

2. Sublingual or buccal route-The tablet or pellet containing the drug is placed under the tongue or crushed in the mouth and spread over the buccal mucosa. It is not swallowed. The drug is absorbed from the buccal mucosa. Drugs given by sublingual routes are- nitroglycerine, methyltestosterone, isoprenaline, clonidine.



First-pass Effect



Advantages-

- Quick absorption and action.
- Drug enters directly into blood circulation.

- c. No first pass metabolism. (FPM).
- d. Action can be terminated by spitting out the tablet.
- e. No drug destruction by the gastric juice.

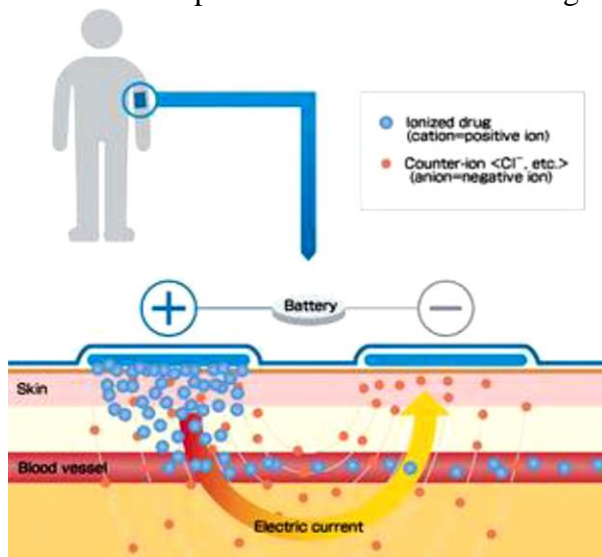
Disadvantages-

- a. Not available for all drugs.
- b. All drugs are not absorbed by this route.
- c. Not suitable for unpalatable drugs.

3. Rectal route of administration- Certain irritant and unpleasant drug can be put into rectum as suppositories or retention enema for systemic effect. It is preferred for the patient with recurrent vomiting. Drugs given rectally are – aminophylline, indomethacin, paraldehyde, diazepam, etc.

4. Transcutaneous- Highly lipid soluble drugs can be applied over the skin for slow and prolonged absorption. It is further classified as

a. Iontophoresis- It is a technique of introducing ionic medicinal compounds into the body through the skin by applying a local current. e.g. salicylates. Anode iontophoresis is used for positively charged drugs and cathode iontophoresis is used for negatively charged compounds. The force of repulsion between similar charges drives the drug deep into the tissues.



Iontophoresis

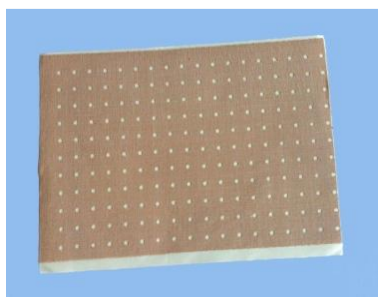


Jet injection

b. Inunction- It is rubbing the drug on the skin. The drug gets absorbed and produces systemic effects. E.g. nitroglycerin ointment for angina.

c. Jet injection- This method does not require a syringe. So it is painless. Using a gun like instrument with a micro-fine orifice, the drug solution is projected as a high velocity jet. This method is useful for mass inoculation.

d. Adhesive patches- It is a transdermal preparation. It is available in the form of adhesive unit. It delivers the drug slowly. So it produces prolonged systemic effect. E.g. belladonna plaster.



Adhesive patch



5. Inhalation-Volatile liquids and gases are given by inhalation for systemic action. The drugs administered by this route are- general anaesthetics, amyl nitrite.

6. Parenteral route of administration. (*par*-beyond, *enteral*-intestinal)

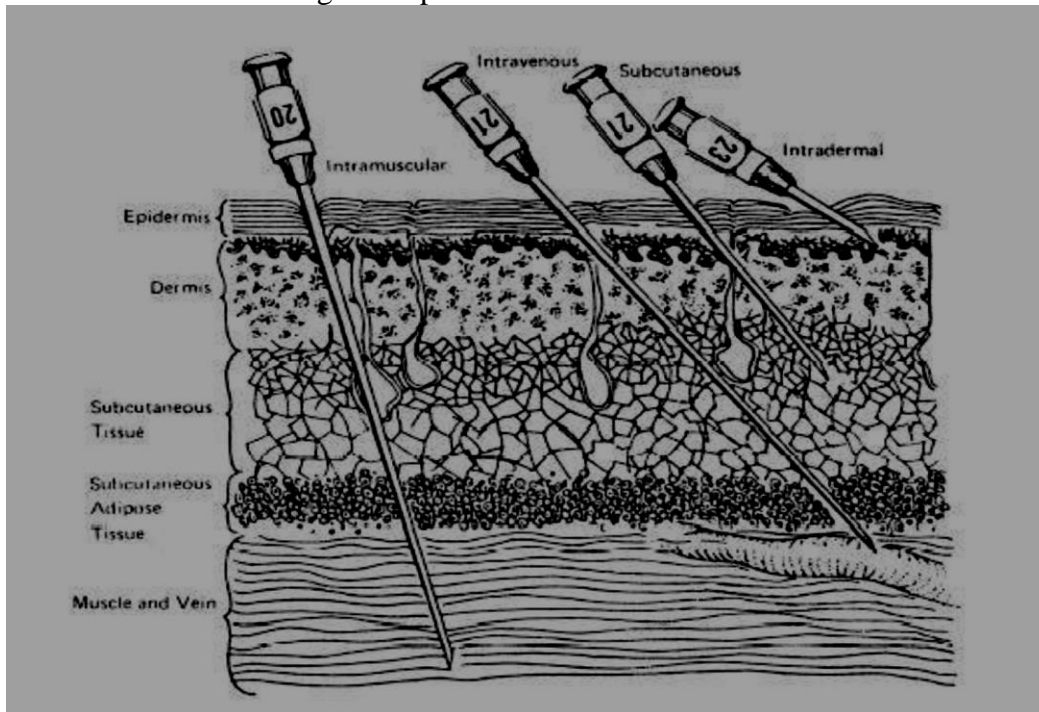
In this route of administration the drug does not pass through the gastrointestinal tract. It directly reaches to the blood. The drugs are administered by injections. Injections can be given in many different ways e.g.intradermal (id), subcutaneous(sc), intramuscular (im), intravenous(iv), intraperitoneal (ip),etc.

Advantages-

1. Injections can be given even in unconscious, uncooperative patients.
2. Quick absorption-hence suitable in emergencies.
3. There is no GIT related problems.
4. Dose requirement is less compared to oral route.
5. Accurate dose adjustment is possible.
6. No first pass metabolism.
7. Drugs having unpleasant smell or taste can be given.

Disadvantages-

1. Inconvenient- injections can be painful, costly.
2. Tissue injury, inflammation and may cause infection.
3. Costly.
4. Self medication is difficult.
5. Withdrawal of the drug is not possible.



a. Intradermal injection (id)- Only 0.1 to 0.2ml can be administered by id route. The drug is injected into the layers of the skin. It is painful. E.g. vaccines (BCG vaccine), test dose of drugs (penicillin), are given by id injections.

b. Subcutaneous injection (sc)- A subcutaneous injection is an injection administered into the fatty area just under the skin. Absorption from sc route is slow but steady. SC injection should not be given in patients with shock, because during shock, blood flow to subcutaneous tissue is reduced. Drugs usually given by sc route are insulin, adrenaline, and local anaesthetics.

c. Intramuscular injection (im)- In this route of administration the drug is given into the skeletal muscles like deltoid, triceps etc. Drug once reaches to the muscles, absorbs into the

blood. Mild irritant or non-irritant drugs can be administered as there is less supply of sensory nerves. But muscles are more vascular, hence absorption is faster. Up to 5ml can be given by im route. Eg many vaccines and antibiotics are administered by IM route.

d. Intravenous injection (iv) - After iv injection drug enters directly in to the blood and goes to the heart. Large volume can be given. Onset of action is very quick and the bioavailability is 100%. The dose requirement is small. Withdrawal of the drug is not possible. E.g cimetidine, ampicillin, digoxin inj etc.

e. Intra peritoneal (ip)- In this route the drug is injected in to the peritoneal cavity. By this route fluids like glucose and saline can be given to the children. It is also used for peritoneal dialysis. It is one of the common routes for administering the drugs to rats and mice.

c. Absorption of drugs

Absorption is the movement of a drug into the blood circulation. Intravenous route does not involve absorption, and there is no loss of drug. Hence the bioavailability is 100%. Drug administration by other routes may result in only partial absorption and thus, lower bioavailability.

Passage of drug across cell membrane- The cell membrane acts as a biological barrier. The following are the processes by which a drug can cross biological membrane.

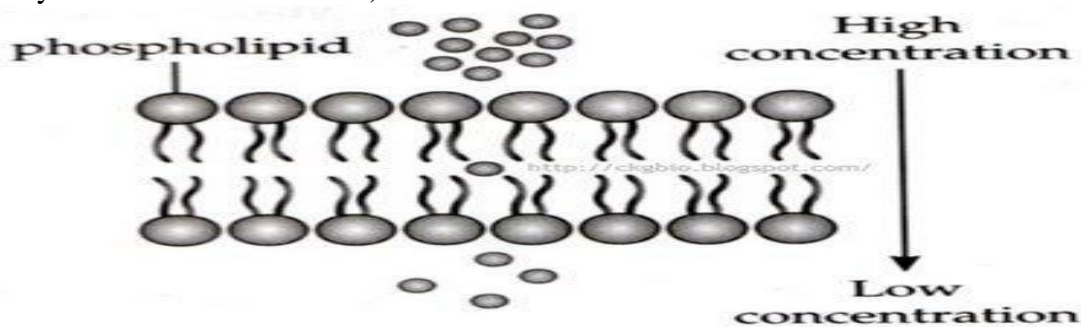
1. Passive transport and 2. Specialized transport.

1. Passive transport- This transport is energy independent and no utilization of ATPs. The four types of passive transports are diffusion, facilitated diffusion, filtration and osmosis.

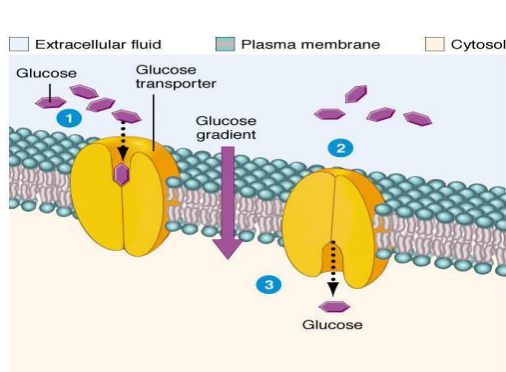
a. Diffusion (simple)- Diffusion is the net movement of drug molecules from an area of high concentration to an area with lower concentration. The difference of concentration between the two areas is termed as the concentration gradient, and diffusion will continue until this gradient has been eliminated. Diffusion across the cell membrane depends on concentration gradient and lipid solubility. Lipid solubility depends on ionization. Un-ionized drugs are more lipid soluble and are better absorbed (more reabsorbed in the kidneys and less excreted). Ionized drugs are less lipid soluble and are less absorbed (less reabsorbed in kidneys and more excreted).

Ionization depends on pH of drug and pH of the medium (surrounding fluid). If the pH is the same the drug remain unionized and become more lipid soluble and absorbed better. Acidic drugs like aspirin, barbiturates, etc. are better absorbed from the stomach. Alkaline drugs like morphine, atropine, chloroquine are better absorbed from the small intestine.

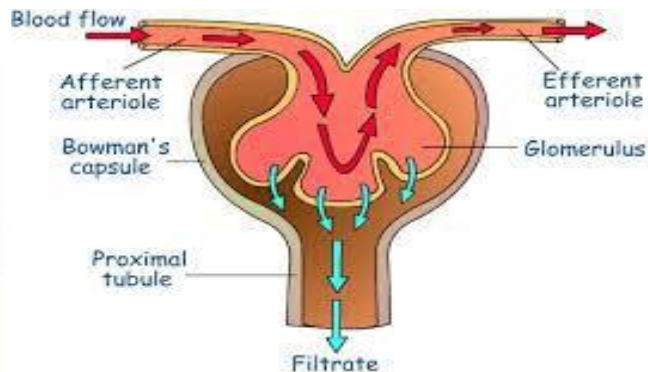
If pH is opposite-> drug is ionized-> less lipid soluble-> less absorption (e.g. alkaline drugs are poorly absorbed in the stomach).



b. Facilitated diffusion (carrier- mediated diffusion) - It is the movement of drug molecules across the cell membrane via special transport proteins that are present within the cellular membrane. Many large molecules, such as glucose, are insoluble in lipids and too large to pass through the membrane pores. Therefore, it will bind with its specific carrier proteins, and moved through the cellular membrane.



Facilitated diffusion



Glomerular filtration

c. Filtration- Filtration is movement of water and drug molecules across the cell membrane due to hydrostatic pressure. Depending on the size of the membrane pores, filtration takes place. For example, the membrane pores of the Bowman's capsule in the kidneys are very small and only albumin (the smallest protein) may pass through these pores. The membrane pores of liver cells are large, most of the drugs pass through these pores and they get metabolized. Capillaries in the CNS have tight junctions called BBB.

d. Osmosis- Osmosis is the movement of water molecule through the cell membrane (semi permeable membrane) from the region of higher water concentration to the region of less water concentration is called osmosis.

2. Specialized transport- Specialized transport of drug across the cell membrane requires carrier proteins. The drug forms a complex with the carrier proteins at the outer surface of the cell membrane and then transported across the cell membrane to the inner surface and the drug is released from the drug carrier complex. These are of two main types- active transport, and endocytosis.

a. Active transport- In active transport, the drug molecule penetrates in the lipid bilayer membrane from lower concentration to the higher concentration of solutes against the concentration gradient with the expenditure of energy and with the help of carrier proteins. There are two types - Primary active transport and secondary active transport.

Primary active transport- (direct active transport). It directly uses energy to transport molecules across a membrane. The energy used in this type of active transport is ATP. The ions Na^+ , K^+ , Ca^{2+} and H^+ are transported by primary active transport using carrier protein and ATP.

Secondary active transport (co-transport)- In secondary active transport, a molecule is moved down its electrochemical gradient as another is moved up its concentration gradient.

There is no direct coupling of ATP. Examples - Sodium-proton or sodium – calcium co transporters.

c. Endocytosis- Endocytosis is the movement of materials into a cell via membranous vesicles. Endocytosis requires the expenditure of energy (ATP). There are 3 types-phagocytosis, pinocytosis and receptor mediated endocytosis.

Phagocytosis- Phagocytosis is also known as cell eating. This transport is utilized by large molecular weight drugs e.g. Uptake of Vit B12 along with intrinsic factor.

Pinocytosis - Pinocytosis is also known as cell drinking. This process requires a lot of energy in the form of ATP. Fat soluble vitamins, folic acid enter the cells by pinocytosis.

Receptor mediated endocytosis- It is also called clathrin-dependent endocytosis. The receptor present on the cell membrane binds with the specific ligand. This ligand-receptor gets ingested using clathrin molecules.

Bioavailability-Bioavailability is the fraction of an administered dose of unchanged drug that reaches the systemic circulation. When a medication is administered intravenously, its

bioavailability is 100%. However, when a medication is administered via other routes (such as orally), its bioavailability decreases (due to incomplete absorption and first-pass metabolism) or may vary from patient to patient (due to inter-individual variation). Bioavailability is one of the essential tools in pharmacokinetics, as bioavailability must be considered when calculating dosages for non-intravenous routes of administration.

Bioequivalence-It is condition in which different formulations of the same drug or chemical are equally absorbed when taken into the body.

d. Factors affecting absorption of drugs

Factors affecting bioavailability- (same- factors affecting drug absorption)

Factors affecting drug absorption-

1. Lipid solubility- Absorption of drugs depends on lipid solubility. Absorption is more if the drug is lipid soluble. Lipid solubility depends on ionization. Un-ionized drugs are more lipid soluble and are better absorbed. Ionized drugs are less lipid soluble and are less absorbed.

2. Molecular size- Smaller the molecular size of the drug rapid is the absorption.

3. Particle size - Particle may be composed either of a single molecule or more than hundred molecules. Larger is the particle size, slower will be the diffusion and absorption and vice versa.

4. Degree of ionization- Un-ionized drugs are more lipid soluble and are better absorbed (more reabsorbed in the kidneys and less excreted). Ionized drugs are less lipid soluble and are less absorbed (less reabsorbed in kidneys and more excreted). Ionization depends on pH of drug and pH of the medium (surrounding fluid). If the pH is the same the drug remain unionized and become more lipid soluble and absorbed better. (e.g. acidic drugs like aspirin, barbiturates, etc. are better absorbed from the stomach. Weakly alkaline drugs like morphine, atropine, chloroquine are better absorbed from the small intestine.

5. Physical forms- Drugs may exist as solids, liquids or gases. Gases are rapidly absorbed than the liquids, while liquids are rapidly absorbed than the solids. Thus the drugs in syrup or suspension form are rapidly absorbed than the tablets or capsules. Volatile general anaesthetics absorbed rapidly through the pulmonary route.

6. Chemical nature-Chemical nature is responsible for the selection of the route of drug administration. Examples- Heparin is a drug with large molecular weight, and is cannot be given orally, insulin is degraded if given orally, benzyl penicillin also get degraded if given orally. Hence these drugs should be administered parenterally to avoid the inactivation.

7. Dosage forms- Dosage forms affect the rate and extent of absorption. Example –nitroglycerin when given by sublingual route disintegrates rapidly but stays for a shorter duration. When it is given orally, it disintegrates slowly and stays for longer duration.

8. Concentration - If the drug concentration increases the drug absorption across the cell membrane also increases.

9. Area of absorptive surface- Most of the drugs are given orally because of the large area of absorptive surface, so that greater absorption occurs. Organophosphate compounds (insecticides) are highly lipid soluble and poisoning can occur even by absorption through skin.

10. Vascularity - If the vascularity (blood supply) is more, the drug absorption also increases. In shock, the blood supply decreases, hence the drug absorption decreases. During IM inj massage increases vascular supply and drug absorption.

11. pH – Acidic pH favours the absorption of acidic drugs and basic pH favours the absorption of basic drugs.

12. Presence of other substances- Food can increase or decrease the drug absorption. Examples- Atorvastatin is better absorbed when taken with the food. Milk decreases the

absorption of iron. Vitamin C enhances the absorption of iron. Milk decreases the absorption of tetracycline.

13. GI motility- The drug absorption gets altered in diarrhoea or constipation.

14-Diseases- In diarrhoea drug absorption decreases, malabsorptive syndrome- decreases drug absorption, in achlorhydria – decreases the absorption of acidic drugs.

e. Drug Distribution

Drug distribution- It is a process whereby an absorbed drug molecule moves away from the site of absorption to other areas of the body. Once a drug enters the blood stream; it gets distributed to other tissues like fat, muscle, and brain tissues. .

Phases of distribution-

Phase I- It is the initial phase. It depends on **a. Circulating status-** If circulatory status is good, distribution is also good.

b. Regional blood flow- The organs like heart, liver, brain and kidney have more blood supply. Hence more amount of drug gets distributed to these areas.

Phase II- In this phase, the drug is distributed to entire body. It depends on

a. Regional blood flow- Muscles are more vascular than adipose tissue. Hence more amount of drug is distributed to muscle than adipose tissue.

b. Diffusibility- If the drug is lipid soluble, then it will be enter intracellular compartment.

c. Equilibrium- Movement of drug will continue till equilibrium is reached or stores are saturated.

d. Selective distribution- Certain drugs gets concentrated in some organs than blood plasma. This can cause toxicity (chloroquine in retina). It becomes beneficial also (CQ-liver).. Examples- CQ-liver, CQ-retina, digoxin-heart, tetracycline and heavy metals-bones and teeth, thiopentane Na-adipose tissue, etc.

Phase III- Redistribution-E.g. in case of thiopentane sodium rapid onset of action is due to high lipid solubility and high blood flow to the brain. This is followed by gradual distribution and storage by adipose tissue. The plasma concentration of thiopentane sodium falls. The drug leaves the brain and thus there is short duration of action. On repeated administration the duration of action increases, because the stores get saturated and drug come out of the brain slowly.

Body compartments- The body is divided into number of compartments. When the drug is absorbed, it enters the blood circulation (vascular compartment). The drug leaves the vascular compartment through capillary pores and enters the extra- vascular space. Some drugs can enter the cell and some drugs cannot .The extra-vascular space can be divided into intra-cellular and extra-cellular compartments.

Approximate size of the body compartment-(as % of body weight)

Vascular-5%

Extracellular compartment (interstitial fluid)-16%

Intracellular compartment- 30-40%

Others-2-4%

Thus body fluids are 60% of body weight. Hence a person weighing 60kg, total body fluid will be approximately 36L.

e. Drug distribution

Factors affecting distribution-

1.pH and solubility- The differences between intracellular and extracellular pH is very small (7.0 : 7.4). In general this factor does not influence the distribution of drugs to a great extent. However, weak acids concentrated more extra-cellularly while weak bases concentrated more intra-cellularly. Alteration in pH of extracellular or intracellular fluid can change distribution of drugs.

2. Placental barrier- Placental membrane is lipoidal and allows lipid soluble drugs and restricts hydrophilic drugs. Lipid soluble drugs e.g. opioids, general anaesthetic agents, digitalis, alcohol, sedatives - hypnotics readily cross the placental barrier.

3. Blood brain barrier (BBB) - If a drug crosses the blood brain barrier, it will affect the CNS. Normally drugs can pass through the pores of the capillaries easily, but the capillaries in the brain have tight junctions. This works as a barrier and prevents the drugs from passing into the CNS. This is called blood brain barrier. Only lipid soluble drugs can enter the CNS by diffusion. Capillary permeability is altered in meningitis and drugs can easily cross the BBB. Lipid soluble drugs enter the brain and CSF easily. Lipid insoluble drugs do not cross the BBB readily.

5. Plasma protein binding (PPB) - All drugs do not bind with plasma proteins. Acidic drugs bind with albumin. Alkaline drugs bind with globulin. Examples of acidic drugs - Aspirin, phenytoin, Examples of alkaline drugs- Quinidine, propranolol. Plasma protein binding is usually through weak bonds. PPB affects the drug distribution as PPB drug remains in the vascular compartment.

f.)Bio-transformation (metabolism) – It is the process whereby a substance is changed from one chemical to another (transformed) by a chemical reaction within the body. The main site of drug metabolism is liver; others are-kidney, intestine, lungs and plasma.

Metabolism of drugs may lead to the following-

a. Inactivation- The active drug is converted into inactive form. Examples- pentobarbitone, morphine, chloramphenicol.

b.Active metabolite from an active drug- Many active drugs gets converted into active metabolite. The effects observed are sum of parent drug and its active metabolite. Examples-

Active drugs Active metabolites

Phenacetin - paracetamol

Digitoxin - digoxin

Imipramine - desipramine

Codeine – morphine

Trimethadione - dimethadione (antiepileptic)

3. Activation of inactive drug. Many inactive drugs get converted into active metabolites. Such a drug is called a pro-drug.

Pro-drug Active metabolites

Levodopa - dopamine

Proguanil - proguanil triazine (antimalarial)

Becampicillin - ampicillin

Fluouracil - fluorouridine monophosphate (anticancer)

Mercaptopurine- methylmercaptopurine ribonucleotide (anticancer)

4. Drug is detoxified- Toxic form is converted into less toxic form.

5. Drug may be converted into water soluble form. This enhances its excretion.

Main processes of drug metabolism-

Phase I- Non synthetic reactions

1. Oxidation 2.Reduction 3.Hydrolysis 4.Cyclization 5.Decyclization.

Phase II- Synthetic reactions

1.Conjugation–glucouronide conjugation 2. Sulphate conjugation 3.Acetylation 4.methylation 5. Conjugation with glycine 6.glutathione conjugation 7.nucleotide synthesis.

Phase I- These are non synthetic reactions. Metabolites may be active or inactive.

1. Oxidation- This reaction involves addition of oxygen/negatively charged radical or removal of hydrogen/positively charged radical. It is the most common pathway of metabolism of drugs. It can occur by microsomal or non-microsomal enzymes. Various oxidative reactions are:

a. N-hydroxylation e.g. Sulfanilamide to p-hydroxylamine benzene sulfonamide.

b. O-dealkylation $\text{ROCH}_2\text{H}_5 \rightarrow \text{ROH}$ e.g. Phenacetin to paracetamol

c. S-oxidation e.g. Chlorpromazine to chlorpromazine sulfoxide

d. Aromatic hydroxylation- e.g. Salicylic acid to gentisic acid

e. Deamination- e.g. Amphetamine to phenylacetate.

e. Deamination- e.g. Amphetamine to phenylacetate.

2. **Reduction of drugs**- Some drugs are metabolized by reduction reactions. The halogenated and nitrated aromatic compounds are reduced by microsomal enzymes. E.g. halothane, chloramphenicol.

CF_3CHBrCl (Halothane) CF_3CH_3 (trifluoroethane)

Some drugs like disulfiram, chloral hydrate are reduced by non-microsomal enzymes

3. **Hydrolysis of drugs**- This is cleavage of drug molecule by taking up a molecule of water. Hydrolysis occurs in liver, intestine, plasma and other tissues. Esters such as acetylcholine, procaine etc. are hydrolyzed by a variety of non-specific esterases in liver, plasma, GIT and other tissues. Amides such as lidocaine are hydrolyzed in the liver.

4. **Cyclization**- This is formation of ring structure from a straight chain compound. E.g. Proguanil.

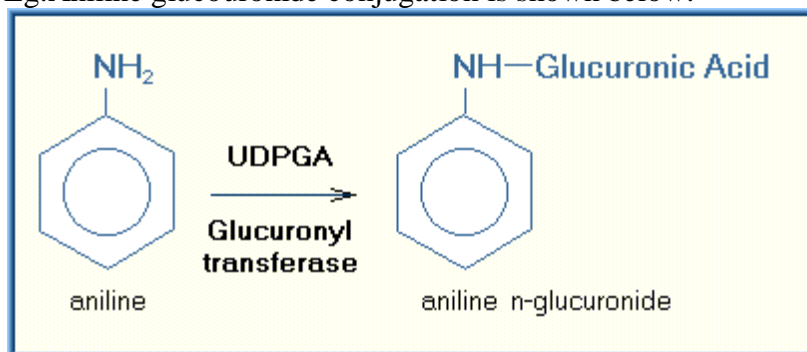
5. **De-cyclization**- This is opening up of ring structure of the cyclic drug molecule. E.g. barbiturates, phenytoin.

f. Biotransformation/metabolism

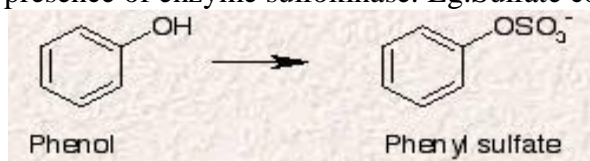
Phase II- Synthetic reactions- These involve enzyme-catalyzed combination of drug (or drug metabolite) with an endogenous substance. These reactions involve covalent attachment of small polar molecule such as glucuronic acid, sulphite or glycine to form water soluble compound. Then these are eliminated through urine or bile.

1. **Glucuronide conjugation**- Conjugation is the addition of a molecule to a drug or xenobiotic. The glucuronidation mainly occur in the liver. Glucuronidation is a major pathway of xenobiotic biotransformation in mammalian species, except for the cat family.

The glucuronide conjugates are hydrophilic and are excreted by the kidney or bile. Eg. Aniline glucuronide conjugation is shown below.



2. **Sulphate conjugation**- The drugs containing functional groups $-\text{OH}$, $-\text{NH}_2$ (Chloramphenicol, adrenaline, estrogen) gets conjugated with endogenous substrate-sulphate in presence of enzyme sulfokinase. Eg. Sulfate conjugation of phenol is shown below.

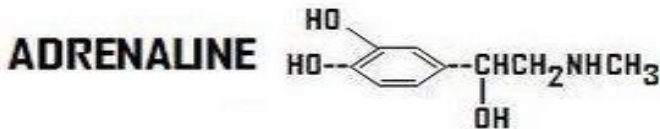
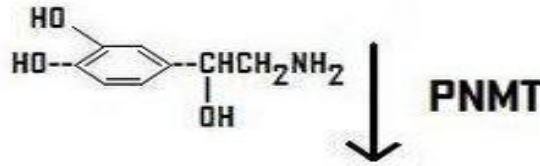


3.Acetylation-Drugs containing functional groups like $-NH_2$, SO_2NH_2 , NH_2NH_2 gets conjugated with endogenous substance-acetyl group.

Eg.Lysine---Acetylated lysine

4. Methylation- Drugs containing functional groups like- OH , NH_2 , $-S$ gets conjugated with endogenous substance-methyl group. Examples- adrenaline, histamine.

NORADRENALINE



5.Glycine conjugation- Salicylates and other drugs having carboxylic acid group are conjugated with glycine, but this is not a major pathway of metabolism.

6. Glutathione conjugation- The drugs are conjugated with glutathione (GSH) moiety. This is catalyzed by glutathione-S-transferase. The glutathione conjugation acts as a detoxification system because it conjugates with toxic substrate.

7. Ribonucleoside /nucleotide synthesis- It is important for the activation of many purine and pyrimidine antimetabolites used in cancer chemotherapy.

Factors affecting biotransformation (metabolism)

1.Genetic disorder (idiosyncrasy)- Abnormal development of enzymes affects the drug metabolism. Example- a. In atypical pseudocholinesterase the metabolism of succinylcholine becomes slow and this leads to paralysis of respiratory muscles. b.Primaquine produces hemolysis in genetic deficiency of the enzyme glucose-6-phosphate dehydrogenase (G-6-PD).

2.Sex-Females have less ability to metabolize the drugs. Example- Oxidation of oestrogen and benzodiazepine is less compared to males.

3. Diet- Starvation can deplete enzymes and alter drug metabolism. Protein deficiency also impairs drug metabolism. Sleeping produced by barbiturates is increased in prolonged protein malnutrition.

4. Age- Metabolism of drugs is poor in young children because of poor development of drug metabolizing enzymes. Example- Chloramphenicol produces gray baby syndrome in new born due to lack of glucuronyl transferase as this enzyme needed for the metabolism of chloramphenicol.



Gray baby syndrome

5.Body temperature- Increase in body temperature increases the drug metabolism, whereas decrease in body temperature has the opposite effect.

6. Stimulators- The activity of drug metabolizing enzymes can be increased by certain drugs. Example- Hexobarbitone metabolism is increased in presence of phenobarbitone.

7.Species- Rabbits metabolize atropine due to the presence of atropinase. Humans lack this enzyme. So atropine is toxic to humans but non-toxic to rabbits.

g. Excretion of drugs

Excretion of drugs is the elimination of unchanged drugs or drug metabolites from the body through various routes. Polar and water soluble drugs (lipid insoluble) are easily eliminated from the body than non-polar drugs. The various routes of drug excretion are milk, saliva and sweat, skin, lungs, bile, intestines, kidneys.

1.**Milk-** Quantitatively it is not an important route of drug excretion. But drug excretion through milk may affect the baby. The milk is more acidic than plasma. Hence basic drugs are eliminated through milk.

2.**Saliva-** Unionized fat soluble drugs are excreted passively from saliva. The bitter after taste in the mouth of a patient is main indication of drug excreted. Drugs usually excreted in saliva are caffeine, phenytoin and theophylline.

3. **Skin-** Drugs like benzoic acid, alcohol, heavy metals e.g.arsenic, mercury are eliminated through skin. This route is not important in drug elimination, but it helps in detection of drug poisoning.

4.**Lungs-** Gases and volatile liquids (general anaesthetics, alcohol) are eliminated by lungs. The presence of alcohol in the exhaled air of vehicle drivers is important for detection of alcohol consumption by traffic police.

5.**Bile-** Drug excreted in bile after conjugation may get re-conjugated in the intestine and may be reabsorbed. This is known as enterohepatic circulation. Action of drug is prolonged as it re-enters the circulation. Examples- Chloramphenicol, tetracycline, morphine.

6.**Intestine-** Some drugs not absorbed in the GIT and gets excreted through the intestine. Examples- streptomycin, neomycin.

7. **Kidneys-** This is the most important route/organ for the elimination of the drugs. In kidney three processes are involved in the drug excretion. a.Glomerular filtration b.Tubular reabsorption c.Tubular secretion

a. Glomerular filtration- The blood enters the Bowman's capsule through afferent arteriole and leaves the capsule through efferent arteriole. The glomerular capillaries have pores larger than usual. The drugs with molecular weight less than 20000 are filtered.

b. Tubular re-absorption- Lipid soluble drugs are reabsorbed more, i.e. they are excreted less. Lipid solubility depends on pH. Re-absorption also depends on concentration gradient. Acidic drugs are excreted in alkaline medium. Examples of acidic drugs- salicylates, barbiturates. Alkaline drugs are better excreted in acidic medium. Examples of basic drugs - amphetamine, pethidine.

c.Tubular secretion- There are two non specific efflux transporters P-glycoprotein and MRP2 (multidrug resistant associated protein) present on the luminal membrane of PCT. These transporters cause the active transport of various organic acids and basic drugs. This drug transport is not fully developed in young children.

Examples-Penicillin, probenecid, salicylates, etc. are excreted through active transport.

h.Mechanism of drug action- Drug-Receptor interactions and molecular & biochemical basis of drug action,

Pharmacodynamics- It is the study of biochemical and physiological effects of drugs including the mechanisms of their actions. (What drug does to the body and how?)

Principles of drug action- Drugs (except gene based) do not impart new functions in any system, organ or cell. Drugs produce their effect by altering the ongoing existing functions. The basic types of drug action can be broadly classified as

1. **Stimulation-** The increased activity of specialized cells is known as stimulation. Examples- adrenaline stimulates the heart, pilocarpine stimulates the salivary glands, and CNS stimulation by amphetamine.

2. **Depression or inhibition-** The decreased activity of specialized cells is known as depression. Examples- Acetylcholine depresses the heart rate and force of heart function, phenobarbitone depresses the brain, quinidine depresses the myocardium of the heart. Certain drugs stimulate one type of organ, but depress the other. E.g adrenaline stimulates the heart but depress the intestine, acetylcholine stimulates the bronchial smooth muscles but depress the heart.

3. **Irritation-** Mild irritation may stimulate associated function. Examples- bitters increase salivary and gastric secretion, alcohol is used as counter irritant to increase blood flow. But strong irritation result in inflammation.

4. **Replacement-** Use of natural metabolites, hormones or their congeners in their deficiency is termed replacement. E.g. insulin in diabetes mellitus, ADH in diabetes insipidus, normal saline in dehydration, iron in anemia.

5. **Cytotoxic action-** Some drugs produces selective cytotoxic effect for parasites or cancer cells without affecting the host cells. e.g. anticancer drugs, antiviral drugs, mebendazole, chloroquine.

6. **Modification of immune status-** These drugs act by changing the immune status of the body. e.g. immune stimulants-vaccines, immune depressants-corticosteroids.

Mechanisms of drug action- The fundamental mechanisms of drug action can be distinguished into four categories.

1. Drug action through physical properties- A physical property of a drug is responsible for its action. e.g.

i. Color, taste, smell - These have psychological effects.

ii. Physical mass- Agar agar produces a purgative effect because of swelling in presence of water which increases its size.

iii. Osmosis- Magnesium sulphate produces a purgative effect due to osmosis.

iv. Adsorption- Magnesium trisilicate acts as an antacid by adsorbing HCl in the stomach.

v. Demulcent effect- Liquid paraffin produces a smooth coating over the lumen of the intestine. This is responsible for its purgative effect.

vi. Electrical charge- Heparin, an anticoagulant drug produces its effect because of negative charge.

v. Radioactivity- Radioactive isotopes used for the treatment of cancer producing their effect by emitting ionizing radiations. E.g. ^{131}I and other radioisotopes.

vi. Radio opacity- diagnosis of intestine using barium sulfate.

2. Drug action through chemical properties-

i. Acidity and alkalisers - HCl is effective in the treatment of achlorhydria. NaHCO_3 acts as an antacid. Urinary acidifiers and alkalisers alter the urinary pH. ii. Oxidation- Drug action by oxidation. e.g. oxidizing agents - KMnO_4 and I_2 – germicidal agents.

iii. Chelation- By chelation water insoluble substances are converted into water soluble form, which are easily excreted. e.g. BAL chelates arsenic and used in arsenic poisoning.

3. Drug action through enzymes- Enzymes are involved in most of the biochemical reactions. The drugs act by stimulating or inhibiting the enzymes.

i. **Stimulation-** Examples- adrenaline when combines with its receptors, this interaction stimulates the membrane bound adenylyl cyclase enzyme.

ii. **Inhibition-** This is divided into nonspecific and specific inhibition.

a. Non specific inhibition- Many drugs and chemical alter the structure of enzymes by denaturation. This inhibits the enzyme function e.g. alcohol, strong acids and alkalis, formaldehyde, phenol.

b. Specific inhibition- Many drugs inhibit a particular enzyme without affecting others. Such inhibition is either competitive or non-competitive.

Competitive- Competitive inhibitors compete directly with the substrate for the active site of an enzyme.

Examples- Physostigmine competes with acetylcholine for acetylcholinesterase. Carbidopa compete with levodopa for dopa decarboxylase.

b.Non-competitive inhibition- The drugs act on the site other than the catalytic site of the enzyme. Due to this the enzyme loses its catalytic activity. Examples- Digoxin inhibit the Na⁺K⁺ATPase, Disulfiram inhibit aldehyde dehydrogenase.

4. Drug action through receptors- Receptors are macromolecules (integral proteins) involved in chemical signalling between and within cells. Receptors may be located on the cell membrane or within the cytoplasm. Examples-alpha, beta, muscarinic, histaminic, GABA, opioid receptors. Activated receptors directly or indirectly regulate biochemical processes (eg. Ion conductance, protein phosphorylation, DNA transcription, etc). Molecules (eg drugs, hormones, neurotransmitters) that bind to a receptor are called ligands.

Important types of receptors-

a. Trans membrane ion channels b. G protein coupled receptors c. Intracellular receptors-

a.Trans membrane ion channels- Ion channels are important in neurotransmission, cardiac contraction and muscle contraction. These are of 3 types. Ligand gated, voltage gated and second messenger regulated.

i.**Ligand gated-** In this type the transmembrane ion channels are opened or closed in response to the binding of a chemical messenger (i.e., a ligand), such as a neurotransmitter. Example ligand gated nicotinic acetylcholine receptor.(Na⁺ ions) (5 subunits), GABA-A receptors (Cl⁻ ions).

ii. **Voltage gated-** In this type the ion channels are activated by changes in electrical potential difference near the channels. E.g. Voltage gated Ca⁺ channels at the nerve endings, voltage gated Na⁺ channels at the axolemma.

iii. **Second messenger gated ion channels-** The second messenger like IP₃ (Inositol triphosphate) bind to the calcium channel present on the sarcoplasmic reticulum. This leads to opening of the channel.

b.G protein coupled receptors- These are most abundant class of receptors in the human body. These receptors are expressed at the extracellular surface of the cell membrane. These receptors have 7 trans-membrane single polypeptide chains. The extracellular domain contain ligand binding region. In the unstimulated (resting) state, the cytoplasmic domain is non covalently linked to a G protein that consists of α and $\beta\gamma$ subunits. Upon activation, the subunit exchanges GDP for GTP. The α -GTP then dissociates from $\beta\gamma$ subunit. The α -GTP and $\beta\gamma$ subunits interact with different effectors. These effectors include adenylyl cyclase, phospholipase C, various ion channels and other classes of proteins.

One major role of the G proteins is to activate the production of second messengers. The first messenger is usually endogenous ligand or an exogenous drug. When a ligand or a drug combines with a G protein receptor, the subunit exchanges GDP for GTP. The α -GTP then dissociates from $\beta\gamma$ subunit. α and $\beta\gamma$ subunits diffuses to interact with different effectors. The activation of adenylyl cyclase (AC), catalyzes the production of the second messenger cyclic adenosine 3,5 monophosphate (cAMP), and guanylyl cyclase, which catalyzes the production of cGMP. In addition, G proteins also activate the enzyme phospholipase C (PLC). The activated PLC cleaves the membrane phospholipid phosphatidylinositol-4,5-bisphosphate (PIP₂) to the

second messenger diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP3). IP3 triggers the release of Ca²⁺ from intracellular stores. DAG activates protein kinase C.

A large number of G α protein isoforms have been identified. A few of these include G-stimulatory (Gs), G-inhibitory (Gi), Gq, etc.

c. Intracellular receptors- These receptors are located in the cytosol. The lipophilic drugs like steroid hormones (estrogens, testosterone, etc) bind with intracellular receptors. Small lipophilic molecules can diffuse through plasma membrane and bind to cytosolic hormone receptors. The resultant hormone-receptor complex enters the nucleus to bind with DNA. This may activate or inhibit the transcription. Depending on this specific mRNA is formed. The mRNA comes out from the nucleus. By using mRNA, rRNA and tRNA specific proteins are formed. The biological effects of steroidal hormones are due to these proteins.

Combined effect of drugs-

Drug Synergism- This is the facilitation of the effects of one drug by another when given together.

Types- a. Additive (summation), b. Supra-additive (potentiation)

a. Additive (summation)- Effect of drugs A+B = effect of drug A + effect of drug B. The total effect is same as the sum of the effect produced by A and B.

Example of summation: Different MOA

Aspirin (- act by inhibiting Prostaglandin (PG) synthesis) ---> Analgesia +
Codeine (Opioid agonist) ---□□ Analgesia + Total effect -----Analgesia ++

Example of summation: Same MOA

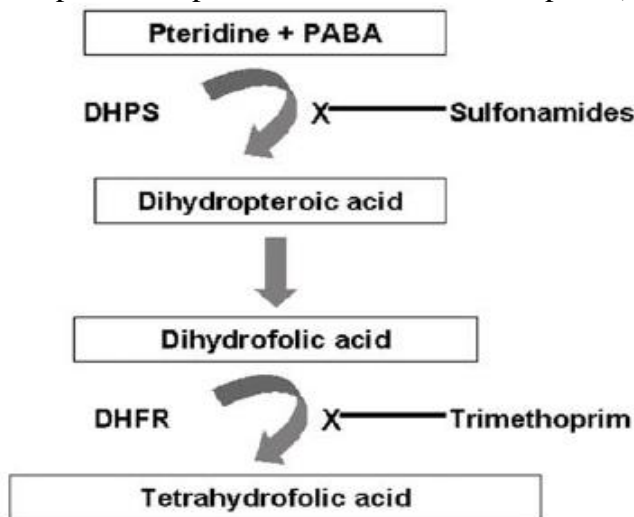
Ibuprofen (act by inhibiting Prostaglandin (PG) synthesis) ---> Analgesia +
Paracetamol (-act by inhibiting Prostaglandin (PG) synthesis) ---Analgesia +
Total effect -----Analgesia ++

Other additive combinations - Amlodipine + Atenolol (antihypertensive), Glibenclamide + Metformin (antihyperglycemic).

b. Supra-additive (potentiation)- When two drugs are given together the final effect is more than the sum of the individual effect.

Effect of A + B > Effect of A + Effect of B

Examples- 1. Sulphamethoxazole + trimethoprim (sequential blockage)



2. Acetylcholine and physostigmine- Physostigmine potentiating the effect of acetylcholine by inhibiting the degradation of acetylcholine by acetylcholinesterase.

c. Drug antagonism- Combined effect of two drugs is **less than** the sum of the effects of individual drugs.

Types

i) Physical antagonism, ii) Chemical Antagonism, iii) Physiological antagonism, iv) Pharmacological antagonism

i) Physical antagonism- This interaction is based on physical property of drugs. e.g. Charcoal adsorb alkaloid in alkaloid poisoning.

ii) Chemical antagonism- Chemical reaction is involved in this type of antagonism. Eg NaHCO₃ antagonizes the HCl.

iii) Physiological/Functional antagonism- In this type of antagonism two drugs act on two different types of receptors and antagonize the action of each other. Eg Histamine & adrenaline. Histamine through histaminergic receptors causes anaphylactic shock (sudden fall in BP), adrenaline through alpha receptors causes vasoconstriction and relieves the sudden fall in BP. adrenaline and insulin on blood sugar level (adrenaline increases and insulin blood sugar levels..)

iv) Pharmacological antagonism- In this type of antagonism one drug act as an agonist (have both affinity and intrinsic property), and another drug act as antagonist (have only affinity). There are three types- a. Competitive b. Non-competitive. c. Non-competitive (non-surmountable antagonist)

a. Competitive antagonism- In this type of antagonism competition occurs between agonist and antagonist for specific site or receptor. Based on the concentration an agonist or an antagonist the agonist effect may be produced or blocked. Examples- Acetylcholine & atropine, adrenaline & propranolol.

b.Non-competitive antagonism- In this type antagonist binds to the receptor. Hence there is no competitive between agonist and antagonist. Example- adrenaline and phenoxybenzamine.

Factors modifying drug effects; Patient related factors & Drug related factors.

The response to a drug varies from one individual to the other. The following are the factors responsible for variation in drug effects.

1.Age- Liver and kidney functions are not fully developed in very small children. They have weak BBB (more permeable).

Examples-a.GIT absorption of ampicillin and amoxicillin is greater in neonates due to decreased gastric acidity.

b.Chloramphenicol– Gray-baby syndrome (inadequate glucouronidation of chloramphenicol).

c.Sulfonamides – Hyperbilirubinemia & Kernicterus

d.Tetracyclines - Permanent teeth staining.

e.Corticosteroids - Growth & development retardation

Elderly constitute 12% of the population. In elderly the renal and liver functions declines with advancement of age.

Changes in the elderly patients are

Stomach pH ; blood flow ; decrease in gut motility (slow onset)

In the elderly, muscle decreases by 25%.

Excretion: decline (40-50%) of renal function in elderly may lead to higher serum drug levels and longer drug half-life. Reduced renal clearance of active metabolites may enhance therapeutic effect or risk of toxicity (e.g., digoxin, lithium, aminoglycosides,)

The dose of a drug for children is calculated from the adult dose

Child dose= Age x adult dose (Young's formula)

Age+ 12

Child dose = Age x adult dose (Dilling's formula)

20

2. Sex-Females are smaller in size (weight).

Examples-

- a. Gynaecomastia is ADR occurring only in men (chlorpromazine).
- b. Antihypertensive drugs interfere with sexual function in males.
- c. The microsomal oxidation of carbamazepine to its active metabolite doubles during pregnancy.
- d. Lipophilic drugs cross placental barrier and slowly excreted.

3. Weight-Body mass has dilutional effect. More is the body weight, more will be the dilution of the drug and less will be the plasma concentration. At extremes of body weight e.g in very thin and lean person (e.g.40-45 kg adult) or obese person (90-100kg or more). The dose for obese or lean individual may be calculated as follows

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

$$\text{Individual dose} = \frac{\text{Body surface area (BSA) m}^2 \times \text{average adult dose}}{70}$$

4. Route of administration- Route of administration governs the speed and intensity of drug response. e.g MgSO₄ produces different actions if it is administered in different routes. If it is given orally it causes purgation effect, if applied on inflamed areas- decreases swelling, if given intravenously it produces CNS depressant and hypotension effect.

5. Race and species- Different species shows different drug effects. E.g. Rabbits are resistant to atropine than humans as atropinase present in the rabbits. Drug effect also differs among races. E.g. Blacks require higher concentration and Mongols require lower dose of atropine to dilate their pupil.

6. Genetics-Genes regulate the synthesis of drug metabolizing enzymes. Gene defect result in altered drug response. Pharmacogenetics is the study of genetic variation in drug response.

Examples-a.G-6-PD deficiency: G-6-PD enzyme is necessary to keep glutathione in reduced state. Reduced glutathione protects RBCs from oxidation. Primaquine, salicylates causes hemolysis in patients with G-6-PD deficiency.

b.Atypical pseudocholinesterase- Succinyl choline causes apnoea in patients with atypical pseudocholinesterase.

d.Acatlasia – In acatalasia (absence of catalase) H₂O₂ is not converted into nascent oxygen.

7. Time of administration- Effect of drug may vary with time of administration. Sedatives are more effective if given at bed-time. Diuretics should be avoided in evening to prevent disturbance in sleep.

8. Pathological factors- Diseases cause individual variation in drug response. Renal failure decreases drug excretion. Liver failure decreases drug metabolism. Presence of disease modifies the drug effect. Examples- Iron absorption is better in presence of anaemia. Paracetamol reduces the body temperature only in presence of fever.

9.Psychological-emotional factors- Placebo- Placebo is an inert substance used in clinical practice. Placebos have the same color, appearance, smell as that of actual medicine. It does not have any pharmacological action, but produces the effects by power of suggestion. It is a dummy medication.

10.Cumulation- Cumulation of a drug may occur due to decreased drug excretion, decreased metabolism, entero-hepatic circulation, high PPB. Examples- chloroquine, digoxin.

11.Dose- Dose is the measured quantity of a therapeutic agent to be taken at one time. Sometimes the type of response depends on the dose. E.g. antiplatelet action of aspirin is seen at 150mg, analgesic effect at 300mg, while anti-inflammatory effect requires 2-6g.

12. Tolerance- It is the unusual resistance to normal therapeutic dose of a drug. So a large dose is required to produce an effect. It can be classified into:

Types-a. Natural tolerance - Species tolerance- Rabbits are tolerant to atropine. Racial tolerance - Black races are tolerant to mydriatics and diuretics.

b. Acquired tolerance- Due to repeated use-e.g. barbiturates- tolerance for sedative action, opioids-tolerance for analgesia and euphoria.

c. Group/cross tolerance- It is the development of tolerance to pharmacologically related drugs. E.g. Barbiturates, morphine.

d. Tissue tolerance- In case of opioids tolerance develops to analgesics and euphoric actions but not constipation and pinpoint pupil effects.

e. Tachyphylaxis – It is an acute type of tolerance. It occurs on repeated administration of the drug at short intervals. For example tyramine produces decreased rise in blood pressure on repeated administration.

Desired to study

Types of doses-

a. Standard (effective) dose- It is the dose that is used in most of the cases.

b. Individualized dose-In impaired renal or hepatic function, it is necessary to adjust the dose. This is particularly needed in patients of hypertension, diabetes, for general anaesthesia.

c. Titrated dose- It is the dose after trial and error. Dose is increased if there is no response and the dose is decreased if there is toxicity.

d. Loading dose- It is the higher dose used at the time of starting the treatment to reach effective plasma concentration quickly.

e. Maintenance dose-It is the dose given for maintenance therapy after starting the therapy with loading dose.

Therapeutic index – It is the ratio of LD50/ED50 or TD50/ED50. It indicates the safety margin of drugs. Larger the difference, safer is the drug.

LD50- Dose that kills (lethal effect) 50% of the population, **ED50-** Dose that generates the desired response in 50 % of the population, **TD50-** Dose that produces toxic effects in 50 % of the population.

Drugs with narrow therapeutic index- Lithium, digitoxin. These are administered with caution.

Drugs with high therapeutic index-Penicillin, propranolol.

Classification and mechanism of action of ADR.

Adverse drug reaction- An adverse drug reaction (ADR) is an injury caused by taking a medication. ADRs may occur following a single dose or prolonged administration of a drug or result from the combination of two or more drugs.

ADR= side effect + toxic effect

Side effect- Side effects are untoward effects occurring at therapeutic doses. E.g. Dryness of mouth with atropine. Side effects are predictable but unavoidable. For example- dryness of mouth caused by atropine is a side effect, but the same is beneficial when atropine is used as pre-anesthetic medication. Sedation caused by antihistaminic drugs may be undesirable, but it is convenient in small children.

Toxic effects- Toxic effects are those occur at higher than the usual therapeutic doses. E.g. Water and electrolyte disturbances due to salicylates. Toxicity also occurs due to prolonged use of a drug in normal dose also. Some toxic effects are predicted and avoidable. Sometimes toxic effects are related to the pharmacological action of a drug. E.g. Respiratory depression by morphine. Sometimes toxic effects are not related to the pharmacological action of a drug. E.g.Paracetamol induced hepatotoxicity.

Iatrogenic diseases- (Iatro means physician). Disease produced by physician (due to use of drugs) is called iatrogenic disease. Examples- Precipitation of diabetes due to corticosteroids, peptic ulcer by aspirin.

Examples of ADRs-

1. Intolerance- It is the inability to tolerate the drug.

a. It can occur at very low dose also. E.g. Chloroquine- vomiting, extrapyramidal reactions- chlorpromazine.

b. Idiosyncrasy- Genes regulate the synthesis of drug metabolizing enzymes. Gene defect result in altered drug response. Pharmacogenetics is the study of genetic variation in drug response.

Examples-G-6-PD deficiency: G-6-PD enzyme is necessary to keep glutathione in reduced state. Reduced glutathione protects RBCs from oxidation. In patients with this deficiency when certain drugs like primaquine, salicylates administered, hemolysis occurs.

Atypical pseudocholinesterase- The presence of this abnormal enzyme fails to metabolize succinyl choline. This results in succinyl choline toxicity (apnoea).

Acatlasia- In absence of catalase enzyme H₂O₂ is not converted into nascent oxygen leading to toxicity.

c. Allergic reactions (hypersensitive reactions)- These reactions are not dose related. These are immunological mediated reactions to drug molecules. Allergic reactions can be minor-like skin rash, urticaria, or it can be life threatening-like anaphylactic reaction. There are 4 types of hypersensitivity (allergic) reactions.

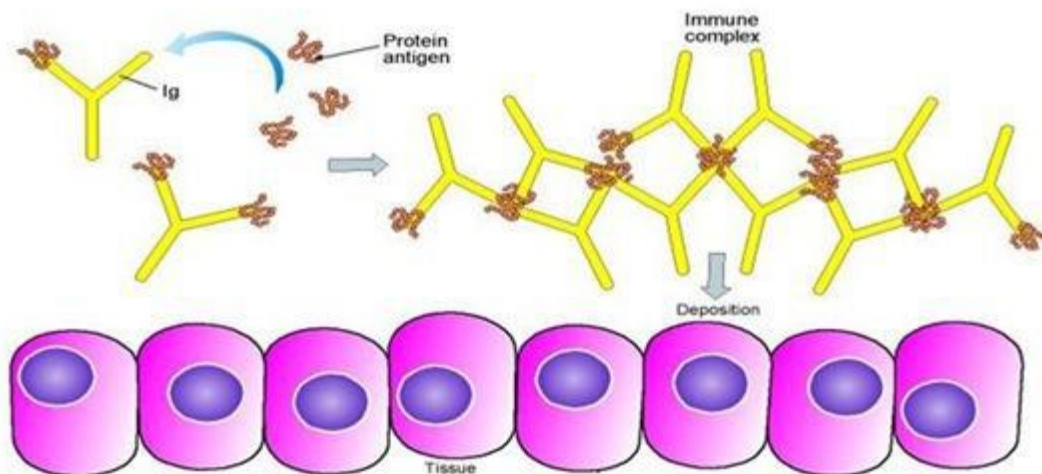
A. Humoral –mediated by B. lymphocytes.

(i) Type I Anaphylactic reaction- It is a type of immediate hypersensitivity reaction due to release of histamine, serotonin (5HT), PG, PAF, leucotrienes, etc. from mast cells. The reactions are mediated by IgE. The manifestations are- urticaria (skin rash), angioedema (swelling in the deep skin), bronchospasm, shock.

(ii) Type II Cytotoxic reactions- It is due to IgG, IgA, IgM. e.g. methyldopa and quinidine - induced hemolytic anemia, thrombocytopenia.

(iii) Type III Immune complex mediated

Type 3 - immune complex hypersensitivity



Binding of multiple IgM or IgG antibodies to soluble antigen causes an insoluble complex to form which is deposited at the surface of tissue.

Type III, immune complex-mediated- The protein antigen binds to antibodies (IgG) to form complex. This complex is deposited in the vascular endothelium. The neutrophils attracted to phagocytize the complexes and liberate enzymes. The liberated enzymes damage vascular walls leading to inflammation (serum sickness).

Drugs like sulfonamides, penicillins and anticonvulsants causes type III hypersensitivity reactions. Symptoms- Arthritis, nephritis, neuropathy, swelling of lymph nodes, etc.

Type IV B.Cell mediated –(mediated by T lymphocytes). Delayed reaction to the antigen, activated T- lymphocytes generated, release lymphokines activate macrophages, infiltration of these cells into organ, e.g halothane-induced hepatitis.

II Effects on various system/organs-

a.CNS- Stimulation/depression, cerebellar dysfunction, convulsions.

b.CVS- Change in BP, HR, effect on myocardium, arrhythmias.

c.RS- Effect on respiratory center, respiratory muscles, bronchi.

d.GIT- Irritation,pain, nausea,vomiting, diarrhoea,constipation,ulceration.

e.Liver- Jaundice,hepatitis, hepatic necrosis, rise in liver enzymes.

F.Kidneys-Damage to tubular function,

g.Muscles- Weakness, myalgia.

h.Bones- Osteoporosis.

i.Skin- Discoloration,Rash, hair loss.

j.Photosensitivity reactions.

K.Endocrine-Thyroid dysfunction, precipitation of diabetes, sex hormones disturbances.

l.Genito-urinary tract- Urinary retention, sexual dysfunction.

m.Eyes- Change in papillary change, disturbance of accommodation, retinal damage.

n.Ear- Vertigo, cochlear damage, deafness, vestibular damage.

o.Blood- Bone marrow depression, aplastic anaemia, coagulation defects.

p.Electrolyte balance- Disturbance in electrolyte balance, acid-base balance.

q.Precipitation of disease- Precipitation of diabetes, peptic ulcer.

r.Withdrawal reactions- In patients with drug dependence.

III-ADR may due to drug interactions- Plasma protein binding (PPB) displacement, enzyme induction, enzyme inhibition.

IV-ADR resulting from withdrawal of the drug.

a.Acute adrenal insufficiency- Withdrawal of glucocorticoids.

b.Rebound-hypertention. Withdrawal of clonidine.

c.Precipitation of angina/MI- Withdrawal of beta blockers.

d.Status epilepticus- Withdrawal of antiepileptic drugs.

V.Carcinogenicity- Radioactive substances, tobacco,hormones.

VI-Mutagenicity- DNA damage, radioactive substances, tobacco, caffeine.

VII Teratogenicity- It is the capacity of a drug to cause foetal abnormalities when administered to the pregnant mother. A drug can affect pregnancy in 3 ways.

a. Interference with fertilization and implantation.

b. During organogenesis (1st trimester) and

c. At the time of development of functions of the organs(later in the pregnancy)

The drugs that cause malformation of the organs or affect functional development are called teratogenic drugs. Since it is very difficult to say that a drug will cause any harm to the fetus, it is a wise thing to avoid all types of drugs during pregnancy unless there are compelling reasons.

In the late 1959-61, in West Germany thalidomide, a sedative was used to provide relief from morning sickness in pregnant women. Thousands of babies born with ‘seal limbs’ (phocomalia).

At present, it is mandatory to test the teratogenicity of any new drug in animals before introduction in therapy. Examples of teratogenicity- Thalidomide-(phocomalia), steroids (cleft palate), phenytoin (cleft palate, cleft lip), Na valproate (spina bifida- incomplete development of spinal cord), tetracycline (bones and teeth defects), sex steroids (virilization- female develops male characteristics), carbamazepine (neural tube defects- birth defects of brain and spinal cord),

anticancer drugs- (hydro-cephalis accumulation of CSF in the brain), ACE inhibitors and alcohol (growth retardation).

Acute toxicity refers to those adverse effects occurring following oral or dermal administration of a single dose of a substance, or multiple doses given within 24 h, or an inhalation exposure of 4h.

Sub acute toxicity- Adverse effects occurring as a result of repeated daily dosing of a substance for part of an organism's lifespan (usually not exceeding 10%). With experimental animals, the period of exposure may range from a few days to 6 months.

Chronic toxicity (more than 50% of the life span)- Adverse effects are observed following repeated exposure to a chemical during a substantial fraction of an organism's lifespan (**usually more than 50%**). For humans, chronic exposure typically means several decades; Chronic exposure to chemicals over periods of 2 years using rats or mice may be used to assess the carcinogenic potential of chemicals.

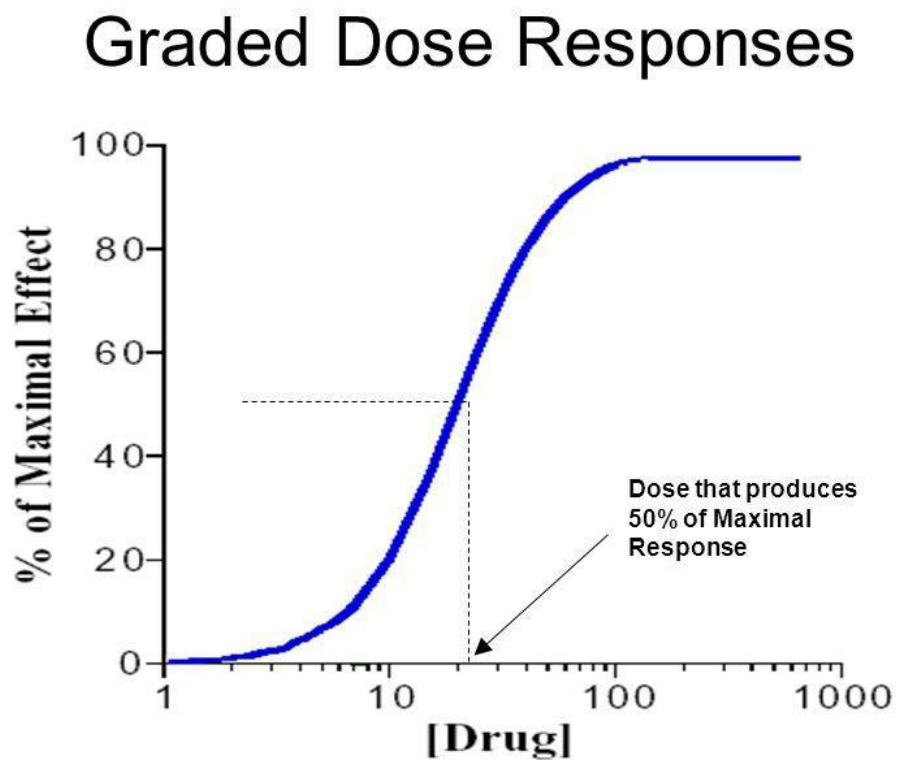
Dose response relationship

Dose response relationship- It is systemic description of the magnitude of the effect of a drug as a function of the dose (very low to very high). The relationship of dose to response can be illustrated as a graph called dose response curve.

Two types of dose response curve

- 1.Graded dose-response curve
- 2.Quantal dose-response curve (all or none) curve

1.Graded dose-response curve- Response is continuous and gradual. Curve is usually sigmoid in shape (log dose or concentration)

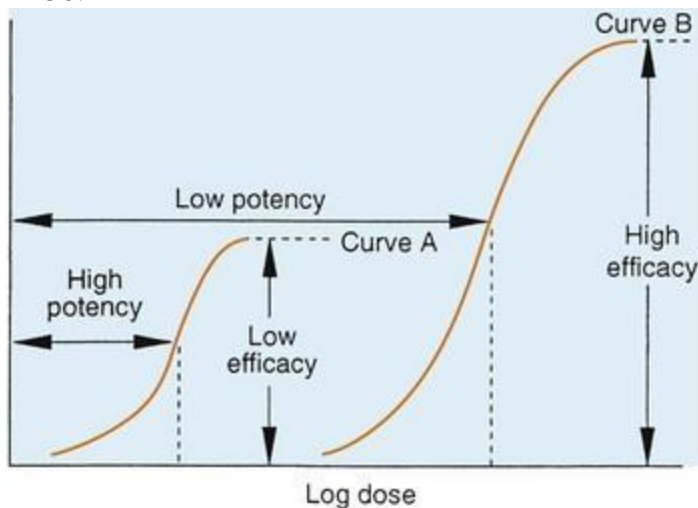


Graded dose response curve is used to calculate ED50. It is also used to calculate potency and efficacy.

Potency is an expression of the activity of a drug in terms of the concentration or amount of the drug required to produce a defined effect. The potency of drugs can be compared using EC50, the smaller the ED50 the more potent the drug.

Efficacy- Efficacy judges the therapeutic effectiveness of the drug in humans. Efficacy is more important than potency.

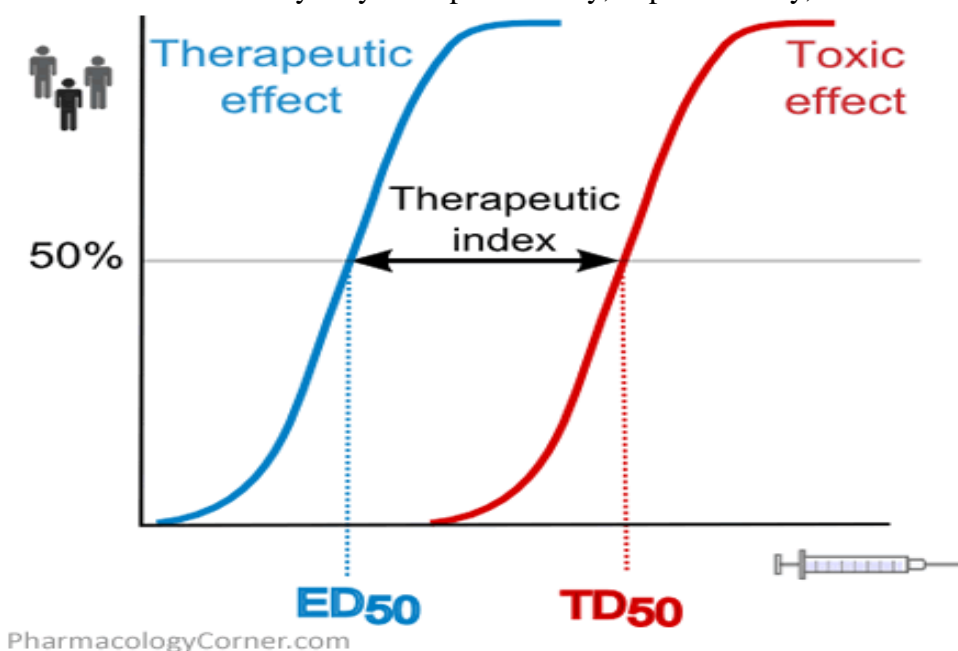
Median effective dose (ED50) - It is a dose of the drug that gives a response equals to 50% of the maximum response. ED50 is a measure of potency. Potency is inversely proportional to ED50.



2. Quantal (all or none curve) - The second type of dose-response curve is the quantal dose-effect curve. In this case, a given quantal effect is chosen (e.g., a certain degree of cough suppression), and the concentration of the drug is plotted against the percentage of a specific population in which the drug produces the effect.

Median effective dose (ED50) – It is a dose of the drug that gives response in 50% of patients.

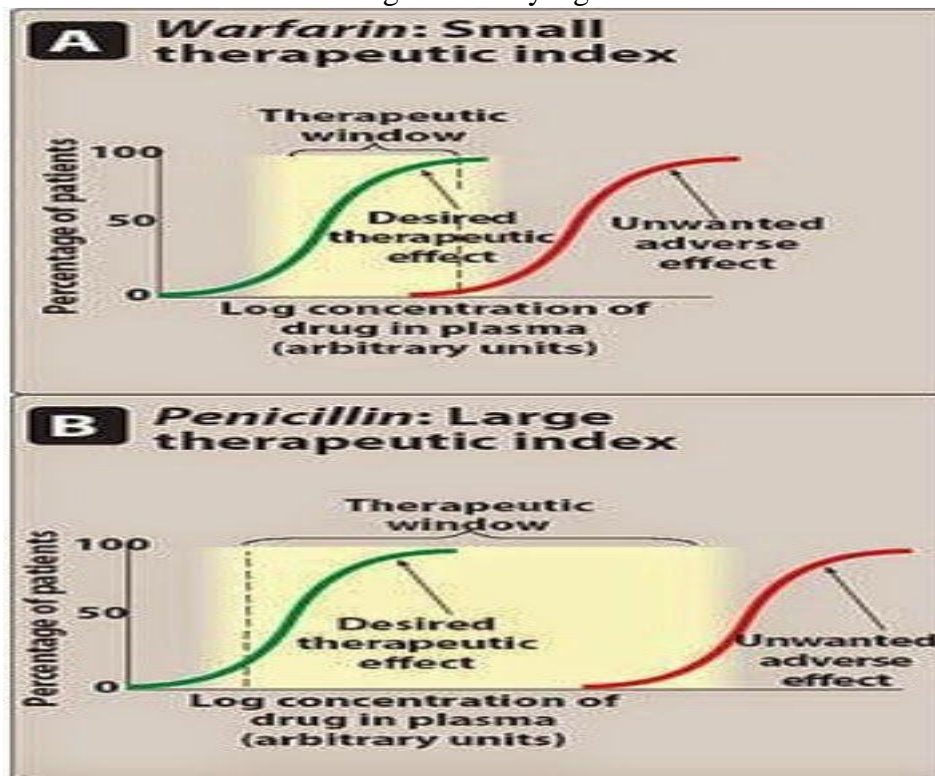
Median lethal dose- (LD50 or TD50) – It is a dose of the drug required to produce toxicity in 50 % of patients (in animal studies LD50 is used as the toxicity is the death, where as in human TD50 is used the toxicity may be hepatotoxicity, nephrotoxicity,cardiotoxicity, etc).



Therapeutic index (TI) - It is the ratio between LD50 and ED 50 or TD50 and ED50.

$$\text{Therapeutic index (TI)} = \frac{\text{LD50}}{\text{ED50}}$$

Therapeutic index is a measure of safety. Large value is a wider margin of safety. eg Penicillin. Smaller value is a narrow margin of safety. eg warfarin.



SAR is the relationship between the chemical or 3D structure of a molecule and its biological activity. It helps to determine the chemical groups responsible for the biological effect in the organism. SAR helps to reduce the unwanted side effects. SAR helps to know the changes in pharmacological properties by performing minor changes in the drug molecule.

1. In 1853 Henry How heated morphine with methyl iodide and he obtained a new compound- quaternary salt of morphine.
2. In 1889 –the semisynthetic derivative of morphine- Morphine-3 ethyl ether (ethylmorphine) was developed for the cough sedative.

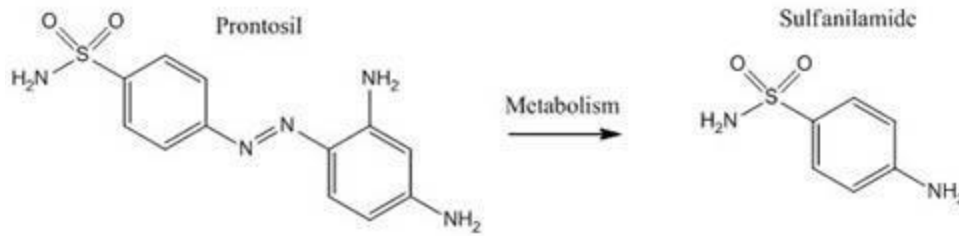
Screening is the systematic examination of a chemical molecule to identify the lead molecule. After pruning the lead molecule give rise to Pharmacophore (part of the drug molecule responsible for pharmacological action).

Methods of screening:

1. Identification by Random screening.
2. Identification by Non-Random screening.
3. Identification by drug metabolism studies.
4. Identification by observing side effects.

1. Identification by Random screening. The lead compound for the development of most drugs is found by screening thousands of compounds randomly.

a. Identification by drug metabolism studies-



b. Identification by observing side effects:

Conversion of benzodioxane -> ethanolamine-> ethylenediamine-> promethazine-> chlorpromazine.

Pruning- Pruning is the refinement of lead structure. It is done to determine the pharmacophore.

Pharmacophore- A pharmacophore is a spatial arrangement of functional groups essential for biological activity.

Morphine-> Levorphanol-> Benxomorphan-> Meperidine.

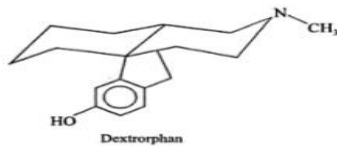
Stereochemistry and drug action- Stereo isomers are compounds containing the same number and kinds of atoms, the same arrangement of bonds, but different three-dimensional structures.

CHEMICAL PROPERTIES

Diastereomers

Dextrorotatory Isomers

- Dextrorphan (anti-tussive)

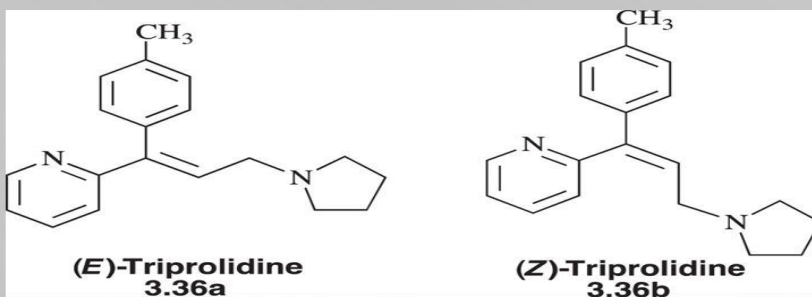


Levorotatory Isomers

- Levorphanol (analgesic)



Diastereomers



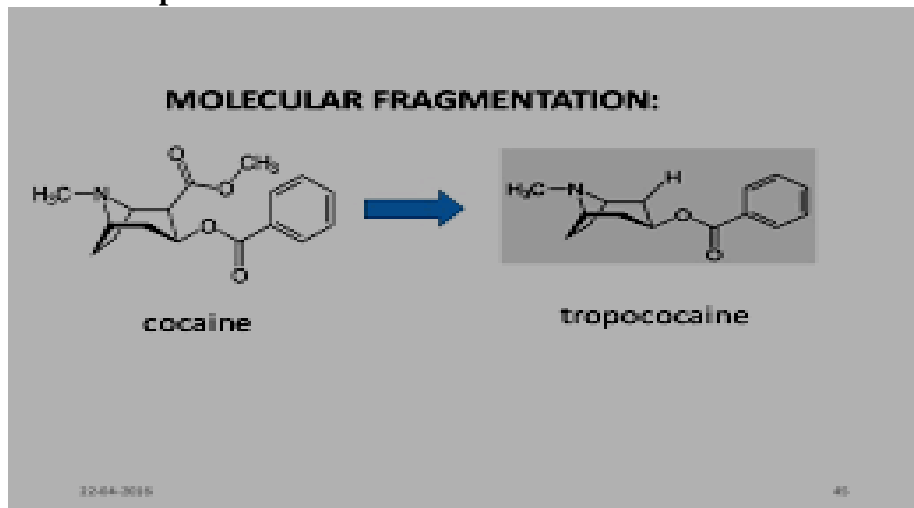
The antihistamine activity of (E)-triprolidine (3.36a) is 1000-fold greater than the (Z)-isomer (3.36b).

2 types □□ Enantiomers (mirror image) and diastereoisomers (not mirror image)

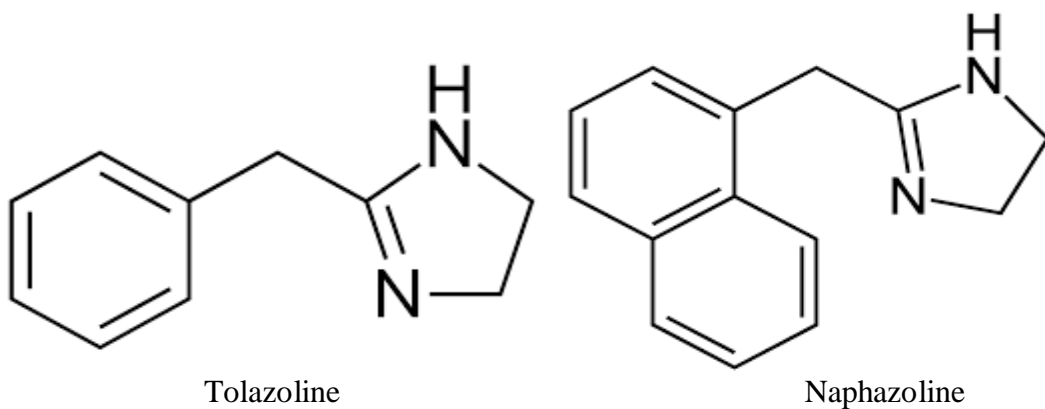
If functional groups are in the proper 3D orientation, the drug can produce a very strong interaction with its receptor.

The physiochemical properties of a drug molecule dependent on (a) functional groups in the molecule (b) spatial arrangement of these groups. Enantiomers when introduced into an Asymmetric environment (human body), it will display different physiochemical properties, producing significant differences in their pharmacokinetic and pharmacodynamics behavior.

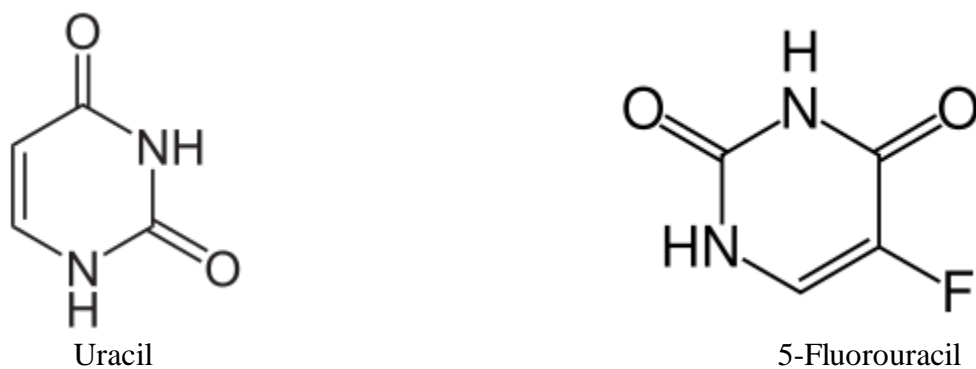
Some examples of SAR studies-



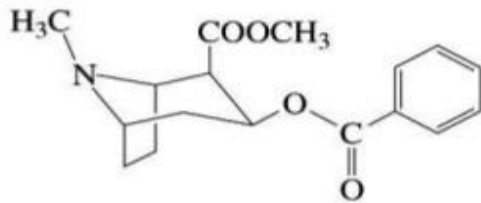
ADDITION OF FUNCTIONAL GROUPS



ISOSTERIC REPLACEMENTS

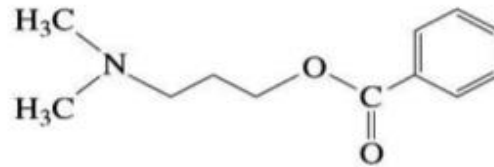


Molecular Modification to Improve the Therapeutic Properties of Cocaine



cocaine
lead compound

local anesthetic, but
bad effect on the
central nervous system



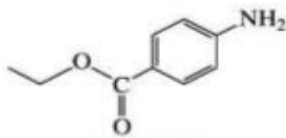
improved lead compound

retains the local
anesthetic property

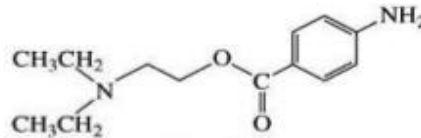
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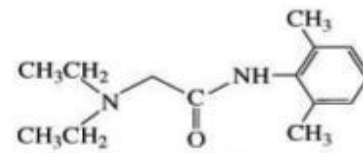
Anesthetics Obtained through Molecular Modification



Benzocaine



procaine
Novocain

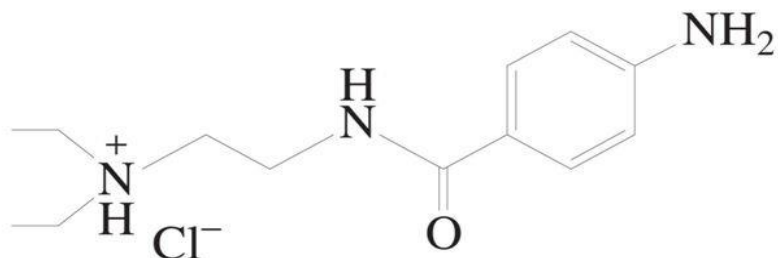


lidocaine
Xylocaine

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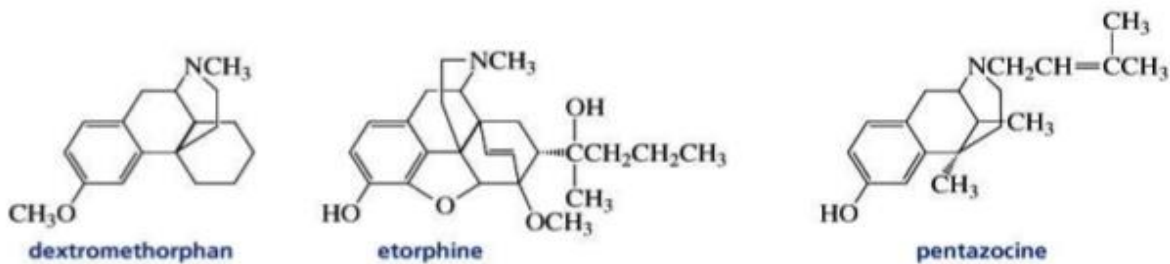
Replacing the ester linkage of procaine with an amide linkage led to procainamide hydrochloride:



procainamide hydrochloride

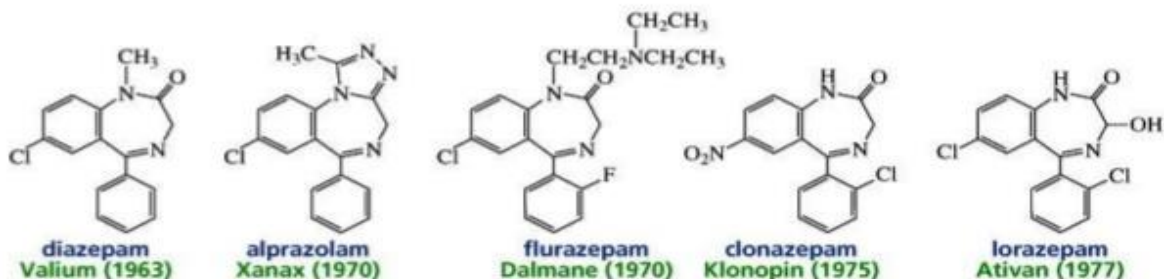
- Active as a cardiac depressant
- Active as a local anesthetic
- Used clinically as an antiarrhythmic

Molecular Modification of Codeine



Dextromethorphan is the major ingredient in most cough medicines

Structural modification of Librium leads to the generation of other tranquilizers



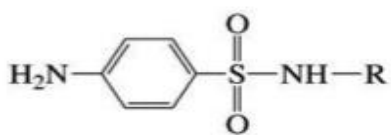
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In screening modified compounds, it is possible to find a compound with completely different pharmacological activity than the lead compound

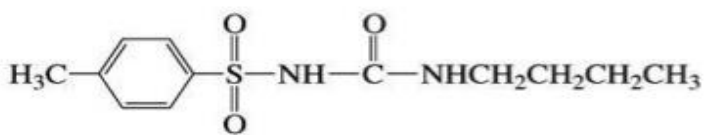
e.g.

in 1942 by the chemist Marcel Janbon et al.



a sulfonamide

an antibiotic



tolbutamide

a drug with hypoglycemic activity

22-04-2016

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Table

IMPORTANT DRUG-DRUG INTERACTIONS

Drug-Drug Interaction	Potential Risk
Amiodarone and haloperidol	This PK and PD interaction may cause arrhythmias
Bepidil and clarithromycin	PK and PD interaction may cause arrhythmias
Colchicine and clarithromycin	Colchicine toxicity
Conivaptan and ergot alkaloids	Ergot toxicity
Cyclosporine and ketoconazole	Cyclosporine toxicity
Cyclosporine and rifampin	Loss of immunosuppressive effect
Ramelteon and fluvoxamine	Ramelteon AUC increase over 100-fold
Simvastatin and ketoconazole	Statin toxicity
Sirolimus and clarithromycin	Marked increase in sirolimus levels with nephrotoxicity

AUC = area under the concentration curve; PD = pharmacodynamic; PK = pharmacokinetic.

Drug-drug interactions-

Drug interaction is the alteration in duration or magnitude of the pharmacological effects of one drug by another drug.

Types of drug interactions-

1. Drug-drug interactions- i) Pharmacokinetics ii) Pharmacodynamic
2. Drug- food interactions
3. Drug- disease interaction
4. Physiological interaction
5. Pharmaceutical interaction

1. Drug-drug interactions- Pharmacokinetics and Pharmacodynamics

Pharmacokinetic drug interactions-

a. **Altered GIT absorption-** Altered pH, Altered bacterial flora, formation of drug chelates or complexes, drug induced mucosal damage and altered GIT motility

Altered pH - For eg. Ketoconazole (acidic) absorption takes place in acidic environment. If this drug is given along with antacid or H₂blockers (ranitidine), pH increases due to neutralization of HCl. Thus ketoconazole absorption decreases in presence of antacids or H₂blockers (ranitidine). These drugs should be given at least 2h gap.

Altered bacterial flora- Digoxin (40%) is metabolized by the bacterial flora. Antibiotics kill a large number of the normal bacterial flora of the intestine. Digoxin concentration increases if given along with antibiotics.

Formation of drug chelates or complexes- Tetracycline chelates with iron (if given along with iron preparations), with Ca^{2+} (with milk), with aluminium or magnesium (if given with an antacid). The absorption of tetracycline decreases 85% due to chelation with metal ions as they form insoluble complexes.

Drug induced mucosal damage- Anticancer drugs like cyclophosphamide, vincristine, etc induces mucosal damage in the GIT. This reduces the absorption of drugs like digoxin.

Altered GIT motility- Drugs like metaclopramide (antiemetic) increases the stomach emptying time. If cyclosporine is given along with metaclopramide, increases the absorption of cyclosporine leading to its toxicity.

b. Displaced protein binding- (distribution)

It depends on the affinity of the drug to plasma protein. Phenytoin is a highly bound to plasma protein (90%), tolbutamide (96%), and warfarin (99%). Drugs that displace these agents are aspirin, sulfonamides and phenylbutazone.

c. Altered metabolism –Liver is the main site of drug metabolism. **CYP450** family is the main metabolizing enzyme.

Enzyme induction- A drug may induce the enzyme that is responsible for the metabolism of another drug or even itself. Eg Carbamazepine (antiepileptic drug) increases its own metabolism. Phenytoin increases hepatic metabolism of theophylline leading to its decreased level. This reduces the effect of theophylline.

Enzyme inhibition- It is the decrease of the rate of metabolism of another drug. This leads to the toxicity. Eg Erythromycin inhibit metabolism of astemizole and terfenadine (antihistamines). This leads to cardiotoxicity. Omeprazole decreases the metabolism of diazepam leading to diazepam toxicity.

d. Renal excretion- It occurs at the PCT. Normally methotrexate is excreted through tubular secretion by combining with specific transporter. But probenecid binds to the same transporter. Hence probenecid and methotrexate result in methotrexate toxicity due to its accumulation. Probenecid + salicylates \square salicylate toxicity, probenecid + indomethacin -- \square indomethacin toxicity.

Pharmacodynamic drug interactions- This occurs when drugs act at the same or interrelated receptor sites, resulting in additive, synergistic or antagonistic effects of each drug. Two types- synergism and antagonism.

a. Synergism- When the therapeutic or toxic effects of two drugs are greater than the effect of individual drug, it is synergism. Two types- addition and potentiation.

1. Addition - The net effect produced by two drugs is equal to sum of the effects produced by individual drugs. ($1+1 = 2$). Eg Thiazide diuretic and beta blocker have an additive antihypertensive effect.

2. Potentiation- When the net effect of two drugs used together is greater than the sum of the effects produced by the individual drugs is known as potentiation. Eg. Sulphamethaxazole + trimethoprim (cotrimaxazole) \square bactericidal effect. ($1+1 = >2$).

b. Antagonism: The effects of one drug can be reduced or abolished by the presence of another drug and this effect is termed drug antagonism. Drug antagonism is of three types- chemical, physiological and pharmacological. Physiological and pharmacological antagonisms involve an interaction of an agonist and an antagonist.

Chemical antagonism- When a drug antagonizes the effect of another drug by simple chemical reaction without action on the receptor. For example, antacid neutralizes the gastric acid.

Physiological antagonism: When the physiological effect of a drug is antagonized by another drug by acting on two different types of receptors. For example, acetylcholine causes contraction of intestinal smooth muscle by acting on M3 muscarinic. Whereas this action of acetylcholine is antagonized by adrenaline through alpha receptors.

Pharmacological antagonism: When a drug antagonizes the effect of another drug by acting on the same receptor it is called pharmacological antagonism. Pharmacological antagonism is of two types- competitive and noncompetitive.

Competitive antagonism- Competitive antagonism is reversible. The inhibitory effect of an antagonist is overcome by using large amount of agonist. Here, both, the agonist and antagonist compete for the same receptor and are able to displace each other at the receptor site. For example, acetylcholine causes contraction of intestinal smooth muscle. Atropine blocks this effect of acetylcholine.

Noncompetitive antagonism- In this type there is no competition between agonist and antagonist for the same receptor. Eg Cyclothiazide (diuretic) act as non-competitive antagonist for mGluR1 receptors.

Drug- food interactions-

Effects of drugs on food intake-

Increased appetite (antihistamines, psychotropic drugs and steroids)

Decreased appetite (amphetamines, insulin and alcohol)

Taste changes (chelating agents and diuretics)

Nausea (cardiac glycosides)

Bulking effects (methylcellulose and other dietary fiber products)

Drug effects on nutrient absorption and metabolism.

Increased nutrient absorption (cimetidine and ranitidine)

Decrease nutrient absorption (colchicine, alcohol, laxatives, antibiotic neomycin)

Mineral depletion (diuretics, chelating agents, alcohol, antacids, aspirin)

Vitamin depletion (vitamin antagonists, oral contraceptives)

Some examples of drug-food interactions-

1. Terfenadine, cyclosporine + grapefruit juice. Reduces the effectiveness of these drugs.

2 Anticoagulants + Food with high Vit K (spinach, broccoli) □ reduces efficacy of anticoagulants.

3 Digoxin + Oat meal -- reduces the absorption of digoxin.

4 . Tetracyclin + milk, dairy products--- reduces the absorption of tetracycline.

5. Para amino benzoic acid decreases the absorption leading to megaloblastic anemia.

6. Corticosteroids decreases the absorption of calcium. This causes bone abnormalities.

7. Diuretics decreases the electrolytes (Zn, Ca, K, Mg). This causes electrolyte imbalance.

8. Frusemide causes urinary loss of thiamine. This causes cardiac muscle weakness.

III Drug disease interactions- Sometimes, drugs that are helpful in one disease are harmful in another disorder.

Hypertension-

a. NSAIDs- increase the BP by increasing fluid retention

b. Oral contraceptives increase the BP by activating rennin- angiotensin-aldosterone system (RAAS).

c. Steroids increase the BP by increasing salt and water retention.

Cardiac failure

a. Beta blockers- exacerbate the cardiac failure.

b. Antacids causes fluid retention and edema.

c. Calcium blockers worsen the cardiac failure.

Arrhythmias-

a. Quinidine- Precipitates the cardiac arrhythmias.

b. Some antacids contain magnesium which precipitates arrhythmias.

Achlorhydria- Antacids precipitates achlorhydria.

Peptic ulcer disease- NSAIDS worsens the PUD.

Liver cirrhosis- Repeated use of morphine causes respiratory depression.

Liver failure- Hypnotics causes toxicity.

Renal failure- Antacids, hypnotics and other drugs gets accumulated leading to toxicities.

Diabetes mellitus- Beta blockers mask the symptoms of hyperglycemia.

PHASES OF CLINICAL TRIALS

Four phases of clinical trials and medicine development exist and are defined below. Each of these definitions is a functional one and the terms are not defined on a strict chronological basis. An investigational medicine is often evaluated in two or more phases simultaneously in different clinical trials. Also, some clinical trials may overlap two different phases.

Phase 0

Phase 0 is a recent designation for exploratory, first-in-human trials conducted in accordance with the U.S. Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies. Phase 0 trials are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was anticipated from preclinical studies. Distinctive features of Phase 0 trials include the administration of single sub therapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (how the body processes the drug) and pharmacodynamics (how the drug works in the body).

A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect. Drug development companies carry out Phase 0 studies to rank drug candidates in order to decide which has the best pharmacokinetic parameters in humans to take forward into further development. They enable go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data.

Phase I: Initial safety trials on a new medicine. An attempt is made to establish the dose range tolerated by volunteers for single and for multiple doses. Phase I trials are sometimes conducted in severely ill patients (e.g., in the field of cancer) or in less ill patients when pharmacokinetic issues are addressed (e.g. metabolism of a new antiepileptic medicine in stable epileptic patients whose microsomal liver enzymes have been induced by other antiepileptic medicines). Pharmacokinetic trials are usually considered Phase I trials regardless of when they are conducted during a medicine's development.

There are different kinds of Phase I trials:

1. SAD

Single Ascending Dose studies are those in which small groups of subjects are given a single dose of the drug while they are observed and tested for a period of time. If they do not exhibit any adverse side effects, and the pharmacokinetic data is roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. This is continued until precalculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up at which point the drug is said to have reached the Maximum tolerated dose (MTD).

Multiple ascending dose (Phase Ib)

Multiple ascending dose studies investigate the pharmacokinetics and pharmacodynamics of multiple doses of the drug, looking at safety and tolerability. In these studies, a group of patients receives multiple low doses of the drug, while samples (of blood, and other fluids) are collected at various time points and analyzed to acquire information on how the drug is processed within the body. The dose is subsequently escalated for further groups, up to a predetermined level

Phase II studies are sometimes divided into Phase IIA and Phase IIB.

Phase IIA is specifically designed to assess dosing requirements (how much drug should be given).

Phase IIA: Pilot clinical trials to evaluate efficacy (and safety) in selected populations of patients with the disease or condition to be treated, diagnosed, or prevented. Objectives may focus on dose-response, type of patient, frequency of dosing, or numerous other characteristics of safety and efficacy.

Phase IIB is specifically designed to study efficacy (how well the drug works at the prescribed dose(s)).

Phase IIB: Well controlled trials to evaluate efficacy (and safety) in patients with the disease or condition to be treated, diagnosed, or prevented. These clinical trials usually represent the most rigorous demonstration of a medicine's efficacy. Sometimes referred to as pivotal trials.

Some trials combine Phase I and Phase II, and test both efficacy and toxicity.

Trial design

Some Phase II trials are designed as case series, demonstrating a drug's safety and activity in a selected group of patients. Other Phase II trials are designed as randomized controlled trials, where some patients receive the drug/device and others receive placebo/standard treatment. Randomized Phase II trials have far fewer patients than randomized Phase III trials.

Example Cancer Design

In the first stage, the investigator attempts to rule out drugs which have no or little biologic activity. For example, the researcher may specify that a drug must have some minimal level of activity, say, in 20% of participants. If the estimated activity level is less than 20%, the researcher chooses not to consider this drug further, at least not at that maximally tolerated dose. If the estimated activity level exceeds 20%, the researcher will add more participants to get a better estimate of the response rate. A typical study for ruling out a 20% or lower response rate enters 14 participants. If no response is observed in the first 14 participants, the drug is considered not likely to have a 20% or higher activity level. The number of additional participants added depends on the degree of precision desired, but ranges from 10 to 20. Thus, a typical cancer phase II study might include fewer than 30 people to estimate the response rate.^[1]

Efficacy vs Effectiveness

When a study assesses efficacy, it is looking at whether the drug given in the specific manner described in the study is able to influence an outcome of interest (e.g. tumor size) in the chosen population (e.g. cancer patients with no other ongoing diseases). When a study is assessing effectiveness, it is determining whether a treatment will influence the disease. In an effectiveness study it is essential that patients are treated as they would be when the treatment is prescribed in actual practice. That would mean that there should be no aspects of the study designed to increase patient compliance above those that would occur in routine clinical practice. The

outcomes in effectiveness studies are also more generally applicable than in most efficacy studies (for example does the patient feel better, come to the hospital less or live longer in effectiveness studies as opposed to better test scores or lower cell counts in efficacy studies). There is usually less rigid control of the type of patient to be included in effectiveness studies than in efficacy studies, as the researchers are interested in whether the drug will have a broad effect in the population of patients with the disease.

Some researchers argue that phase II studies are generally smaller than they ought to be.

Phase IIIa: Trials conducted after efficacy of the medicine is demonstrated, but prior to regulatory submission of a New Drug Application (NDA) or other dossier. These clinical trials are conducted in patient populations for which the medicine is eventually intended. Phase IIIa clinical trials generate additional data on both safety and efficacy in relatively large numbers of patients in both controlled and uncontrolled trials. Clinical trials are also conducted in special groups of patients (e.g., renal failure patients) , or under special conditions dictated by the nature of the medicine and disease. These trials often provide much of the information needed for the package insert and labeling of the medicine.

Phase IIIb: Clinical trials conducted after regulatory submission of an NDA or other dossier, but prior to the medicine's approval and launch. These trials may supplement earlier trials, complete earlier trials, or may be directed toward new types of trials (e.g., quality of life, marketing) or Phase IV evaluations. This is the period between submission and approval of a regulatory dossier for marketing authorization.

Phase IV: Studies or trials conducted after a medicine is marketed to provide additional details about the medicine's efficacy or safety profile. Different formulations, dosages, durations of treatment, medicine interactions, and other medicine comparisons may be evaluated. New age groups, races, and other types of patients can be studied. Detection and definition of previously unknown or inadequately quantified adverse reactions and related risk factors are an important aspect of many Phase IV studies. If a marketed medicine is to be evaluated for another (i.e., new) indication, then those clinical trials are considered Phase II clinical trials. The term post-marketing surveillance is frequently used to describe those clinical studies in Phase IV (i.e., the period following marketing) that are primarily observational or non-experimental in nature, to distinguish them from well controlled Phase IV clinical trials or marketing studies.

Phase-1

Patients: 20 to 100 healthy volunteers or people with the disease/condition.

Length of Study: Several months

Summary of clinical trial phases

Phase	Primary goal	Dose	Patient monitor	Typical number of participants	Notes
Preclinical	Testing of drug in non-human subjects, to gather efficacy, toxicity and pharmacokinetic information	unrestricted	scientific researcher	not applicable (<i>in vitro</i> and <i>in vivo</i> only)	
Phase 0	Pharmacokinetics particularly oral bioavailability and half-life of the drug	very small, subtherapeutic	clinical researcher	10 people	often skipped for phase I
Phase I	Testing of drug on healthy volunteers for dose-ranging	often subtherapeutic, but with ascending doses	clinical researcher	20-100	determines whether drug is safe to check for efficacy
Phase II	Testing of drug on patients to assess efficacy and safety	therapeutic dose	clinical researcher	100-300	determines whether drug can have any efficacy; at this point, the drug is not presumed to have any therapeutic effect whatsoever

Phase III	Testing of drug on patients to assess efficacy, effectiveness and safety	therapeutic dose	clinical researcher and personal physician	1000-2000	determines a drug's therapeutic effect; at this point, the drug is presumed to have some effect
Phase IV	Postmarketing surveillance – watching drug use in public	therapeutic dose	personal physician	anyone seeking treatment from their physician	watch drug's long-term effects