**Pharmacokinetics**

It is the quantitative study of drug movement in, through and out of the body. Intensity of response is related to concentration of the drug at the site of action, which inturn is dependent on the pharmacokinetic properties. Pharmacokinetic considerations, therefore determine the routes of administration, dose, latency of onset, time of peek action, duration of action, frequency of administration of a drug. For all pharmacological action, the drug should cross the biological membrane.

**Biological membranes**

Biological membrane is a bilayer of phospholipids and cholesterol molecules, the polar groups (glyceryl phosphate attached to ethanolamine / choline hydroxyl group of cholesterol) of these are oriented at the 2 surfaces and the known polar hydrocarbon chains are embedded in the matrix with absorbed intrinsic and extrinsic protein molecule. Glycoproteins or glycolipids are formed on the surface by attachment to polymeric sugars, amino sugars or sialic acid. The proteins are able to truly float through the membrane and some of the intrinsic ones which extend through the full thickness of the membrane, surround 5 aqueous pores. Paracellular spaces or channels also channels also exist between certain epithelial / endothelial cells. Other proteins have enzymatic matrix or carrier properties.

**Fluid mosaic model**

Biological membranes may be viewed as mosaic’s functional units composed of lipoprotein complex. Most membranes are composed of a fundamental structure called unit membrane or plasma membrane with 80-100Ao thick . Surrounds single cell and nucleic. Complex barrier such as the intestinal epithelia and the skin are composed of multiples of this functional structure. The plasma membrane consists of bilayer of thick lipids with their hydrocarbon chain oriented within to form a continuous hydrophobic face and their hydrophilic heads oriented outwards. Individual lipid molecules in the bilayer can move laterally making the membrane fluidic, flexible, electrically resistant relatively impervious to highly polar molecules.. This type of membrane structure is known as fluid mosaic modal. Membrane proteins embedded in the bilayer serves as receptor to elicite electrical or chemical signalling pathways and provide selective targets for drug action. The proteins are able to truly float through the membrane and some of the intrinsic ones which extend to full length of membrane surrounding fine aqueous pores. Paracellular spaces or channels also exists between certain epithelial and endothelial cells and other proteins have enzymatic or carrier properties.

Biological membranes behave as if they were lipoid punctured by aqueous pores and allow drugs and physiological materials across by passive or carrier mediated processes. Which mechanism operates is determined by physiochemical properties of the drug and the options in the membrane.

**Functions of membranes**

* They provide structural stability to the cell
* They act as barriers restricting the entry of substances inside the cell.
* They provide vital communication though the entry of messengers for various cellular process.

**Pharmacokinetics**

**Membrane transport**

Passive diffusion Specialised

and filtration transport

Carrier mediated Pinocytosis

Facilitated transport Active transport

Primary active Secondary active

transport transport

Symport Co Antiport

transport transport

**Passive diffusion and filtration**

Passive diffusion is a Random movement of drug molecules from an area of higher concentration to an area of lower concentration. When a drug is injected into the body, it passively diffuses from the injection site to areas of lower concentration eventually reaching a blood capillary and entering the systemic circulation. In this process no cellular energy is expended and no transport carrier protein is involved hence the term passive diffusion is used. Many drug pass through the biological membrane such as cell membrane by passive diffusion.

For a drug to passively diffuse from one side to another the drug must dissolve in membranes compound of phospholipids and diffuse down the concentration gradient. Passive diffusion continues until enough molecules have passed from an area of higher concentration to an area of lower concentration on either side till equilibrium is attained. Drug molecules continue to move, however an equal number move into and out of both the areas. Passive diffusion is the most important mechanism of many number of drugs. Lipid soluble drugs diffuse by dissolving in the lipoidal matrix of the membrane etc. The rate of transport being proportional to lipid water partition coefficient of the drug. Passive diffusion is mostly dependent on

* Concentration gradient (Greater is the concentration of drugs on two sides of membrane faster is the diffusion)
* Drug molecule size smaller molecules move more rapidly than bigger ones.
* Lipophilic nature of the molecule (Higher lipid solubility higher is the diffusion)
* Temperature (Lower the temperature slower the diffusion)
* Thickness of the membrane (Thicker the membrane shower the diffusion)

**Specialised transport**

1. **Carrier mediated transport**

Carrier present in the membrane and the complex then translocate from one side of the membrane to the other. The carriers for polar molecules appear to form a hydrophobic coating over the hydrophilic group, and thus facilitate transport. Substances permitting transportation across membranes are called ‘ionophores’. Carrier transport is specific, saturable and competitively inhibited by analogues that have same requirement. Intestinal absorption sometimes depends on carrier mediated transport. Eg: of carrier mediated transport are

1. Levodopa is taken up by a carrier that normally transport phenyl alanine.
2. Iron is absorbed via a specific carrier on the surface of mucosa cells on the intestine and calcium is absorbed by means of a vitamin D dependent carrier system

**i) Facilitated diffusion**

It is a transport mechanism across biological membrane that involve a special carrier molecule in the membrane which facilitates the movement of certain molecules across the membrane. As in passive diffusion, facilitated diffusion involves no energy to move the drug molecules and the direction of drug movement is determined by the concentration gradient. In addition, once the equilibrium is attained the number of drug molecules crossing the membrane in either direction remains the same. This process proceeds more rapidly the simple diffusion and even translocate non diffusible substances but along their concentration gradient. However the transporter may become saturated and other compounds may compete or inhibit the transport.

Examples of facilitated diffusion are

* Vitamin B12 absorbed from the gut
* Transport of sugar and amino acids across the membrane

**Active transport**

Like facilitated diffusion, active transport also involves a specialized carrier molecule. However in active transport a drug molecule is taken up by a specialized carrier molecule in the membrane and the cell expands energy to move the drug molecules across or to reset the carrier molecule for the next transport movement. Unlike diffusion in which the of net drug movement is determined by the concentration gradient, active transport can move the drug molecules against the concentration gradient (from areas of lower concentrate to higher concentration). Glucose entry within the cell is facilitated diffusion while passage across gastric mucosa and excretion by proximal renal tubular cells is active transport. Drugs related to normal metabolites are actively absorbed from the gut by the aromatic amino acid transport processes. Drugs actively transported may potentially reach very high concentration within cell that they exert a toxic effect.

Eg: Aminoglycoside antibiotics.

When the energy production of the cell is disrupted such as toxicities, action transport of drug across biological membrane may be prevented. Non specific active transport of drugs and their metabolites occurs in renal tubules and hepatic sinusoids separately for organic acids and organic bases. Certain drugs have been found to be actively transported into the brain and choroid plexes also. Examples for active transport are levadopa crossing the blood, brain barrier, secretion of some drugs into the bile and secretion of many organic acids and bases by renal tubular cells.

**Pinocytosis and Phagocytosis**

Pinocytosis is cell drinking and Phagocytosis is cell eating. Drug molecules may enter a cell by being physically engulfed by the cell. In bath pinocytosis and phagocytises, a portion of the cellular membrane surrounds the drug molecule and takes it within the cell. In these processes transport across the cell membrane is facilitated by formation of vesicles. This is an active process and requires the cell to expend energy. If the engulfed particle is not susceptible to enzyme degradation, it will persist like particles of talc or droplets of liquid paraffin. Pinocytosis and Phagocytosis are especially important for movement of large drug molecules such as complex protein or antibodies that would otherwise be unable to enter a cell or pass intact through a membrane barrier. The absorption of immunoglobulin’s through the gut mucosa of young ones depends on phagocytosis. Pinocytosis and phagocytosis are of less important in pharmacology.

**Direct filtration**

Filtration is the passage of drugs through aqueous pores in the membrane or through peracellular spaces. This can be accelerated by if hydrodynamic flow of the solvent is occurring under the hydrostatic or osmotic pressure gradient. Lipid insoluble drugs cross biological membranes by filtration if their molecular size is smaller than the diameter of the pores. Majority of the cells have very small pores and drugs with higher molecular weight will not be able to penetrate. However capillaries expect those in brains have large pores and most drugs and filter through these pores. Passage of drugs across capillaries is dependent on the rate of blood flow through them rather than lipid solubility of the drug or pH of the medium. Filtration seems to play a minor role in drug transfer within the body except for glomerular filtration, removal of drugs from CSF and passage of drugs from hepatic sinusoidal membrane.

**Absorption of drugs**

Absorption is the movement of drug from the site of administration to circulation. Often the entire quantity of administered drug does not reach the systemic circulation. Only the fraction of drug that was absorbed is available for action. During the process of absorption. The quantity of drug absorbed and also the rate of drug absorbed determines the drug action. In all routes of administration except with intravenous administration the drug have to cross the biological membrane to enter the systemic circulation and hence are governed by factors effecting passage of drugs across membrane.

**Factors effecting absorption through GI tract**

Before a drug can be absorbed, it must dissolve in the aqueous content of the gut. Thus the actual amount of drug present in a dose is only one of the factors that will affect the amount of drug actually absorbed or available. Factors affecting absorption include.

1. Molecular size of the drug and its concentration
2. Degree of ionization (PKa) depends on the PKa of the drug, pH of the medium.
3. Lipid solubility of natural or non ionized form of the drug.
4. Chemical or physical interaction with co-administered preparation and food constituents.
5. Pharmaceutical preparation and dosage form especially their disintegration rate and dissolution rate
6. Gastric mobility and secretion as well as gastric emptying
7. Intestinal mobility and secretion as well as intestinal transit time.
8. Fluid volume within the gastro intestinal tract.
9. Osmolality of the intestinal content
10. Intestinal blood and lymph flow
11. Disruption of the functional and structural integrity of gastric and intestinal epithelium (like in gastric enteritis)
12. Drug biotransformation within the intestinal lumen by microflora or within the mucosa by host enzymes.
13. Volume and surface area of the absorbing surface stomach has a relatively small surface area compound to the duodenum. Hence absorption is more in the duodenum.
14. Presence of food in the stomach. Normally in full stomach there is delay in absorption because the drug gets diluted in stomach content.

**Role of ionization and lipid solubility in drug absorption**

Many drugs are weak electrolytes ie. They can ionize to a greater or lesser extent, according to environmental pH. Usually most molecules are present pertly in the ionized and pertly in unionized state. The degree of ionization influences lipid solubility and in turn, their absorption, distribution and elimination. The degree to which these drugs are lipid soluble (non ionized, the form in which the drugs are able to cross the membrane) is determined by their PKa and pH of the medium containing the drug. PKa of a drug is the pH at which 50% of the drug is ionized and 50% is non ionized. In monogastric (simple stomach) animals with a low pH in the stomach, weak acids like aspirin with a PKa of 3.5 tend to be better absorbed from the stomach them the weak bases because of the acidic condition weak bases are poorly absorbed from the stomach because they exist mostly in the ionized state in the acidic environment of the stomach. Week bases are better absorbed from the small intestine where the environmental pH is more alkaline.

**Absorption of drugs after parenteral administration**

Drugs injected intramuscularly a subcutaneously may readily diffuse through tissue fluid and reach a capillary to be absorbed. Anything that interferes with diffusion of the drug from the site of administration of alters the flow to the injection site can delay absorption of the drug. The major factors that determines the absorption is the blood flow to the muscle Aqueous solutions of drugs are usually absorbed from intramuscular injection site within 10 -30 minutes provided the blood flow is unimpaired. Faster or slower absorption is possible, depending on the concentration and lipid solubility of the drug, vascularity of the site, volume of injection, the osmolality of the solution and other pharmaceutical factors. Absorption of drugs from subcutaneous tissues is influenced by the same factors that determine the rate of absorption from intramuscular sites. Some drugs are absorbed rapidly from subcutaneous tissues as from muscles, although absorption from injection sites in subcutaneous fat is significantly delayed. Increasing the blood supply to the injection site by heating (rubbing) massage or exercise hastens the rate of absorption. Spreading and absorption of large fluid volume which has been injected subcutaneously may be facilitated by including ‘hyaluronidose’ in this solution.

**Absorption of drugs after inhalation**

The volatile and gaseous anaesthetics are the most important group of drugs administered by inhalation. These substances enter the circulation by diffusion across the --------------membrane. Since they all have relatively high lipid – water partition coefficient and generally are rather small molecules they equilibrate practically instantaneously with the blood in the -------- capillaries. Particles contained in aerosols may be deposited, depending on the size of the droplets on the mucosal surface of the bronchi or bronchioles or even in the alveoli.

**Absorption of drugs from topical sites of administration**

Drugs may be absorbed through the skin following topical application. The intact skin allows the passage of small lipophilic substances but efficiently retards the diffusion of water soluble molecules in most cases. Highly lipid soluble preparation may be absorbed in considerable preparations encouraging the use of topical route. Lipid insoluble drugs generally penetrate the skin slowly in comparison with their rates of absorption through the other body membranes.

Absorption of drugs through the skin may be enhanced by ‘inunctions’ or more rarely by ‘Iontophoresis’( **Iontophoresis** is a process of [transdermal drug delivery](https://en.wikipedia.org/wiki/Transdermal_drug_delivery) by use of a voltage gradient on the [skin](https://en.wikipedia.org/wiki/Skin)) if the compound is ionized. Certain solvents like dimethyl sulfoxide (DMSO) may facilitate the penetration of drug through the skin. Damaged, inflamed or hyperaemic (high blood circulation) skin allows many drugs to penetrate the dermal bovine much more readily. The same principles that govern the absorption of drugs through the skin also apply to the application of topical preparations on the epithelial surfaces. Many drugs traverse (more) the cornea at rates that are related to their degree of ionization and lipid solubility, thus organic bases such as Atropine, Ephedrine and pilocarpine often penetrate quite readily whereas the highly polar amino glycoside does not.

**Bioavailability**

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

1. Drug may be incompletely absorbed
2. The absorbed drug may undergo first pass metabolism in intestinal well / liver or may be excreted in bile.

In complete bioavailability after subcutaneous (sc) or intramuscular (IM) injection is less common but may occur due to local binding of the drug.

Two preparation of drug are considered bro-equivalent when the rate and extent of bioavailability of the drug from them is not significantly different under suitable best condition in oral administration.

The reason are

* Biologically in equivalent because breaking into individual form from solid or incorporation of diluent, stabilizing agent, binders, lubricants etc.

Difference in bioavailability are seen mostly with poorly soluble and slowly absorbed drugs. Reduction in particle size of the drug increases rate of absorption.

Plasma - with platelets (here only RBC, WBC are separates)

Serum - without platelets (Here all cells are removed)

**Distribution**

Once drug has gained access to blood stream it gets distributed to other tissues that initially no drug, concentration gradient being in the dissection of plasma to tissue. The extent of distribution of drug depends on its lipid solubility, ionization at physiological pH or dependant on PKa and extent of binding to plasma and tissue proteins and differences in regional blood flow, disease condition. Movement of drug proceeds until on equilibrium is established between unbound drug in plasma and tissue fluids. Subsequently there is a decline in both due to elimination.

**Apparent volume of distribution (V)**

Presuming that the body behaves as a single homogenous compartment with volume V into which the drug gets immediately and uniformly distributed.

V = Dose administered

Plasma concentration of drug

V = 1000 mg of Ephedrine

50 mg / litre of ephedrine in plasma

= 20 litres (litres because volume)

Since the drug does not actually distribute in 20 litres of body water with the exclusion of rest of it this is only on apparent volume of distribution which can be defined as “the volume that would accommodate all the drug in the body, if the concentration throughout was same as in plasma”. Thus it describes the amount of drug present in the body as a multiple of that contained in a unit volume of plasma, considered together with drug clearance this is a very useful pharmacokinetic concept.

Lipid insoluble drugs do not enter cells then ‘V’ approximates extracellular fluid volume.

Eg: Streptomycin, Gentamycin

Where V is 0.25 litre / kg organism

Distribution is not only a matter of dilution but also binding and sequestration (remain separate in a area).

Drugs extensively bound to plasma proteins are largely restricted to the vascular compartment and have low values.

Eg: Phenyl butazone (anti-inflammatory) and warfarin

Here V is very low ie. 0.1 litre 1 Kg

Drugs sequestrated in other tissues may have ‘V’ much more than total body water or even body mass

Eg: Digoxin - V = 6 litre / kg

Morphine – V = 3.5 litre /kg

Because most of the drug are present in other tissue than plasma concentration. Therefore in case of poisoning drugs with large volume of distribution are not easily removed by ‘haemodialysis’ (also kidney can’t excrete it)

**Redistribution**

Highly lipid soluble drugs given intravenous or by inhalation initially gets distributed to organs with high blood flow

Eg: Brain, heart, kidney etc., later less vascular but bulky tissue like muscle, fat take up the drug thus plasma concentration falls and the drug is withdrawn from the highly blood flow organs. If the site of action is highly perfused organ redistribution results in extermination of drug action. Greater the lipid solubility of the drug faster is its redistribution.

Eg: Thiopentone action is terminated in few minutes so repeated dose is given.

Factors governing the distribution of drugs

1. Lipid solubility, pH and PKa of the drug.
2. Blood flow to the organ
3. Binding and tissue affinity of the drug
4. Circulatory disorders, kidney diseases.
5. Competition among the drugs for binding sites.

**Plasma protein binding of drugs**

Most drugs have physio-chemical affinity for plasma proteins. Drugs tend to become associated with several blood constituents. Many drugs are bound to plasma proteins, it is only the unbound or free fraction of the drug that can diffuse out of the capillaries into the tissue.

Acid drugs generally binds to plasma albumin and basic drugs to α acid glycoprotein.

Tetracycline damages teeth, bone structure. Hence deals to yellow colouration of the teeth.

Binding to albumin is quantitatively more important. Extent of binding depends on the individual compounds, no generalization for a pharmaceutical or chemical class can be made. Even small chemical change can markedly alter protein binding, for example sulphamerazine has 30% binding, sulfadiazine 50% binding, sulfisoxazole (**Sulfisoxazole** is a broad-spectrum, short-acting sulfanilamide and a synthetic analog of para-aminobenzoic acid with antibacterial propert). has 90% binding.

Increasing the concentration of drug can progressively saturate the binding site (albumin). Fractional binding may be lower when large amount of drugs are given. The generally expressed percentage binding refers to the usual therapeutic plasma concentration of the drug. The clinical significant implication of plasma protein bindings are

1. Highly plasma protein bound drugs are largely restricted to the vascular compartment and tend to have lower volume of distribution. The bound fraction is not available for action. However it is in equilibrium with the free drug in plasma and dissociates when concentration of the latter is reduced due to elimination (ie. won’t remain bound always). Plasma protein binding thus tantamount to temporary storage of drugs.
2. High degree of protein binding make the drug long acting because bound fraction is not available for metabolism and excretion unless it is actively extracted by liver or kidney tubule.
3. Glomerular filtration does not reduce the concentration of free form in the afferent vessels because water is also filtered. Active tubular secretion (active transport however removes the drug without the attendant solvent – concentration of free drug fell-bound drug dissociates and eliminated, resulting in higher renal clearance value of the drug than the renal blood flow.
4. Generally expressed plasma concentration of drug refers to bound as well as free drug.

Once drug can bind to many sites on the albumin molecule. Conversely more than one drug can bind to the same site. This can give rise to displacement interaction among drugs bound to the same site. Drugs bound with lower affinity. If just 1% of the drug which is 99% bound is displaced the concentration of free form will be doubled. Conditions with hypoalbuminia (less albumin in the body) binding may be reduced and high concentration of free drug may be attained.

**Tissue storage**

Drugs may also accumulate in specific organs or get bound to specific tissue constituents.

Eg: In liver chloroquin (antimalarial) will be accumulated, skeletal muscles accumulate Digoxin (Cardiac Patients), kidney accumulate Emetine (for inducing vomiting), Thyroid accumulates iodine, Brain accumulates chlorpromazine (Tranquilizer)

Bone and teeth accumulates Oxy tetracycline (OTC) as well heavy metals, Adipose tissue accumulates DDT.

Drugs sequestrated in various tissues are differentially distributed tend to have large volume of distribution and long duration of action. Some may exert local toxicity due to high concentration and intracellular binding to mitochondria, nuclei etc.

Eg: OTC

**1. Blood brain barrier**

A physical / functional barrier which doesn’t permit ionized and non lipid insoluble drugs to pass through into the central nervous system. It is mainly formed by the endothelial cells of the CNS blood vessel. It’s purpose is to protect the brain from the chemical environment of the rest of the body due to the delicate balance between excitation and inhibition maintained within the CNS. The brain capillaries do not contain fenestrations (Pores), there are more tight junctions in brain capillaries decreasing the rate of diffusion through interstitial spaces. Glial cells ensheath the brain cells providing a second set of cell membrane which must be traversed where cellular metabolic process can transform entering substances. (Glia, also called glial cells or neuroglia, are non-neuronal cells in the central nervous system and the peripheral nervous system. They maintain homeostasis, form myelin, and provide support and protection for neurons. In the central nervous system, glial cells include oligodendrocytes, astrocytes, ependymal cells, and microglia, and in the peripheral nervous system glial cells include Schwann cells and satellite cells. They have four main functions: to surround neurons and hold them in place).

**Chemical or enzymatic barrier**

Mono amino oxidase, acetyl choline esterase  **enzyme** barriers prevents 5 HT (neurotransmitter) Catecholamines, acetyl choline (Ach) from entry into the CNS.

Carrier mediated transport is present to facilitate exit of drugs. Highly lipophilic drugs enter easily because they cross membrane. Unionized forms of drugs enter more easily than ionized forms.

**Metabolism / Biotransformation / Xenobiotic**

Biotransformation means chemical alteration of the drug in the body. It is needed to render non polar lipid soluble compounds to polar lipid insoluble so that they are not reabsorbed in the renal tubules and are excreted. Most hydrophilic drugs.

Eg: Streptomycin, neostigmine etc. are not bio transformed and are excreted unchanged. Mechanism which metabolized drugs have developed to protect the body from ingested toxins. The primary site for drug metabolism is liver, others are kidney, intestine, lungs and plasma. Biotransformation of drugs leads to the following

1. Inactivation, here most drugs and their active metabolites are rendered inactive or less active.

Eg: Pentobarbitone, morphine, chloramphenicol, propranolol (hypertensive drug) and it’s active metabolite 4-hydroxy propranolol.

1. Active metabolite from an active drug – Many drugs have been found to be partially modified into one or more active metabolites, the effects observed are the sum total of that due to the parent drug and its active metabolites.
2. Activation of inactive drug – Few drugs are inactive as such and need conversion in the body to one or more active metabolites. Such a drug is called ‘Prodrug’. The product may offer advantage over the active form in being more stable, having better bio-availability or other desirable pharmacokinetic properties or less side effects and toxicity.

Biotransformation reactions can be classified into

1. Non synthetic / Phase I reaction : Here metabolites may be active or inactive.
2. Synthetic / conjugation / Phase II reaction : Here metabolites are mostly inactive.

**1. Non synthetic reactions**

**(i) Oxidation**

This reaction involves addition of oxygen / negatively charged radical / remove of hydrogen /positively charged radical .

Oxidation is the most important drug metabolising reaction. Various oxidation reactions are Hydroxylation, Oxygenation in C, N or S atom of the drug molecule. N (Nitrogen) or O (Oxygen) dealkylation or oxidative deamination can occur.

In many cases the initial insertion of oxygen atom into the drug molecule produces short lived highly reactive quinone or epoxide or super oxides intermediates which converts to more stable compounds. Oxidative reactions are mostly carried out by a group Monooxygenases in the liver, which in the final step involves cytochrome p450 (haemoprotein) or NADPH, Cytochrome p450 reductase and O2. More than hundred cytochrome isoenzymes differing in their affinity for various substrates (drugs) have been identified.

Eg: Cy P3A4/5, Cy P2D6

Barbiturates, Phenothiazine, Paracetamol, steroids etc. are oxidised in this way. Some other drugs Eg: Adrenaline, alcohol etc. are oxidized by mitochondrial on cytoplasmic enzymes

**ii) Reduction**

This reaction is the inverse of oxidation and involves cytochrome p450 enzymes working in the opposite direction. Drugs primarily reduced are chloralhydrate, chloramphenicol, Halothane.

**iii) Hydrolysis**

This is cleavage of drug molecule by taking up a molecule of water.

Ester + H2O Esterase Acid + Alcohol

Similarly Amides and Polypeptides are hydrolysed by Amidases and peptidases respectively. Hydrolysis occurs in liver, intestine, plasma and other tissues.

Eg: Choline esters, procaine (local anaesthetic), lidocaine, pethidine (euphoric drug), oxytocin (polypeptide)

**iv) Cyclization**

This is formation of ring structure from a straight chain compound

Eg: Proguanil (**Proguanil**, also known as **chloroguanide**, is a medication used to treat and prevent [malaria](https://en.wikipedia.org/wiki/Malaria). It is often used together with [chloroquine](https://en.wikipedia.org/wiki/Chloroquine) or [atovaquone](https://en.wikipedia.org/wiki/Atovaquone) and When used with chloroquine the combination will treat mild chloroquine resistant malaria.It is taken by mouth).

**v) Decyclization**

This is opening of ring structure of cyclic drug molecule

Eg: Barbiturates, Phenytoin Phenytoin, sold under the brand name Dilantin is an anti-seizure medication. The intravenous form is used for status epilepticus that does not improve with benzodiazepines .Useful for heart arrhythmias or neuropathic pain.

**2. Synthetic reactions**

These involve conjugation of the drug or its phase I metabolite with an endogenous substrate generally derived from carbohydrates, amino acids to form a polar, highly ionized organic acid, which is easily secreted in urine or bile. Conjugation reactions have high energy requirements.

i) **Glucuronide conjugation**

This is the most important synthetic reaction. Compounds with hydroxyl or carboxylic acid group are easily conjugated with glucuronic acid which is derived from Glucose.

Eg: Aspirin, Phenocitine, chloramphenicol, morphine, Metronidazole (anti-protozoan drug). Not only drugs but endogenous substance like Bilirubin, Steroidal hormone and thyroxin utilize this pathway. Drug glucoronides excreted in bile can be hydrolyzed by bacteria in the gut, thus the liberated drug is re-absorbed and undergoes the same phase. This enterohepatic cyclic of drugs prolongs its action.

**ii) Acetyl action**

Compounds having amino or hydrazine residues are conjugated with the help of Acetyl co-enzyme Eg: sulfonamide Isoniazide, (to treat tuberculosis). Multiple genes control the acetyl transferases and rate of acetylation. This is called genetic polymorphism.

**iii) Methylisation**

The amines and phenols can be methylated. Here methionine and cysteine act as methyl donors.

**iv) Sulphate conjugation**

The phenolic compounds and steroids are sulphated by sulphokinase

Eg: Chloramphenicol, adrenaline and sex steroids (Estrogens, testosterone, androgens)

**v) Glycine conjugation**

Salicylates and other drugs having carboxylic acid groups are conjugated with Glycerine (This is not a major pathway)

**vi) Glutathione conjugation**

Forming a Mercapturate is normally a minor pathway. However it serves to inactivate highly reactive quinine or epoxide intermediate during metabolism of certain drugs. .Eg: Paracetamol (Acetyl salicylate)

**vii) Ribonucleoside / nucleotide synthesis**

It is important for the activation of many purine and pyrimidine anti metabolites used in cancer chemotherapy.

**Drug metabolism**

Most drugs are metabolized by many pathways simultaneously or sequentially. Only few drugs are metabolized by enzymes of intermediary metabolism .

Eg: Alcohol-bile dehydrogenase, succinyl - choline and procaine, by plasma cholinesterase adrenaline by monoamine oxidase. Majority of drugs are acted on by relatively non specific enzymes, which are directed to types of molecules, rather than the specific drugs. The same enzyme can metabolize many drugs. The drug metabolizing enzymes are divided into 2 types

1. Microsomal enzymes
2. Non microsomal enzymes

**Microsomal enzymes**

These are located on smooth endoplasmic reticulum (a system of microtubule inside the cell) primarily in liver, kidney, intestinal mucosa and lungs. The monogeneses cytochrome. P450, glucuronyl transferees etc. are microsomal enzymes. They catalyse most of the oxidation, reductions, hydrolysis and glucuronide conjugation. Microsomal enzymes are inducible by drugs, diets and other agencies.

**2. Non microsomal enzymes**

These are present in the cytoplasm and mitochondria of hepatic cells as well as other cells including plasma. Flavoprotein oxidases, Esterases, amidases and conjugations are non microsomal enzymes. Some oxidations and reductions and many hydrolytic reactions and all conjugations except glucuronidases are catalysed by non microsomal enzymes. The non microsomal enzymes are not inducible. But many show genetic polymorphism.

Both microsomal and non microsomal enzymes are deficient in the new born making them more susceptible to many drugs.

Amount and kind of drug metabolizing enzymes are controlled genetically and is also altered by environmental factors. This is one of the major causes of individual variation in drug response.

**Inhibition of drug metabolism**

One drug may competitively inhibit metabolism of another if it utilises the some enzyme or co-factors. A drug may inhibit one iso-enzyme while being itself a substrate of another iso-enzyme.

Eg: Quinidine is metabolized by cytochrome 3A4 but inhibits cytochrome 2D6.

**Microsomal drug induction**

Many drugs, insecticides and carcinogens interact with DNA and increases the synthesis of microsomal enzyme protein especially cytochrome P450 and Glucoronyl transferases. As a result rate of metabolism of inducing drugs itself or other drugs increases.

**Factors affecting / altering drug metabolism**

**a) Metabolic drug interactions:** Enzyme inductors and inhibition by drugs and environmental pollution.

**b) Age:**  Very young and only have reduced functional capacity of liver

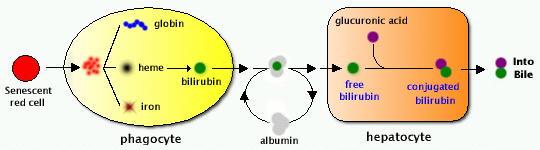
**c) Diseases :**  Reduced in hepatic dysfunction

**d) Gender:**  Reduced activity of same enzymes in females.

**e) Genetic Polymorphism** : Genetic deficiency of drug metabolizing enzymes like cytochrome P450 and related enzymes in individual or race of population.

**First pass metabolism or pre systemic metabolism**

This refers metabolism of drug during its passage from the site of absorption into the systemic circulation. All orally administered drugs are exposed to drug metabolising enzymes in the intestinal well and live where they first read through the portal vein. The extent of first pass metabolism differs for different drugs.



**Excretion of drugs**

Excretion is the passage out, of systemically absorbed drugs. Drugs and their metabolites are excreted in the urine, faeces, exhaled air, relive and sweet, milk, bile etc.

**Urine**

Kidney is the most important channel of excretion for most drugs.

**Faeces**

A part from unabsorbed fraction, most of the drug present in faeces is derived from bile. Liver actively transports into bile organic acids, organic bases and several steroids by separate non specific active transport mechanism. Larger molecules with Molecular weight more than-frequently eliminated in the bile. Certain drugs are excreted directly in Colon.

**Renal excretion**

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

**Glomerular filtration**

Glomerular capillaries have pores longer than usual. All non protein (free drug) bound drug whether lipid soluble or insoluble presented to the glomeruli is filtered. Thus glomerular filtration of a drug depends on plasma protein binding and renal blood flow. Glomerular filtration rate (GFR) decreases progressively after age.

**Plasma half life**

Plasma half-life of a drug is the time taken for its plasma concentrations to be reduced to half of its original value. It is a simple and useful guide to study the drug in the body. Here in one t ½, 50% of the drug is eliminated ;in 2 t ½, 75% of the drug is eliminated. in 3 t ½, 82.5% of the drug is eliminated. in 4 t ½, 94.25% of the drug is eliminated.

Thus nearly complete drug elimination occurs in 4 – 5 hours.

**Pharmacodynamics**

It is the study of drug effects and attempts to elucidate the complete action effect sequence and the dose effect relationship. Modification of the effects of one drug by another drug and by other factors is also a part of Pharmacodynamics.

**Principles of drug action**

Drugs except those gene based do not impart new functions to any system, organ or cell. They only alter the pace of ongoing activity. The basic types of drug action can be broadly classified as

**1. Stimulation**

It is selective enhancement of the level of activity of specialised cells. Eg: Adrenaline stimulates heart, however excessive stimulation is often followed by depression of that function.

**2. Depression**

It is selective reduction of the activity of specialised cells.

Eg: Barbiturates depress CNS. Certain drug stimulates one type of cells but depresses the other Eg: Acetyl choline stimulates intestinal smooth muscle but depresses SA node (Sino atrial node). Most drugs cannot be just classed as stimulates or depressants.

**3. Irritation**

Here are a non selective often noxious affect and is particularly applied to less specialized cells like epithelium, connective tissues etc. Mild irritation may stimulate associated function.

Eg: Bitters (bitter drugs) increases salivary secretion, gastric secretion and blood flow.

Strong irritation results in inflammation, corrosion, necrosis and loss of function.

**4. Replacement**

This refers to the use of natural metabolites hormones or their derivatives in deficiency states Eg: Levodopa in Parkinsonism, Insulin in Diabetes, Iron in anaemia.

**5. Cytotoxic action**

Selective cytotoxic action for invading parasites or cancer cells, attenuating them without specifically affecting the host cells.

**Mechanism of drug action**

Barring a handful of drugs whose action can be explained on the basis of their physical or chemical activities, majority of drugs act in complex manner / all elements of which are seldom known. The fundamental mechanism of drug action can be distinguished into 4 categories.

**1. Physical action**

Here physical property of the drug is responsible for its action.

* Mass is the drug which will be used for production of bulk (Eg. Banana)
* Absorption propertyof some materials used for removal of poison Eg: Charcoal, kaolin
* Osmotic active drug Eg: Mannitol, Magnesium sulphates (Meg. Sulf.)
* Radio opacity Eg: 131 Iodine
* Radio opacity Eg: Barium meal (After taking this intestine becomes opaque, then X-ray is taken).

**2. Chemical action**

The drug acts intracellularly

Eg: Antacid (Al(OH)3, Alkanalizers – NO2HCO3 (during acidity ie. blood pH is changed from 7.4)

* Oxidising agents EG: KMnO4, as germicide and inactivates ingested poisonous alkaloids.
* Chelating agents : Calcium disulphide editite, it detoxifies toxic metals like Arsenic poison.

**3. Through enzyme**

Almost all biological processes are carried out under catalytic influence of enzymes. Hence enzymes are very important target of drug action. Drugs can either increase or decrease the rate of enzymatically mediated reactions.

**a) Stimulation**

In physiological systems enzymatic actions are optimally set. Thus stimulation of enzymes by drugs that are truly foreign substrate is unusual. Enzymes stimulation is relevant to many endogenous mediators and modulators.

Eg: Adrenaline stimulates, Adenylyl cyclase. Pyridoxine acts as co-factor and increases decarboxylase activity. Apparent increase in enzyme activity also occurs by enzyme induction ie. Synthesis of more enzyme protein, this cannot be called ‘stimulation’.

**b) Inhibition**

Inhibition of enzymes is a common made of action. Inhibition can be classified into 2 Specific – Nonspecific.

**i) Non specific inhibition**

Many chemicals and drugs on capable of denaturing proteins. They would alter the tertiary structure of any enzyme with which they come in contact and thus they inhibit it. Heavy metal salts, strong acids and alkali, alcohol, formaldehyde, phenol inhibit enzyme non specifically.

**ii) Specific inhibition**

Many drugs inhibit a particular enzyme without affecting others such inhibition is either competitive or non competitive

competitive **/ Equilibrium type**

**4. Through Receptors**

A large no. of drugs act through specific macro molecular components of the cell which regulates critical functions like enzyme activity, permeability / transport processes, structural features, template functions etc.

**Receptors**

Macromolecules or the sites on them which bind and interact with the drug are called receptors. They are lipo or glyco proteins. It will have a effector system generating biological response.

It is also defined as a specific binding site with functional co-relates. Receptors are situated on the surface or inside of effector cells and specific against ----------- combine with them to initiate the characteristic response.

**Agonists**

It activates a receptor to produce an effect similar to that of the physiological signal molecular.

**Inverse agonists**

It activates a receptor to produce an effect in the opposite direction to that of the well recognised agonist.

Eg: One drop of Etropine dilates the eye – It is an agonists.

But Physostigmine constricts the eye – Inverse agonist.

**Antagonist**

It prevents action of an agonist on a receptor or the substrate response, but does not have effects of its own.

**Partial agonist**

It activates a receptor to produce sub-maximal effect but antagonises the action of a full agonist.

**Legend (To bind)**

It is a molecule which attaches selectively to particular receptors or sites. The term only indicates affinity without regards to functional change. Agonists and competitive antagonists are both legends of the same receptors.

Eg: Etropine and Physostigmine are legends for a same site (eye)

**Basic evidences for drug action through receptors**

1. Many drugs exhibit structural specificity of action ie. specific chemical configuration is associated with a particular action.

Eg: Isopropyl substitution on the ethyl amine side chain produces compounds with marked cardiac and bronchial activity. Thus cell have same mechanism to recognize a particular chemical configuration.

1. Competitive antagonism is seen between specific agonists and antagonists. Largely (1878) was so impressed by mutual antagonism among 2 alkaloids pilocarpine and Etropine that he proposed both reacted with the same receptive substance on the cell. Ehrlich (1970) observed quantitative neutralization between toxins and antitoxins and further developed ideas which were later crystallized in the “Receptor theory of drug action”.
2. It was calculated by Clark that Adrenaline and Acetyl choline produce their maximal effect on frog heart by occupying only 1/6000Tn cardiac cell surface, thus special regions of reactivity to such drugs must be present on the cell.

**Receptor occupational Theories**

After studying quantitative aspects of drug action Clark (1937) propounded the theory of drug action based on the occupation of receptor by specific drugs and that the pace of cellular function can be altered by interaction of receptors with drugs (small molecular legends). He perceived the interaction between the two molecular species ---------- drugs and receptor to be governed by law of mass action ----------- and the effect to be direct function of the drug receptor complex formed.

D + R DR + E (Effect)

Accordingly the cardinal postulate of this theory were

1. The intensity of response is proportional to the fraction of receptors occupied by a drug and maximal response occurs when all receptors occupied.
2. Drug exert an all in none action on each receptor ie. either a receptor is fully activated or not at all. There is no partial activation.
3. Drug and its receptors have complementary structural features and stand in rigid lock and key relationship. This theory gave a fundamental concept but the postulates were later found to be only partially correct and needed to be modified.

**Arians and Stephenson Theory (1930)**

Found that agonists adrenaline and Histamine could still produce maximal response when lesser than 99% receptors were occupied by non competitive antagonists. Thus all receptors need not be occupied for a maximal response for full agonists. There often was a large receptor region in other words, a member of space receptors were present. In relation to action through receptors they introduced the concept of

1. Affinity
2. Intrinsic activity (Efficiency)

**Affinity**

It is the ability of the drug to combine with the receptor.

**Efficiency**

It is the ability of the drug to activate or induce a conformational changes in the receptor consequent to receptor occupation.

Different drugs had different capacities to induce a resp are consequently they must occupy the different fractions of the available receptors while inducing equal response. Accordingly it should be possible to sub maximally activate a receptor and all or none action is not necessary. They interpose a theoretically quantity denoting strength of stimulates imported to the cell by activation of the receptor.

D + R S + E (Effect)

Depending on the agonist DR (Drug receptor complex) would be stronger or weak ‘S’ (theoretical quantity or strength of stimulates) probably as a function of the conformational change brought about by the agonist in the receptor. The two properties, affinity and intrinsic activity are independently variable ie.drug with same affinity can posses different degrees of intrinsic activity and vice verse.

Accordingly agonists have affinity and maximal intrinsic activity ie. IA – 1 Eg: Adrenaline

Competitive antagonists have affinity but no intrinsic activity IA – O Eg: Atropine.

Partial agonists have affinity are sub maximal intrinsic activity IA = 0.1

Eg: Nalopine.

**Drug Receptor Interactions**

**Two state receptor model**

The actions of agonist – antagonists, partial agonists and inverse agonists can be better explained on the basis of the two state receptor model. According to this model, a receptor is believed to exist in atleast two conformational states. Active (Re) and inactive (Ri) which are in equilibrium. In the absence of drug the inactive state predominates so that no low intensity signal is generated (I). The agonist (A) has a higher affinity for the active conformation than for the inactive confirmation and shifts the equilibrium to the active state and thereby activates the receptor generating the response depending on the concentration of A (II). The competitive antagonist (B) binds to Re and Ri with equal affinity, will not alter the equilibrium hence no response is generated. A partial agonist (c) has only slightly greater affinity for Re then Ri, the equilibrium is moderately shifted towards Re even at saturating concentration (IV) and will produce a submaximal response. The inverse agonist (D) has high affinity for Ri state and will produce an effect opposite to that of agonist (V).

1. Electro static bond
2. Hydrogen bond
3. Vander Walls forces

Importantly the afore said bond variants play an extremely vital and critical role in the precise and accurate determination pertaining to the actual selectivity receptors by virtue of the fact that the strength of the sum total of these non covalent bonds viz H-bonds (Hydrogen bonds), Vander walls forces is strategically related almost inversely to the prevailing distance between the interacting atoms. Hence it is absolutely necessary that in order to accomplish the most successful binding of drug, essentially needs an accurate perfect fit of the legend atoms specifically to the most probable complementary receptor atoms. Salient features of fruitful binding of drug to receptor atoms are

1. Bonds are invariably reversible in nature.
2. A few exceptions for drugs which bind covalently to this targets.
3. Variants present in drug molecules like size, shape and charge distribution.
4. The simile of lock and key provides the most befitting concept of binding.
5. A high degree of specificity measures the actual interaction.

**Action Effect Sequence (Sequella)**

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

**Drug action**

It is the initial combination of the drug with its receptors resulting in a conform------- change in the latter (in case of agonists) or presentation of conformational change through exclusion of the agonist (in case of antagonists).

**Drug effect**

It is the ultimate change in the biological function brought about as a consequence of drug action through a series of intermediate steps. These are called ‘transducers’ (intermediate steps). Receptors sub serve two essential functions.

1. Recognition of the specific legend molecule.
2. Transduction of the signal into response.

Accordingly the receptor molecule has a legend binding domain (speciously and energetically suitable for binding of the specific legend) and an effector domain which undergoes a functional conformational change. These domains have now actually been identified in some receptors. The perturbation (disturbance) in the receptor molecule is variously translated into the response.

**Classification of receptors**

**a) Transmembrane enzymes**

These are protein embedded in the cell membrane are the transmembrane proteins that have an extracellular part called receptor and an intracellular part and change conformation of the receptor. This change activates the intracellular enzymes.

Eg: Insulin binds to its receptor activating Tyrosine kinase and then phosphorylates intracellular amino acids.

**b) G – protein coupled receptors**

These receptors are also transmembrane receptors, however in contrast to transmembrane enzymes the intracellular part is not an enzyme but an signal amplifier G-protein. The amplified signal activates an intracellular enzyme.

Eg: Adrenaline binds to Adrenergic β receptors then the G-protein activates the intracellular adenyl cyclase converting ATP to cyclic AMP (c AMP), then the cyclic AMP so called second messenger modifies intracellular biochemical reactions. G-protein coupled receptors function through 3 major pathways

1. Adenyl cyclase cAMP pathway
2. Phospholipase cIP3 (cIP3DAG) pathway
3. Channel regulation DAG ie. opening or closing of ionic channels

**c) Proteins or glycoprotein’s** form ionic channels in the cell membrane and enable passage of certain ions. In most of the cases drugs bind to the extracellular part of the ionic channel except local anaesthetics act intracellularly and modify the ionic flow through the channel.

Eg: The neurotransmitter δ-amino butyric acid (GABH) enhances the flow of the chloride ion into the intra neuronal space causing hypex polarization of the neuronal membrane. In general no second messenger is produced because the ion directly modifies the potential of the membrane.

**d) Intracellular receptors**

Drugs and certain hormones having high lipid solubility diffuse into the cell and further to cell organelle and bind to intracellular receptors. Eg: Gluco corticoids reach the intracellular DNA (receptor) and induce lipocortine production responsible for the decrease of inflammatory mediator production.

**e) Other receptors**

i) Intracellular enzymes

ii) Structural proteins

iii) Ion pumps

**i) Intracellular enzymes**

In these cases there are no second messengers because the change in the conformation of the receptor by the drug in the effect by itself.

Eg: Intracellular enzymes mono amino oxidase inhibitory drug *Selegiline* inhibits the degradation of secratoxin in the brain resulting in an antidepressant effect.

**ii) Structural proteins**

Colchicine inhibits polymerization of tubulin thus inhibiting migration of competent cells.

**iii) Ion pumps**

Digoxin inhibits Na+ / K+ ATP are resulting in membrane depolarization and excitation of cardiac cell membrane.

**Effectors**

These are in most cases intracellular signal messenger.

Eg: Calcium ions, cyclic AMP, Inozitol 1, 4, 5 try phosphate (IP3), Diecyl glycerol (DG)

A messenger activates intracellular kinases that phosphorylates proteins. The result is the modification of a certain function in the cell Eg: Muscle contraction.

**Transducer Mechanisms**

Considerable progress has been made in the understanding of transducer mechanisms which in most instances have been found to be highly complex multistep process that provide for amplification and integration of concurrently received extra and intracellular signals at each step. These mechanisms of translation of receptor activation into functional response are done by the above 4 major classes of receptors. Receptors falling in one category have also been found to posses considerable structural homology.

To bring out an effect, receptor acts as a first messenger in turn it summaries (confirmation) of drug molecule and the second messengers are the 4 molecules in the last page and may be considered to belong to one family of receptors.

**Functions of Receptors**

These can be summarized as

1. To propagate regulatory signal from outside to within the effector cell when the molecular spaces carrying the signal cannot itself penetrate the cell membrane.
2. To amplify the signal
3. To integrate various extracellular and intracellular regulatory signals.
4. To adopt to short term and long term changes in the regulatory functions and maintain homeostasis.

**Second messenger**

Refers to an information carrier that usually belong to any of the several categories of intracellular signals either acting at or strategically located very much within the plasma membrane and translating electrical or chemical massage from the environment into the cellulose responses. In other words, the second messengers represent the particular chemical whose intracellular concentration get increased or undergoes definite decrease in response to the receptor activation by agonists, and thus give rise to such processes which ultimately produce cellular.

**1. Calcium ions**

These are involved in several physiological processes, they are needed for heart --- muscles, blood clothing etc.

**2. Cyclic AMP**

It is a cyclic nucleotide, serves as intracellular and extracellular second messenger, mediating action of several amines or peptide hormones.

**3. Inositol 1, 4, 5 – triphosphate (IP3)**

It causes the release of calcium ions from certain intracellular organelles

**4. Diacyl – glycerol (DG)**

It is compounds of glycerol linked to 2 fatty acids, triglyceride and phospholipids

degradation product / compound. These are second messengers in the calcium mediated response to hormones.

Many hormones, neurotransmitters, autacoids and drugs act on specific membrane receptor, the immediate consequences of which is activation of a cytoplasmic component of the receptor, which may be an enzyme as Adenyl - cyclase, guanyl cyclase or activation of transport system or opening of an ion channel.

These cytoplasmic components which carry forward the stimulus from the receptors are known as second messengers. The receptor itself is the first messenger. Cyclic AMP (cAMP) serves as second messenger for Adenosine, Opioid, α & β Adrenoceptor & H2 receptors.

Cyclic GMP serves as second messenger for Angiotensin receptors, IP3 and DG serve as second messenger for α 1 adrenoceptor, H2 receptor and cholecystokinin.

Cyclic AMP has varied regulatory effects on cellular function. For Eg: Energy metabolism, cell division cell differentiation, ion transport, ion channel function, smooth muscle contraction etc.

Cyclic GMP has been identified in cardiac cells, bronchial smooth muscle cells and other tissues. For most effects produced, cyclic AMP seems to be stimulatory while cyclic GMP seems to be inhibitory in nature. When cyclic GMP and cyclic AMP systems are both present in a single cell or tissue they are linked to receptors through which drug produce opposite effect (antagonist nature). IP3 and DG are degradation products of membrane phospholipids by the enzyme phospholipase-C.

**Non receptor mediated action**

The functional property of regulatory bio macromolecules is dependant on their tertiary or three dimensional structure assumed through interaction with solvent molecule. Drugs directly interacting with a part of the macromolecule (Receptor) exhibit structural and stereospecificity of action and high potency and their specific antagonist are available and can be found. On the other hand drugs altering solvent do not need any structural specificity, are required in large quantities and no specific antagonists are found. Rather they act by virtue of their hydro or lipophilicity, altering membrane volume or the degree of disorder in its structure. Drugs which act by simple physical / chemical means including ethylating agents and the anti metabolite which leads to production of non functional or dysfunctional cellular components constitute other non receptor mediated.

**Dose Response Relationship**

When a drug is administered systemically, the dose response relationship has 2 components

1. Dose plasma concentration relationship
2. Plasma concentration – Response relationship

The former is determined by pharmacokinetic consideration and ordinarily, dose response relationship refer to the better which can be more easily studied in-vitro. Generally the intensity of response decreases with increase in dose or more precisely concentration of the receptor and the dose response curve is a rectangular hyperbola. This is because the drug, receptor interaction obeys ‘Law of mass action’

According,

E = Emax X1 (D)

KD + (D)

Where,

E is the observed effect at a ‘D’ dose of the drug Emax is the maximal response.

KD is the dissociation constant, of the drug receptor complex, which is equal to the dose of the drug at which half maximal response is produced.

**Explation of second graph**

Dose response curve for 4 drugs producing the same effect, drug B is less potent but equal affices as drug ‘A’. Drug C is less potent and has less afficacy than drug ‘B’. Drug ‘D’ is more potent than drugs A, B & C but less efficacious then drug A and B and equally efficacious as drug ‘C’.

If the dose is plotted on a logarithmic scale, the curve becomes sigmoid and a lineose relationship between log of dose and the response is seen in the intermediate zone \*(30 – 70% zone). As can be predicted from the above equation. This is not facular to drugs. Infect all stimuli are graded biologically by the functional changes stimuli intensity.

Eg: 1 kg and 2 kg weight held in 2 different hands can be easily differentiated but not 10kg & 11 kg weights though the absolute difference remains 1kg. There is 100% fractional change in former case but only 10% change in better case. In other words response is proportional to an exponential function (log) of the dose. Other advantages of plotting log dose response curve are

1. A wide range of drug doses can be easily displayed on a graph.
2. Comparison between agonists and study of antagonists becomes easier.
3. The log dose response curve (DRC) can be characterized by its slope and position.

**Drug potency and efficiency**

The position of DRC on the dose axis is the index of drug potency which refers to the amount of drugs needed to produce a certain response. A DRC positioned rightwards indicates lower potency. Relative potency is often more meaningful than absolute potency.

Eg: 10mg of Morphine is equivalent to 100 mg of pethidine (CNS depressants) Morphine is 10 times more potent than pethidine.

The upper index of DRC is indication of ‘Efficacy’. It refers to the maximum response that can be elucided by the drug.

Eg: Morphine produces a degree of analgesia not obtainable with any dose of aspirin.

Often the terms drug potency and drug efficacy are used interchangeably but these are not synonymous and refers to the different characteristic of the drug. The two can very independently.

Eg: a) Aspirin is less potent as will as less offices analgesic than Morphine.

b) Pathadine is less potent but equally officious or Morphine

c) Furasamide is less potent but more effective than Metalozone.

d) Doazapan is more potent but less effective than pentaborbritone as a CNS depressant.

Depending on the type of the drug both higher efficiency as in the case of Furesomide (diuretics) or lower efficacy as in the case of Diazepam could be clinically advantageous. The slope of DRC is also important. A steep slope indicates that a moderate increase in dose will markedly increase the response while a flat one implies that little increase in response will occur over a wide range of dosage.

There are 2 types of dose response curves

1. Graded dose response curve
2. Quantel dose response curve

**Graded dose response curve**

The intensity of response gradually increases with the increase in dose upto a level where the size of response to a drug is measured in a single biological unit with animal / tissue / organ. It shows that when the dose exceeds a critical level (threshold dose) the response also increases progressively until it reaches the maximum or scaling level (also called study level sealing effect).

**Threshold dose**

It is the minimum dose required to produce a miserable response. The minimum dose producing the maximum or sealing effect is called sealing dose and any further increase in dose will not result in further increase in response.

**Quantal dose response relationship (QDR)**

It gives the proportion of subjects (quantum or percentage) in a population responding or not responding to the effect of a drug. All or none / Yes or no dose response relationship is there. As in graded dose response there is no gradation of intensity of response in QDR, but indicates only percentage responding or percentage not responding, percentage awake or percentage slept. Percentage deed or percentage awake, percentage cured or percentage not cured.

The graded response does not reflect individual variation as noted under QDR. The QDR curve is used to determine the affective, toxic, lethal or any other fixed responses. In case of graded response relationship when the magnitude of response is plotted agonist arithmetic units of doses, a hyperbolic curve is obtained. However when response is plotted against logarithmic doses sigmoid or S. Shaped curve is obtained, when the centre portion is lincar log dose response curves or LDRC helps to know relative potency, efficacy and selectivity of different drugs. The quantal LDRC is used to find out median affective or toxic / lethal dose (LD50) of different drugs in arriving at therapeutic efficacy from a simple ratio of ----------- lethal dose (LD50) and median effective dose (ED50)

Therapeutic index = LD50

ED 50

Therapeutic ratio (TR) is the ratio of LD50to ED50 and it is expressed by LD25 + ED75.

The therapeutic gives better index of safety of drugs as it also includes steepness of the curve.

The margin of safety of a drug can be better expressed through standard safety margin (SSM) which is a ratio of extremes of the QDR such as LD1 / ED99 or LD0.1 / ED99.9 ie. minimum toxic or lethal dose divided by maximum effective dose. This factor also indicates the aim of drug usage ie. achieving therapeutic effect without causing toxicity among patients. Drug safety can also be determined by finding out its certain safety factor which is calculated by

Certain safety factor = ( LD1 – ED99)-1 X 100

Or

CSF = ( LD0.1 – ED99.9) -1 X 100

Which shows that the dose effective in 99 out of 100 patients or 999 out of 1000 patients has to be raised by a certain percentage factor to be lethal to 1 out of 100 or 1000 patients.

**Latency or Latent period**

It is the time interval between termination of administration of drug and time and at which its concentration in plasma is high enough to produce the effect.

Latency various depending upon route of administration and is short by intravenous injection followed by intramuscular then by intraperitoneal then by subcutaneous and longest after oral administration.