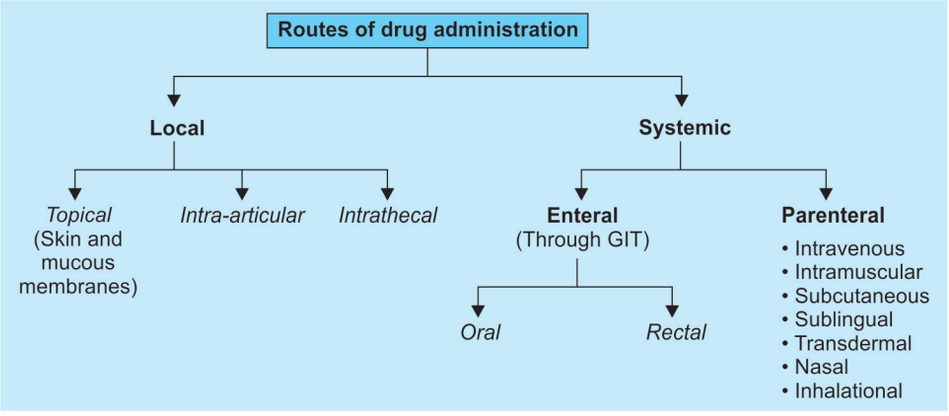
Chapter

1 General Pharmacology

Pharmacology is the science dealing with drugs. It is divided into several branches like *pharmacokinetics, pharmacodynamics, pharmacotherapeutics, chemotherapy and toxicology* etc.

When a drug is administered to a person, it will exert some effect on the patient (*Pharmacodynamics*) and the patient's body will have some effect on the drug (*Pharmacokinetics*). These are the two major branches of pharmacology. Before discussing about these branches, we will summarize, how drugs can be administered to a patient (with some important points only).

ROUTES OF DRUG ADMINISTRATION



Local Routes include topical application on the skin and mucous membranes as well as the routes like *intra-articular* (e.g. hydrocortisone) and intrathecal (e.g. amphotericin *B*).

Systemic Routes include oral, sublingual, transdermal, nasal, inhalational, rectal and other parenteral routes (intravenous, intramuscular, intradermal and subcutaneous).

- **Oral route** is safer and economical but several drugs are not effective by this route because of *high first pass metabolism* in the liver and intestinal wall (e.g. *nitrates, lignocaine, propanolol, pethidine*).
- **Sublingual route** *avoids first pass metabolism*, can be used in *emergencies,* can be self-administered and also after getting the desired action, rest of the drug can be spitted. Drugs like *nitroglycerine, isosorbide dinitrate, clonidine, nifedipine* etc. can be administered by this route.
- **Transdermal route** is used only for the drugs which are *highly lipid soluble* and can be absorbed through intact skin. By this route, there is a constant release of the drug (rate of drug delivery to skin is *less than the maximum absorptive capacity of the skin* so that absorption does not become the limiting factor and there is a constant level of the drug in the blood) and it may be administered less frequently. *Nitroglycerine, nicotine, fentanyl and hyoscine* are administered through transdermal patch.
- Drugs administered by **nasal route** are *nafarelin* (GnRH agonist), *calcitonin* and *desmopressin.*
- **Inhalational route** is the route by which the rate of drug *delivery can be controlled like i.v.* infusion. The drugs administered by this route include drugs for asthma (*e.g., salbutamol, ipratropium, montelukast and inhalational steroids*) and inhalational anaesthetic agents like *nitrous oxide*.
- **Rectal route** avoids first pass metabolism to 50% extent. *Diazepam* is given by this route in children for febrile seizures.

- **Intravenously**, drugs can be given as **bolus** or via **infusion**.
- Other parenteral routes include *i.m., s.c. and intradermal* routes.

PHARMACOKINETICS

It is the effect of body on the drug i.e. movement of the drug in, through and out of the body. It is also called **ADME** study as it deals with **A**bsorption, **D**istribution, **M**etabolism and **E**xcretion of a drug.

1. Absorption

It depends on several factors. Only lipid soluble drugs can cross the biological membranes. So, if a drug is administered by oral route, it has to cross the membranes of GIT and blood vessels to reach the blood. Therefore, it should be in lipid soluble form. If a drug is a weak electrolyte, it is the unionized form which is lipid soluble and the ionized form is water soluble.

WHEN MEDIUM IS SAME, DRUGS CAN CROSS THE MEMBRANE

From this statement, we can find that *acidic drugs can cross the membranes in acidic medium* i.e. acidic drugs are lipid soluble in acidic medium (for this acidic drugs must be mainly in the un-ionized form in acidic medium). Opposite is also true for basic drugs. As gastric pH is acidic, therefore acidic drugs are more likely to be absorbed from the stomach, because these will be in unionized (lipid soluble) form here. Thus, aspirin is more likely to be absorbed in the stomach than morphine or atropine (basic drugs).

Note:

There is never 100% lipid solubility or water solubility, because ionization of a drug is never 100% or 0%. As we have already discussed, when medium is same the drug is lipid soluble. Suppose, we are talking about an acidic drug having pKa of 5.0 (i.e. at pH = 5.0, it will be 50% ionized and 50% un-ionized). If it is present in a medium with pH=4.0, it is lipid soluble. But, if the pH of the medium changes to 3.0, what will happen? Obviously, it will become more lipid soluble because more of the drug become un-ionized. We need to remember few concepts:

- If pH of the medium is equal to pKa, then drug is 50% ionized and 50% un-ionized.
- If the pH of the medium is more than pKa (medium becomes alkaline).
  - For acidic drugs, ionized form increases and non-ionized form decreases.
  - For basic drugs, un-ionized form increases and ionized form decreases
- If the pH of the medium is less than pKa, opposite happens, i.e. acidic drugs will be in more un-ionized form and basic drugs be more ionized.
- This ionized or unionized fraction depends on difference (d) between pH and pKa.
- When pH = pKa (d=0) Ionization is 50% and un-ionized fraction is also 50%.
- When pH - pKa = 1 (d=1) one form is 90% and other form is 10%
- When d = 2, one form is 99% and other is 1%
- When d = 3, one form is 99.9% and other is 0.1%

Example for a drug with pKa = 5.0

pH of Medium	Nature of drug	(pH-pKa)	Ionized form	Non-ionized form
3.0	Acidic	2	1%	99%
4.0	Acidic	1	10%	90%
5.0	Acidic	0	50%	50%
6.0	Acidic	1	90%	10%
7.0	Acidic	2	99%	1%
8.0	Acidic	3	99.9%	0.1%
3.0	Basic	2	99%	1%
4.0	Basic	1	90%	10%
5.0	Basic	0	50%	50%
6.0	Basic	1	10%	90%
7.0	Basic	2	1%	99%
8.0	Basic	3	0.1%	99.9%

Note :

This is a simplified version of Henderson Hasselbalch equation which states that

$$\log\left(\frac{\text{Protonated form}}{\text{Unprotonatal form}}\right) = \text{pKa - pH}$$

Bioavailability

- It is the fraction of administered drug that reaches the systemic circulation in the unchanged form.
- When we administer a drug orally, first it is absorbed into the portal circulation and reaches the liver. Here, some of the drug may be metabolized (*first pass metabolism or pre-systemic metabolism*) and rest of the drug reaches the systemic circulation. Thus *absorption and first pass metabolism are two important determinants of bioavailability*.
- By *i.v. route* it is *100%.*
- It can be *calculated by comparing the AUC* (area under plasma concentration time curve) for i.v. route and for that particular route. It can also be calculated by comparing the excretion in the urine.

- AUC tells about the extent of absorption of the drug.
- Tmax. tells about the time to reach maximum concentration i.e. rate of absorption
- Cmax is the maximum concentration of a drug that can be obtained

Bioequivalence: Many different pharmaceutical companies can manufacture same compound (with same dose as well as dosage form) e.g. phenytoin is available as tab. Dilantin as well as Tab. Eptoin. If the difference in the bioavailability of these two preparations (same drugs, same dose, same dosage forms) is less than 20%, these are known to be bioequivalent. As the term implies, these are biologically equal i.e. will produce similar plasma concentrations.

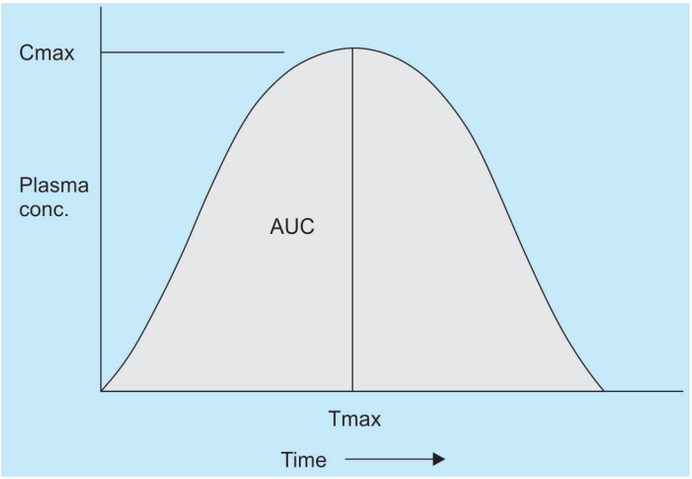


Fig 1.1. Plot between plasma concentration and time to calculate bioavailability

2. Distribution

After the drug reaches the blood, it may be distributed to various tissues. This is determined by a hypothetical parameter, **Volume of distribution** (V_d). It is the volume that would be required to contain the administered dose if that dose was evenly distributed at the concentration measured in plasma. If more amount of drug is entering the tissues, it has a higher volume of distribution and vice-a-versa. It depends on several factors like lipid solubility and plasma protein binding.

- Drugs which are **lipid soluble** are more likely to cross the blood vessel wall and thus have **high volume of distribution**.
- If a drug is highly **bound to plasma proteins**, (*e.g.,* warfarin, benzodiazepines, furosemide, calcium channel blockers, digitoxin etc.) it will behave like a large molecule and more likely to stay in the plasma. Therefore, less will go to tissues resulting in **reduced volume of distribution.**

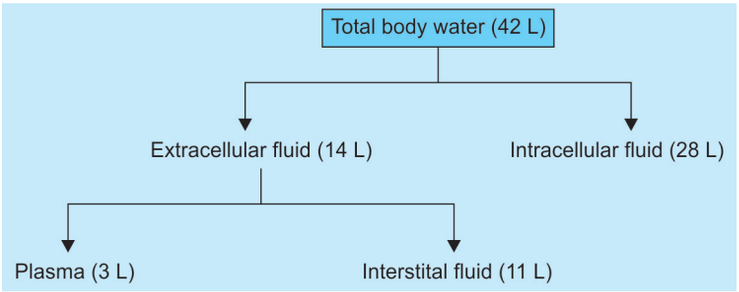
It is the free form (which is not bound to plasma proteins) of a drug that is responsible for the action as well as the metabolism of a drug. Therefore **plasma protein binding** *makes a drug long acting* by reducing its metabolism. This property can also expose the drug to several drug interactions due to displacement from the binding site by other drugs. The drugs which have low V_d are restricted to the vascular compartment and thus their poisoning can be benefited by dialysis. *Dialysis in not effective in the poisoning due to amphetamines, antidepressants, antipsychotics, benzodiazepines, digoxin, opioids, β-blockers, calcium channel blockers and quinidine.*

Volume of distribution

It can be calculated by dividing the plasma concentration attained to the dose of a drug administered i.v. Initial plasma concentration (Co) is calculated by extrapolating the graph of plasma concentration vs time to y-axis.

$$V_d = \frac{\textbf{Dose administratrd i.v.}}{\textbf{Plasma concentration } (C_o)}$$

It is a measure of the distribution of a drug. If V_d is more, it means more amount of drug is in the tissues and less is in the plasma. Thus, higher dose has to be administered to attain the same plasma concentration for drugs having high V_d than those having low V_d. This high dose is called **loading dose**. Thus, **V_d is the main determinant of loading dose**. **Chloroquine** is the drug with **highest V_d** (1300 L/Kg).



After a drug reaches plasma, four different possibilities are:

1. Drug is *highly ionized* (water soluble) and has *high molecular weight*. It is not able to cross the membranes of blood vessel, so remains in plasma. Thus, the V_d will be low (i.e. around 3L i.e. almost equivalent to plasma volume).
2. Drug is *highly ionized* but has *low molecular weight*. Some of it can reach interstitial fluid (ISF). Thus V_d will be around 14L (volume of plasma + volume of interstitial fluid).
3. Drug is *non-ionized* (lipid soluble) and it has *low molecular weight*, it can enter in cells also, thus having high V_d of around 24L (Plasma + ISF+ ICF).
4. Drug has *low molecular weight*, *non-ionized* as well as *high affinity for tissues*, then it can have V_d even greater than total body water (≥ 42L).

3. Metabolism

The primary site of metabolism is liver. Most of the drugs are inactivated by metabolism but some may be activated from the inactive compounds (**Prodrugs**) and others may give rise to active metabolites from the active compound.

- Metabolism may occur with the help of **microsomal** (*present in smooth endoplasmic reticulum*) or **non-microsomal** enzymes. Microsomal enzymes (*monooxygenases, cytochrome P450 and glucoronyl transferase*) may be **induced** or **inhibited** by other drugs whereas non-microsomal enzymes are not subjected to these interactions.

Cytochrome P-450 (CYP) enymes are a superfamily of enzymes located in endoplasmic reticulum (microsomes). These are named with root CYP followed by a number (designating the family), a letter (denoting sub-family) and another number (designating the CYP form). e.g. CYP 3A4 is family 3, sub family A and gene number 4. CYP 3A4 is involved in metabolism of more than 50% of clinically used drugs. Other important isoforms involved in drug metabolism are CYP 2C and CYP 2D. On the other hand, CYPIA, 1B, 2A, 2B and 2E are not significantly involved in metabolism of drugs but catalyse the metabolic conversion of procarcinogens to the active carcinogenic compounds. CYP inducers, stimulate a nuclear receptor that induces the expression of genes encoding drug metabolizing enzymes. Important receptors that are involved in microsomal enzyme induction are AHR (aryl hydrocarbon receptor), constitutive androstane receptor (CAR), pregnane x receptor (PXR), farsenoid X receptor, vitamin D receptor, retinoic acid receptor (RAR), retinoic X receptor (RXR) and peroxisome proliferator activated receptor (PPAR).

- The drug which is metabolized by a microsomal enzyme is known as substrate and the chemical increasing or decreasing the number of enzymes is known as inducer or inhibitor respectively.
- **Enzyme inducers** will increase the metabolism of other drugs and thus their effect will decrease. Therefore dose of such drugs (which are metabolized by microsomal enzymes) should be increased when administered along with microsomal enzyme inducers. Potent inducers of microsomal enzymes include **rifampicin, phenobarbitone, phenytoin, griseofulvin, phenylbutazone and chloral hydrate**.

Enzyme inducers

G – **G**riseofulvin
P – **P**henytoin
R – **R**ifampicin
S – **S**moking
Cell – **C**arbamazepine
Phone – **P**henobarbitone

- **Further, rate-limiting** enzyme of porphyrin synthesis i.e. δ-ALA synthase is a microsomal enzyme. Enzyme inducers like phenytoin and phenobarbitone induce it and increase porphyrin synthesis. Thus, these drugs are contra-indicated in acute intermittent porphyria.
- **Enzyme inhibitors** will decrease the metabolism of drugs metabolized by microsomal enzymes, thus predisposes to the toxicity by such agents. Inhibitors include **ketoconazole, cimetidine, erythromycin and metronidazole**.

Enzyme inhibitors

Vitamin – **V**alproate
K – **K**etoconazole
Cannot – **C**imetidine
Cause – **C**iprofloxacin
Enzyme – **E**rythromycin
Inhibition – **I**NH

CYP	Substrates	Inducers	Inhibitors
1A2	Paracetamol, Tacrine, Imipramine, Theophylline, Warfarin	Smoking, Omeprazole	Cimetidine, Fluvoxamine
2C9	Celecoxib, Diclofenac, Phenytoin, Tolbutamide, Warfarin, Glipizide, Losartan	Rifampicin, Barbiturates	Amiodarone, Fluconazole, Isoniazid
2C19	Diazepam, Omeprazole, Propanolol, Mephenytoin, Ticlopidine, Clopidogrel	Rifampicin, Barbiturates	Fluconazole, Ketoconazole Omeprazole, Fluoxetine
2D6	Beta blockers (Metoprolol, Timolol), Mexiletine, TCA (Imipramine, Desipramine, Clomipramine), Paroxetine, Codeine, Dextromethorphan Haloperidol, Thioridazine, Risperidone	Unknown	Quindine, Paroxetine, Cimetidine, Ritonavir
2E1	Halothane, Enflurane, Paracetamol	Ethanol, Isoniazid	Disulfiram
3A4	Calcium channel blockers (Verapamil, Diltiazem, Nifedipine), Statins (Atorva, Lova, Simva), Macrolides (Clarithromycin, Erythromycin), Protease inhibitors (Ritonavir, Indinavir, Saquinavir), Immunosuppressants (Cyclosporine, Tacrolimus), Astemizole, Cisapride, Terfenadine, Diazepam, Triazolam, Midazolam.	Barbiturates, Carbamazepine, Phenytoin, Rifampicin, Pioglitazone, St. John's wort	Cimetidine, Eythromycin, Clarithromycin, Cimetidine, Ritonavir Indinavir, Calcium channel blockers, Isoniazid, Imatinib, Ketoconazole

Prodrugs

- All ACE inhibitors except captopril and lisinopril
- Methyl-dopa
- Prednisone
- Fluorouracil
- Proguanil
- Minoxidil (activated by phase II reaction)
- Talampicillin
- Levo-dopa
- Dipivefrine
- Sulfasalazine
- Mercaptopurine
- Sulindac
- Cyclophosphamide
- Prontosil

Metabolic reactions may be classified into phase I (non-synthetic) and phase II (synthetic) reactions. Function of **phase I reactions** is to attach a **functional group** to the drug molecule whereas **phase II** reactions serve to **attach a conjugate** to the drug molecule. After phase I reaction, drug may be water soluble or lipid soluble whereas **after phase II reaction**, **all drugs become water soluble** (lipid insoluble). *Phase I reactions include oxidation, reduction, hydrolysis, cyclization and decyclization etc. whereas phase II reactions include glucuronidation, acetylation, methylation, sulfation and glycine conjugation etc.*

4. Excretion

The major route of excretion is kidney. Excretion through kidneys occurs by glomerular filtration, tubular reabsorption and tubular secretion.

Glomerular filtration depends on the *plasma protein binding and renal blood flow*. It **does not depend on the lipid solubility** because all substances (whether water soluble or lipid soluble) can cross the fenestrated glomerular membrane.

Tubular reabsorption depends on the *lipid solubility*. If a drug is lipid soluble, more of it will be reabsorbed and less will be excreted. Opposite is true for lipid insoluble drugs. As lipid solubility depends on ionization, the ionized drug will be excreted by the kidney. Thus, in acidic drug poisoning (*salicylate, barbiturates, chlorpropamide, methotrexate* etc.) urine should be *alkalinized* with sodium bicarbonate because weak acids are in ionized form in alkaline urine and thus are easily excreted. Similiary for basic drug poisoning (e.g. *morphine, amphetamine* etc.), urine should be *acidified* using ammonium chloride.

Tubular secretion does not depend on lipid solubility or plasma protein binding. In the nephron, separate pumps are present for acidic and basic drugs. Drugs utilizing the same transporter may show drug interactions e.g. *probenecid decreases the excretion of penicillin* and increases the excretion of uric acid. Remember, exogenous substances e.g. penicillins are removed whereas endogenous substances like uric acid are retained by these pumps.

KINETICS OF ELIMINATION

Pharmacokinetic models can be one-compartment or two-compartment models.

One-compartment model: If the drug is having less or no distribution in tissues, the elimination of the drug from plasma is continuous and the log plasma concentration versus time curve is linear (for drugs following first order kinetics)

- Slope of this curve (– k) is rate constant of elimination and is related to $t_{½}$, V_d and CL as

$$CL = k \times V_d$$
$$k = 0.693/t_{½}$$

- The extrapolation of this curve on y-axis is C_0 and is used to calculate V_d.

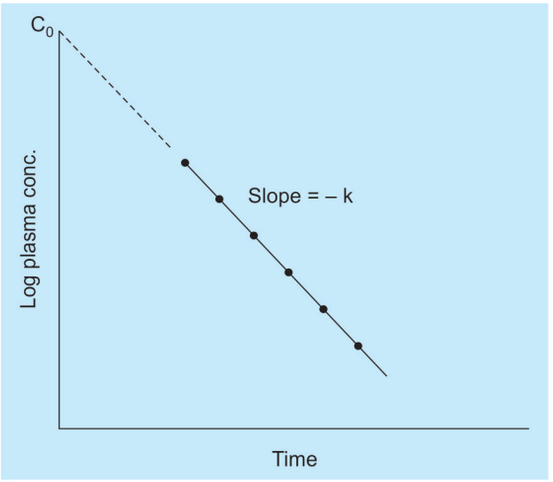


Fig. 1.2: Plasma concentration time curve for a drug following one compartment model

Two-compartment Model: For most of the drugs, initial rapid decline in plasma concentration occur (due to distribution in tissues) followed by a slower decline (due to elimination).

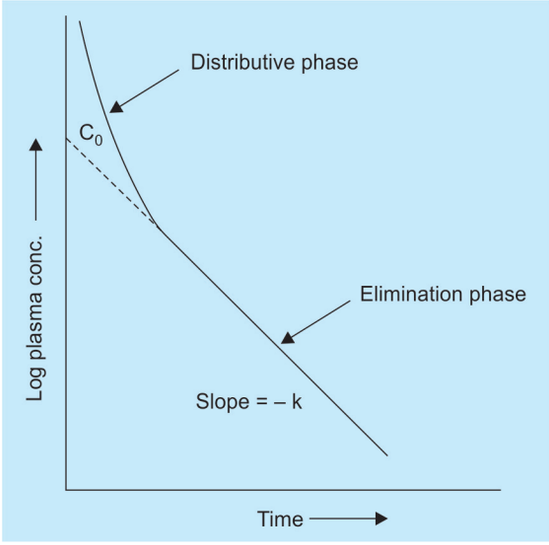


Fig. 1.3: Plasma concentration time curve for a drug following two compartment model

- Half life as well as Co are calculated from elimination phase for drug following two compartment model of distribution and elimination.

Rate of Elimination is the *amount of drug eliminated* (in units of weight like grams) *per unit time*. If it is seen as a function of plasma concentration, we derive an important parameter known as clearance (CL). Thus, **total body clearance is the rate of elimination of a drug divided by its plasma concentration. However, Renal clearance can be calculated by the formula**

$$\textbf{Renal Clearance} = \frac{uv}{p}$$

Here, u = Urine concentration of drug
p = Plasma concentration of durg
v = Rate of urine flow

Order of kinetics

Drugs may follow zero order or first order kinetics. It depends on the following formula:

$$\textbf{Rate of Elimination} \propto \{\textbf{Plasma Concentration}\}^{\textbf{order}}$$

- Thus, if a drug follows zero order kinetics, $\{\text{Plasma Concentration}\}^0$ is equal to one, in other words rate of elimination is independent of plasma concentration or rate of elimination is constant.
- From the above formula, rate of elimination is proportional to plasma concentration for the drugs following first order kinetics.

First Order Kinetics (Linear kinetics)	Zero Order Kinetics (Non linear Kinetics)
1. Constant fraction of drug is eliminated per unit time.	1. Constant amount of the drug is eliminated per unit time.
2. Rate of elimination is proportional to plasma concentration.	2. Rate of elimination is independent of plasma concentration.
3. Clearance remains constant.	3. Clearance is more at low concentrations and less at high concentrations.
4. Half life remains constant.	4. Half life is less at low concentrations and more at high concentrations.
5. Most of the drugs follow first order kinetics.	5. Very few drugs follow pure zero order kinetics e.g. alcohol
	6. Any drug at high concentration (when metabolic or elimination pathway is saturated) may show zero order kinetics.

The drugs whose kinetics changes from first order to zero order at therapeutic concentrations are said to follow **pseudo-zero order kinetics**.

Drugs showing zero/ pseudo zero order kinetics

• **Zero**	Zero order kinetics shown by
• **W**	**W**arfarin
• **A**	**A**lcohol and **A**spirin
• **T**	**T**heophylline
• **T**	**T**olbutamide
• **P**ower	**P**henytoin

Why some drugs follow zero order and other first order Kinetics?

Elimination of a drug depends on metabolism and excretion. For most of the drugs, these pathways are not a limiting factor i.e. present in excess. Suppose, we give 100 molecules of the drug and enzyme to metabolize this drug are 10,000.

Now, only 100 out of 10,000 enzymes will act and metabolize the drug. Suppose these can metabolize 50% of molecules in one hour.

If we give 200 molecules of the drug, now 200 out of 10,000 enzymes will start acting and can metabolize 50% of drug in same time i.e. one hour.

If we give 500, 2000 or any number of molecules till 10,000, same will occur.

Thus, till this point, constant fraction of a drug is eliminated in a particular time i.e. drug follows first order kinetics. Most of the drugs, therefore, follow this kinetics.

Suppose we give 20,000 molecules or 30,000 molecules of the drug. Now, enzymes become the limiting factor and can break only 10,000 molecules in one hour i.e. amount of a drug eliminated become constant i.e. the drug start following zero order kinetics.

Half Life ($t_{1/2}$)

It is the time required to reduce the plasma concentration to half (50%) of the original value. If metabolism is more, half life is less and vice-versa. It is a *secondary pharmacokinetic parameter derived from two primary parameters ; V_d and CL. It determines the dosing interval and time required to reach the steady state* (It does not affect the dose of the drug). Drugs having short half lives are administered more frequently than those having longer half life. It takes 4 to 5 half lives for a drug to reach its steady state.

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

If a drug follows **first order kinetics**, its **half life is constant**. This is *true both for rising as well as falling plasma concentrations*. When a drug is given by constant i.v. infusion, initially the plasma level rises, it reaches a steady state and when infusion is stopped this level starts declining. Elimination of the drug from plasma is 50% in one half life, 75% (50 + 25) in two half lives, 87.5% (50 + 25 + 12.5) in three half lives and so on. The same is true for rising plasma concentration also i.e. with constant i.v. infusion, in one half life the plasma concentration is half of steady state and in two half lives, it is 75% and so on.

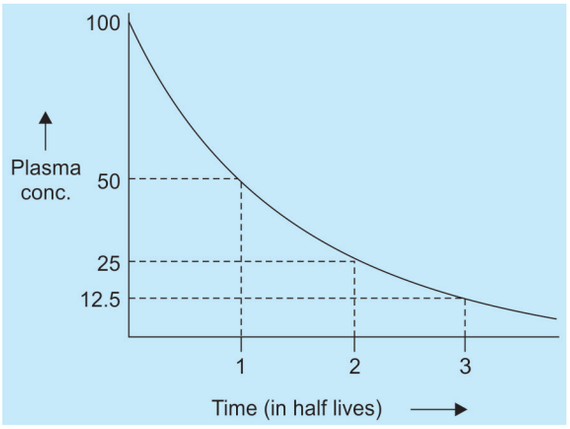


Fig. 1.4: Plasma concentration time curve in first order kinetics when drug administration is stopped at steady state concentration

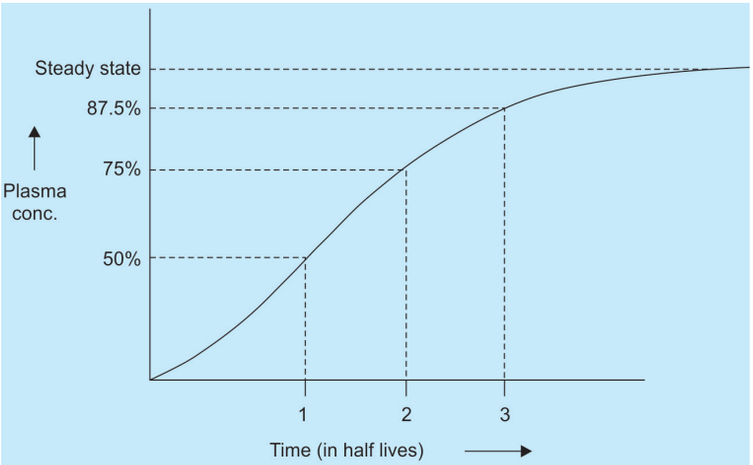


Fig. 1.5: Plasma concentration time curve in first order kinetics with constant i.v. infusion

Dosing Regimen

It includes the *dose, frequency and route of administration*. Dosing regimen influences the onset and duration of a drug action. Effect of single dose (oral as well as i.v.), continuous i.v. infusion and intermittent dose on plasma concentration of a drug are discussed below.

1. **Single Dose:** Plasma concentration increases initially, becomes maximum and then starts decreasing as the drug is eliminated and distributed to tissues. By i.v. route peak occurs early as compared to oral route (delayed onset by oral route).
2. **Continous intravenous infusion:** Plasma concentration keep on increasing till it becomes maximum, known as steady state (Rate of administration becomes equal to rate of elimination). Time to reach steady state depends upon half-life (takes approx. 5 half-lives). Increasing the rate of infusion will not affect the time to reach steady state, however steady state will be at higher plasma concentration.
3. **Intermittent Dose:** If a fixed dose is administered after every half-life, plasma concentration keep on increasing till it reaches steady state. Now, it fluctuates between two points, so that average concentration becomes constant. It also takes 4-5 half-lives to reach steady state. The fluctuation will be more with more dosing interval and less with more frequent administration.

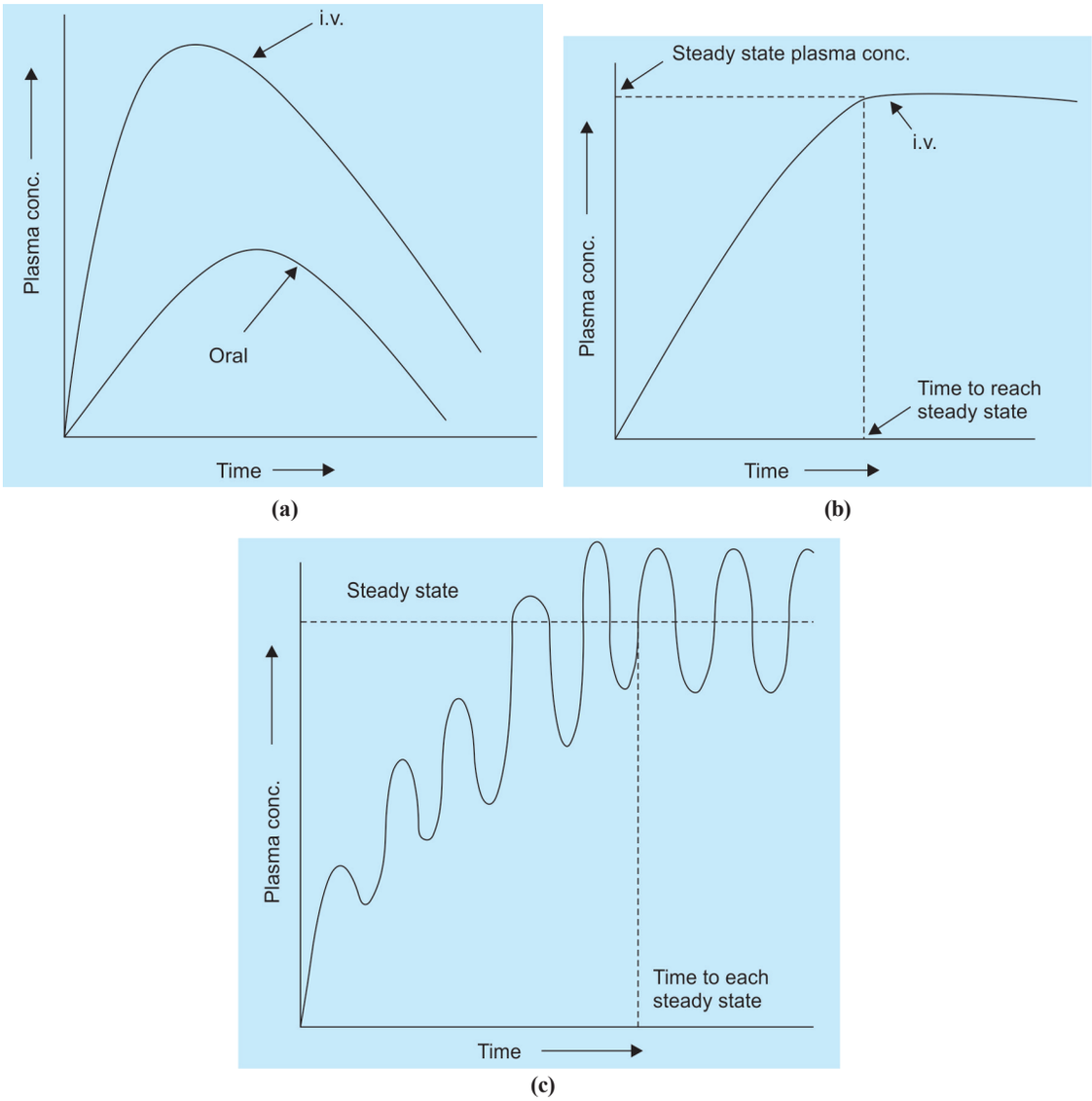


Fig. 1.6: Plasma concentration time curve after (a) single i.v. and oral dose (b) continuous i.v. administration (c) Repeated doses after every half-life

Two Dose Strategy

The drugs having high volume of distribution are given by this strategy. First a large dose (loading dose) is administered to attain the steady state quickly and later on, to maintain the plasma concentration smaller dose is given (maintenance dose).

Loading dose: It is mainly used for drugs having long $t_{½}$ and large volume of distribution. It is given to load (saturate) the tissue stores. So it is mainly dependent on V_d.

Loading dose = V_d × Target plasma concentration

Maintenance dose: It is mainly dependent on CL.

Maintenance dose = CL × Target plasma concentration

Therapeutic Drug Monitoring (TDM)

- TDM is a process by which the dose of a drug is adjusted according to its plasma concentration.
- It is done for drugs having *known correlation between serum level and toxicity.*
- It is done for drugs having *wide variation in pharmacokinetics* (absorption, metabolism or excretion), both intra- as well as inter- individual.
- It is done for the drugs having *low therapeutic index* like digitalis, aminoglycosides, tricyclic antidepressants, theophylline, lithium, antiepileptics, immuno-modulators and antiarrhythmics etc.
- TDM is done for those drugs whose *effect cannot be easily measured* (like effect of antihypertensive drugs can be easily measured by monitoring BP, so TDM is not used).
- TDM is **not done for** the drugs which are *activated in the body* or produce active metabolites.

PHARMACODYNAMICS

This is the study dealing with the effect of drugs on the body. It includes actions of drugs as well as their mechanism. Drugs may act by *physical mechanism* (e.g. osmotic diuretics), *chemical action* (e.g. antacids), stimulation or inhibition of *enzymes* (competitive and non-competitive inhibition) or via *receptors*.

Enzyme Inhibition

Drugs may act by inhibiting the enzymes competitively or non-competitively.

Competitive Inhibition : Important points about this type of enzyme inhibition (e.g. sulfonamides) are :

- Drug should have *similar structure* as that of substrate of the enzyme.
- Inhibitor *binds to the active site* of the enzyme.
- This type of inhibition is *surmountable*, i.e. inhibition can be overcome by increasing the dose of the substrate.
- It results in *increase in K_m but does not affect the V_{max}.*
- If the drug binds very strongly to the active site, so that it cannot be displaced even by large concentration of substrate, it can result in **irreversible competitive inhibition**. In this type of inhibition, *K_m rises and V_{max} decreases.*

Note: Km looks like kilometers. In competition one need to run more kilometers i.e. Km increases

Noncompetitive Inhibition : Important points about this type of enzyme inhibition (e.g. carbonic anhydrase inhibitors) are :

- Drug *need not have similar structure* as that of substrate of the enzyme.
- It *binds to* a different site of the enzyme, known as *allosteric site*.
- This type of inhibition is *insurmountable*, i.e. inhibition cannot be overcome by increasing the dose of the substrate.
- It results in *decrease in V_{max} but does not affect the K_m.*

Receptors

These are the binding sites of the drug with functional correlate. Two important terms related to the receptors are affinity and intrinsic activity (IA).

Affinity is the *ability of a drug to combine with the receptor*. If a drug has no affinity, it will not bind to the receptor. So, all type of drugs acting via receptors (agonist, antagonist, inverse agonist and partial agonist) possess some affinity for the receptors.

After binding to the receptor, the *ability to activate the receptor* is called its **intrinsic activity**. It *varies from –1 through zero to +1*.

Drugs may be divided into four types *based on their intrinsic activities.*

- **Agonist:** It will bind to the receptor and *activate it maximally*. i.e. **IA is +1**
- **Antagonist:** Binds to the receptor but produces **no effect** (**IA is 0**). But now agonist is not able to bind to the receptor because these are already occupied by the antagonist. Thus, it decreases the action of the agonist but itself has no effect.
- **Partial agonist:** It activates the receptor submaximally (**IA between 0 and +1**). It will produce the similar effect in the absence of agonist but it will decrease the effect of a pure agonist. e.g. pindolol has partial agonistic activity at β_1 receptors. In the presence of agonists like adrenaline and nor-adrenaline it will produce antagonistic effect i.e. decrease in heart rate but even in high doses it does not result in severe bradycardia due to some agonistic action.
- **Inverse agonist:** These type of drugs bind to the receptor and produce opposite effect (**IA is negative**) e.g. β carboline is an inverse agonist at BZD receptors.

Antagonist : These may be physical, chemical, physiological or pharmacological.

- **Physical antagonist** binds to the drug and prevents its absorption like charcoal binds to the alkaloids and prevents their absorption.
- **Chemical antagonist** combines with a substance chemically like chelating agents bind with the metals.
- **Physiological antagonist** produces an action opposite to a substance but *by binding to the different receptors* e.g. adrenaline is a physiological antagonist of histamine because adrenaline causes bronchodilation by binding to β_2 receptors, which is opposite to bronchoconstriction caused by histamine through H_1 receptors.
- **Pharmacological antagonists** produce opposite actions by *binding to the same receptor* e.g. beta blockers.

CLASSIFICATION OF RECEPTORS

The receptors are classified into four types based on the signal transduction mechanisms.

G Protein Coupled Receptors

These are **heptahelical (serpentine) receptors** i.e. have *seven transmembrane spanning segments.*

Drugs bind to the receptor which in turn activates a G protein (GTP activated protein) that may result in activation or inhibition of **adenylyl cyclase** (resulting in increase or decrease of **cAMP**) like β adrenergic receptors, **phospholipase C** (resulting in conversion of PIP_2 to IP_3 and DAG, which increases intracellular calcium) like alpha adrenergic receptors or **stimulation** or **inhibition of ion channels** like muscarinic cholinergic receptors. G-proteins consist of three subunits; α, β and γ. When all three are joined together (along with GDP), G-protein is inactive. When GTP replaces GDP, α-subunit seperates from β–γ subunit and become activated. Cyclic AMP, IP_3 and DAG act as second messengers whereas Ca^{2+} is a third messenger. Cyclic AMP activates protein kinases (like protein kinase A) which in turn result in action by phosphorylation of their substrates.

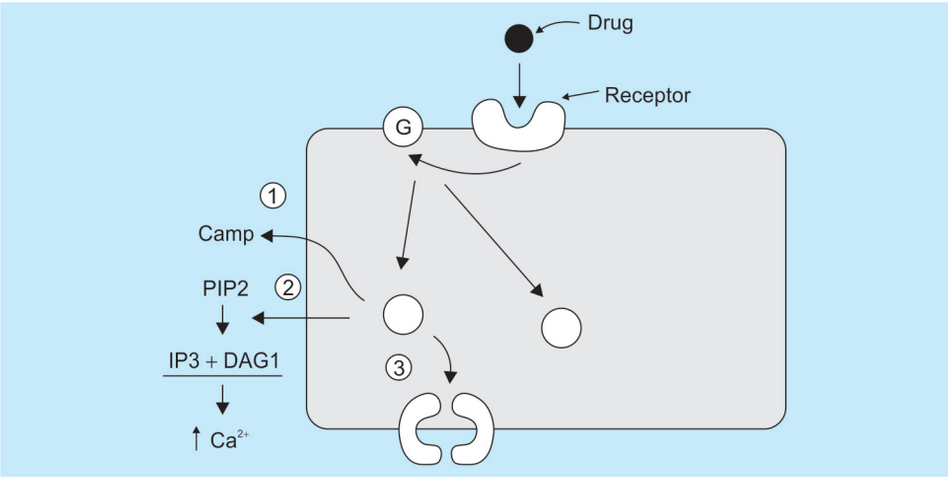


Fig 1.7.: G-protein coupled receptor

Ionotropic Receptors

The drug binds directly to the receptor located on an ion channel without mediation by G proteins. These are the **fastest acting receptors**. It includes **$GABA_A$, N_M, N_N, NMDA** (receptor of glutamate) and **$5\text{-}HT_3$** receptors.

Enzymatic Receptors

This type of receptor has two sites, the drug binds on the extracellular site and the intracellular site has enzymatic activity (mostly *tyrosine kinase*). This enzyme can be activated via JAK-STAT pathway. **Insulin, growth hormone, prolactin** and **cytokines** act via enzymatic receptors.

Intracellular Receptors

These types of receptors are **slowest acting**. These may be present in the **cytoplasm** (**glucocorticoids, mineralocorticoids, and vit. D**) or in the **nucleus** (**T_3, T_4, Retinoic acid, PPAR, estrogen, progesterone and testosterone**). *Both type of receptors finally act by nuclear mechanisms* (i.e. by affecting transcription).

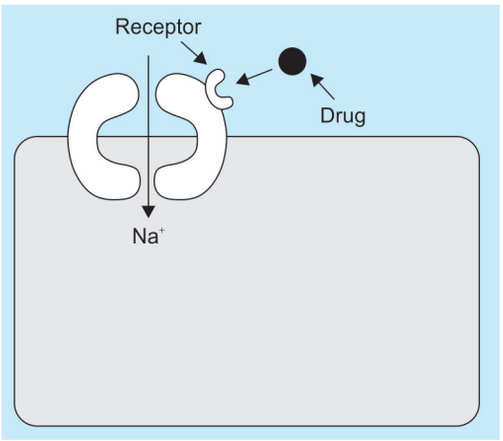


Fig 1.8.: Ionotropic Receptors

DOSE RESPONSE CURVE (DRC)

It is a graph between the dose of a drug administered (on X-axis) and the effect produced by the drug (on Y-axis). It consists of two components; *dose-plasma concentration curve and plasma concentration-response curve*. As plasma concentration is more closely related to response, the graph between plasma concentration and response is usually called **DRC**. Two types of DRC can be described: *Quantal and graded.*

Quantal DRC: When the response is an '*all or none' phenomenon* (e.g. antiemetic drug stopping the vomiting or not), the y-axis (response axis) shows the number of person responding and x-axis shows the plasma concentration. It is used to calculate ED_{50} and LD_{50}.

Graded DRC: When the response can be graded (e.g. reduction in BP), the y-axis shows the magnitude of response

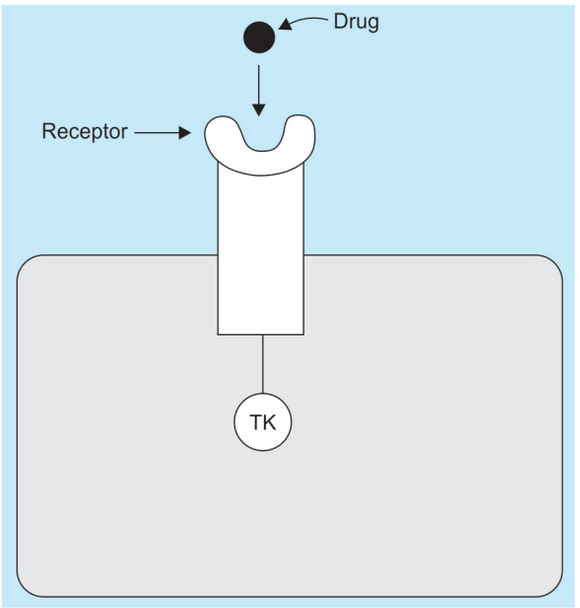


Fig 1.9.: Enzymatic Receptors

DRC is **usually hyperbola** in shape. As curved lines cannot give good mathematical comparisons, so usually the dose is converted to log dose to form **log DRC**, which gives a **sigmoid shaped curve**. The middle portion (which is of therapeutic importance) is straight line in the log DRC. Another advantage of converting it into logarithmic form is that large variation in doses can be plotted on the same curve. **Three important parameters** (*potency, efficacy and slope of curve*) can be determined from DRC.

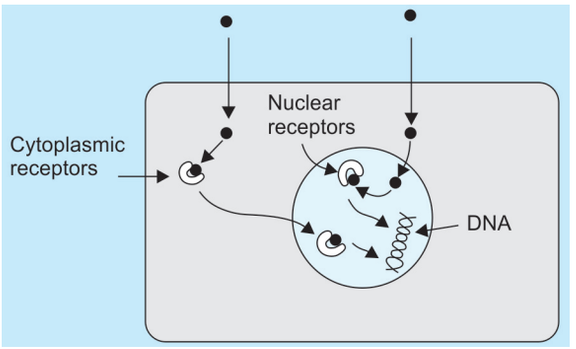


Fig 1.10: Intracellular Receptors

Potency: It is the measure of the amount of a drug needed to produce the response. *Drugs producing the same response at lower dose are more potent* whereas those requiring large dose are less potent. *In DRC, more a drug is on left side* of the graph, *higher is its potency* and vice a versa. In Fig. 1.11, drug A is more potent than drug B.

Efficacy: It is the *maximum effect produced by a drug. More the peak of the curve greater is the efficacy.* It is *clinically more important* than potency. In Fig. 1.11, drug B is more efficacious than drug A.

Slope: If the DRC is steeper, that means the response will increase dramatically with slight increase in dose. Thus, *drugs having steeper DRC have narrow therapeutic index* (like barbiturates) than those having less steep curves (e.g. benzodiazepines).

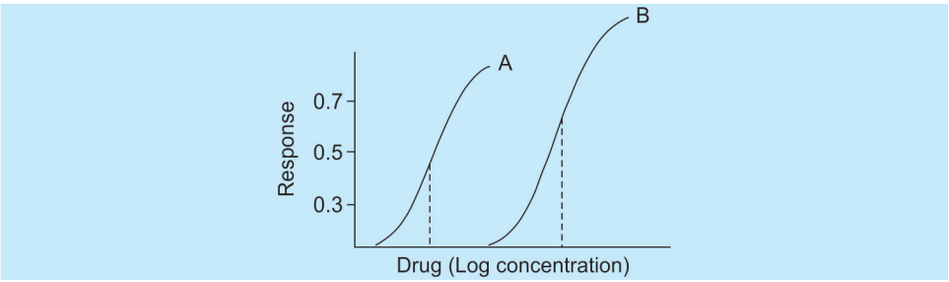


Fig. 1.11. Log DRC of two drugs A and B

DRC can also be utilized to know whether a drug is competitive or non-competitive inhibitor.
In case of competitive inhibitor, curve will shift to right, i.e. now the same agonist will have less potency in the presence of antagonist. It does not affect the efficacy.
In case of **non competitive inhibitor**, there will be **flattening of DRC**, i.e. efficacy decreases. It usually does not affect potency.If the antagonist is **irreversible competitive**, then there will be *decrease in potency as well as efficacy.*

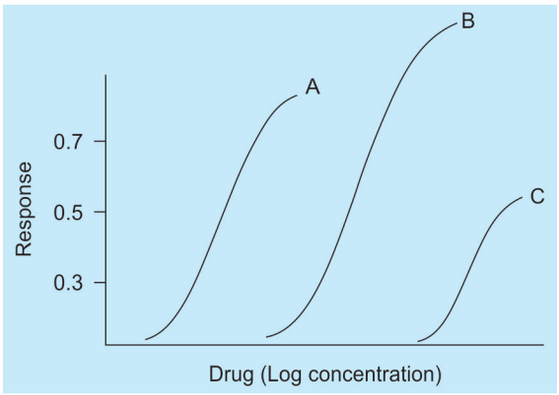


Fig. 1.12. Log DRC of agonist A in presence of a competitive (B) and non-competitive antagonist (C)

Median Effective Dose (ED_{50}) : It is the *dose that* will *produce the half of the maximum (50%) response*. More is ED_{50}, lower is the potency and vice a versa.
Median Lethal Dose (LD_{50}) : It is the dose that will result in death of 50% of the animals receiving the drug. *More is LD_{50}, safer is the drug.*
Therapeutic Index (T.I.) : It is a *measure of the safety* of a drug. It is calculated as a ratio of LD_{50} to ED_{50}. Drugs having high T.I. are safer whereas those having low T.I. are more likely to be toxic.

$$\textbf{T.I.} = \frac{\textbf{LD}_{50}}{\textbf{ED}_{50}}$$

PHARMACOGENETIC CONDITIONS

Due to different genetic make up, some drugs have different effects in different individuals, so these drugs may show either toxicity or lack of effect in certain individuals, if used in conventional dosage. These conditions include :

1. **Acetylator polymorphism**: Some individuals are *slow acetylators* and some are *fast acetylators*. The drugs metabolized by this route may be ineffective in fast acetylators and may show toxicity in slow acetylators. Important drugs metabolized by acetylation include (remembered as **SHIP**)
   - **S**ulfonamides including dapsone and PAS
   - **H**ydralazine
   - **I**soniazid
   - **P**rocainamide

   * **Note :** • All these drugs (SHIP) can also cause SLE.
   • Other drugs that can be metabolized by acetylation include *acebutolol, amantadine, amrinone, benzocaine, clonazepam, nitrazepam and phenelzine etc.*
2. **Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency**: Oxidant drugs may produce *hemolysis* in the patient with deficiency of this enzyme. The important drugs are :

- Primaquine
- Sulfonamides including dapsone
- Quinine
- Chloroquine
- Nitrofurantoin
- Nalidixic acid
- Menadione
- Isoniazid

3. **Atypical pseudocholinesterase and Succinylcholine**: Succinylcholine is a very short acting drug due to metabolism by pseudocholinesterase. In some individuals, this enzyme is not functioning well (atypical). In such individuals this drug may produce *prolonged apnea.*
4. **Inability to hydroxylate Phenytoin**
5. **Resistance to coumarin anticoagulants**
6. **Malignant hyperthermia by halothane**

COMBINED EFFECT OF DRUGS

If two or more drugs are administered simultaneously, following interactions can occur:

Term	Meaning	Mathematical Expression	Example
Addition	Effect of one drug simply adds to that of second drug	2 + 2 = 4	Ibuprofen + Paracetamol as analgesic
Potentiation	Inactive drug increases the effect of active drug	2 + 0 = 4	Levo-dopa+Carbi-dopa in Parkinsonism
Synergism	Combined effect of two drugs is greater than that can be obtained by simple addition	2 + 2 = 10	Cotrimoxazole
Antagonism	Combined effect is less than simple addition	2 + 2 = 1	Atropine and acetylcholine

SPECIAL ASPECTS OF GERIATRIC PHARMACOLOGY

Pharmacokinetic changes:

- *Absorption* of drugs *do not change* with age.
- *Volume of distribution decreases* with age for most drugs. Elderly have reduced lean body mass, reduced body water and increased fat as percentage of body mass. There is usually *decrease in serum albumin* (that binds acidic drugs) and *increase in serum α1– acid glycoprotein* (that binds basic drugs). These changes may alter the appropriate loading dose of a drug.
- *Metabolism through liver declines* for most of the drugs with age. *Phase I reactions are mainly affected* whereas there are much smaller changes in the ability of liver to carryout conjugation (Phase II) reactions.
- Age related *decline in renal capacity* is most important consideration in elderly. This decline is not reflected in equivalent rise in serum creatinine, because production of creatinine is also reduced as muscle mass decreases with age.

Pharmacodynamic changes:

It was believed that sensitivity of receptors to drugs increases in elderly but now it has been recognized that most of these changes are due to pharmacokinetic alterations and diminished homoestatic responses. Baroreceptor sensitivity usually decreases with age, which predisposes to increased risk of postural hypotension. However, for few drugs altered receptor sensitivity also play a role e.g increased analgesic effect of opioids and increased sedation from benzodiazepines occur in elderly whereas decreased sensitivity to beta-blockers is seen in geriatric age group.

CLINICAL TRIALS

Before a new drug comes to the market, it is extensively tested in animals and in vitro studies for safety and efficacy. If the drug is found to be promising in these studies, an application called **IND (Investigational New Drug)** is filed with the United States Food and Drug Administration (main regulatory authority). If the permission is granted, then drug is tested in humans. This testing is called clinical trials. These are divided into four phases.

Phase 1: Here, the drug is tested in **normal human volunteers** (exremes of ages ; elderly and children are excluded). As the drug is not tested in the patients, so we **cannot determine efficacy** in this phase. This is mainly for **toxicity** and pharmacokinetic studies. This is *first in human study.* The idea of testing the new drug in normal humans is based on the fact that healthy persons are more likely to tolerate the adverse effects of the drug than diseased persons. Because anti-cancer drugs can produce unacceptable toxicity and we cannot expose healthy humans to such a toxicity, the *phase-1 trials for anticancer drugs are done in the patients.*

Phase 2: The drug in this phase is tested in *small number of (20-200) patients*. We can determine *both efficacy and safety* in this phase. This is **first in patient** study.

Phase 3: Here the drug is tested in *large number* of patients *at several centers* to include patient with different genetic makeup. This is done to generalize the results of the study to variable genetic and ethnic groups.

If the drug is found to be safe and effective in these trials, then another application is filed with FDA (**New Drug Application or NDA**) to market the drug. If approval is granted, the drug is marketed.

Phase 4: This is **post marketing surveillance** of a drug to know the rare adverse effects or those occurring with prolonged use of the drug. In this phase **ethical clearance is not required**.

All phases of clinical trials must follow the ICH-GCP (Good clinical practice guidelines given by International Conference for Harmonization, so that the data generated is credible and interest of the patients/volunteers can be safeguarded.

Note: Recently, Phase O trial has also been added and is known as microdosing studies. This is added to expedite the marketing of the drug.

PHARMACOVIGILANCE

Pharmacovigilance is the science and activities relating to the *detection, assessment, understanding and prevention of adverse effects* or any other possible drug-related problems. Recently, its concerns have been widened to include herbals, traditional and complementary medicines, blood products, biologicals, medical devices and vaccines. In India, The Central Drugs Standard Control Organization (CDSCO) launched the National Pharmacovigilance Programme (NPP) in November, 2004. The whole country is divided into zones and regions for operational efficiency.

ORPHAN DRUGS

An **orphan drug** is a pharmaceutical agent that has been developed specifically to treat a rare medical condition (affecting fewer than 200,000 people), the condition itself being referred to as an orphan disease. Examples include *deferipirone* to treat iron overload in thalasemia patients, *N-acetylcysteine* to treat paracetamol poisoning etc. Since the pharmaceutical companies will not like to develop such a drug due to lack of financial benefits, a separate law known as '*The Orphan Drug Act*' was passed in 1983. The intent of the Orphan Drug Act is to stimulate the research, development, and approval of products that treat rare diseases.