CHAPTER

# 1 HISTORY OF PHARMACOLOGY

1. **Father of Pharmacology** is *Oswald Schmiedberg*.
2. **Father of Indian Pharmacology** is *Col. Ramnath Chopra*
3. **Father of Modern Pharmacology** is *Sir James Black*. He also discovered beta blockers and $H_2$ blockers (Cimetidine)
4. **Essential Drugs:**

   First Model list by WHO in 1977

   First National EDL of India in 1996

   Current edition of India is 17th National list of Essential Medicines. It was modified in 2011. It contains 348 drugs
5. **Clark (1937)** gave *Theory of drug action based on* occupation of *receptors* by specific drugs.
6. **Uppsala Monitoring Centre (Sweden)** is the international collaborating centre for Pharmacovigilance.

   **In India** it is Central Drugs Standard Control Organization **(CDSCO)**
7. **Otto Loewi** – Direct proof of *transmission across nerve junctions* to be mediated *by neurotransmitters*. Previously, it was considered to be electrical. He profused 2 frog hearts in series. Stimulation of vagus nerve of first heart caused arrest of both. Thus, a chemical must have been released by vagal stimulation of first heart (called vagusstoff now known as ACh) which passed in the perfusate and arrested the second heart.
8. **Ahlquist** classified adrenergic receptors into $\alpha$ *and* $\beta$ *types.*
9. Vasomotor reversal of **Dale** was first demonstrated with *ergot alkaloids.*
10. **Bergstrom, Samuelsson and Vane** got Noble prize for work on *PGs and LTs.*
11. Insulin: Discovered by **Banting and Best** in 1921

    **Chemical structure** was fully worked out by *Sanger* in 1956.
12. **Kendall, Reichstein** and **Hench** got Noble Prize in 1950 for work on *corticosteroids* in Rheumatoid arthritis.
13. **Centchroman** is a non-steroidal SERM **developed at CDRI India** as an oral contraceptive.
14. First LA to be used – **cocaine** (1884) for Ocular anaesthesia.
15. First i.v. anaesthetic – **Thiopentone**
16. Term balanced anaesthesia was coined by **Lundy** in 1926
17. **Horace Wells** used $N_2O$ (laughing gas) in 1844 for dental anaesthesia.
18. **Guedel** (1920) described 4 stages of anaesthesia with Ether.
19. Synthetic toxin N-methyl-4-phenyl tetrahydropyridine **(MPTP)** produces nigrostrial degeneration and manifestations similar to **Parkinson's disease.**
20. First drug used for treatment of schizophrenia was **chlorpromazine.**
21. **Serturner** isolated active principle of opium and named it morphine after greek God of dreams **(Morpheus).**
22. First ACE inhibitor to be synthesized was **Teprotide.** It was a peptide, cannot be given orally. First oral ACE inhibitor was captopril.
23. **William Withering** published his work on medicinal uses of Foxglove (digitalis) named 'An account of the Foxglove and some of its medicinal uses: with practical remarks on dropsy and other diseases'.
24. Classification of **anti-arrhythmic drugs** was done by **Vaughan Williams and Singh.**
25. **Blaud's pills** (for anemia) consists of $FeSO_4$ and potassium carbonate.
26. Vitamin $B_{12}$ is also known as **Extrinsic factor of Castle.**
27. Vitamin K was isolated from alfa *alfa grass.*
28. Rat poison contains oral anticoagulants like warfarin.

29. Name of drug warfarin is coined from **W**isconsin **A**lumni **R**esearch **F**oundation and its chemical structure being couma **RIN**.
30. Streptokinase is the first fibrinolytic drug to be used clinically. It is obtained from Group C beta hemolytic streptococci.
31. New formula WHO-ORS was released in 2002. It contains low $Na^+$ (75 mM), low glucose (75 mM) and has low osmolarity (245, mOsm/L)
32. **Ehrlich** coined the term *chemotherapy*. He used the idea that if certain dyes can selectively stain microbes, they can also be toxic to these microbes. He developed arsenic compounds **(Salvarsan)** for treatment of *syphilis*.
33. **Modern** era of **chemotherapy** was ushered by **Domagk**. He demonstrated therapeutic effect of *prontosil* (containing sulfonamide) in pyogenic infections.
34. **Fleming** discovered *penicillin* and **Walksman** discovered *streptomycin*.
35. First antibiotic to be used clinically was penicillin. It was originally obtained from fungus *Penicillium chrysogenum*.
36. First antitubercular drug introduced was PAS followed by streptomycin.
37. **8-Hydroxyquinolines** like quiniodochlor and iodoquinol were used in ameobic dysentry but were banned in Japan and few other countries because on long-term use these resulted in epidemics of Subacute Myelo-optic Neuropathy **(SMON)**.
38. **Thalidomide** caused **phocomelia** in Germany in 1960s when it was used for treatment of vomiting due to morning sickness.

CHAPTER

# 2 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).

**DRUGS ADMINISTERED BY VARIOUS ROUTES**

**Sublingual**
- *Nitroglycerine*
- *Isosorbide dinitrate*
- *Clonidine*
- *Nifedipine*

**Transdermal**
- *Nitroglycerine*
- *Nicotine*
- *Fentanyl*
- *Hyoscine*

**Nasal**
- *Nafarelin* (GnRH agonist)
- *Calcitonin*
- *Desmopressin*

## 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 sublingual 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 adminstered through transdermat patch.
- Drugs administered by nasal route are nafarelin (Gn RH agonist), *calcitionin 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. and s.c.* routes.

**Inhalational route** is the route by which the rate of drug *delivery can be controlled like i.v.* infusion.

## PHARMACOKINETICS

It is the effect of body on the drug i.e. movement of the drug in, through and out of the body.

### 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.

Pharmacokinetics is also called **ADME** study as it deals with **A**bsorption, **D**istribution, **M**etabolism and **E**xcretion of a drug.

## 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).

**Weak Acids**
- *Barbiturates e.g. phenobarbitone*
- *NSAIDS e.g. aspirin, diclofenac*
- *Methotrexate*
- *Sulfonamides*
- *Penicillins*

**Weak Bases**
- *Morphine*
- *Atropine*
- *Amphetamines*
- *Quinine*
- *Hyoscine*

**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% |

Bioavailability is the fraction of administered drug that reaches the systemic circulation in the unchanged form.

Absorption and first pass metabolism are two important determinants of bioavailability.

### 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 absoprption and first pass metabolism are two important determinants of bioavaility.
- 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

**Drugs with High First pass Metabolism**

**Nitrates**
**H**ave - **H**ydrocortisone
**L**arge - **L**ignocaine
**P**re - **P**ropanolol
**S**ystemic - **S**albutamol
**M**etabolism - **M**orphine

**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.

AUC Signifies extent of absorption whereas $T_{max.}$ tells rate of absorption.

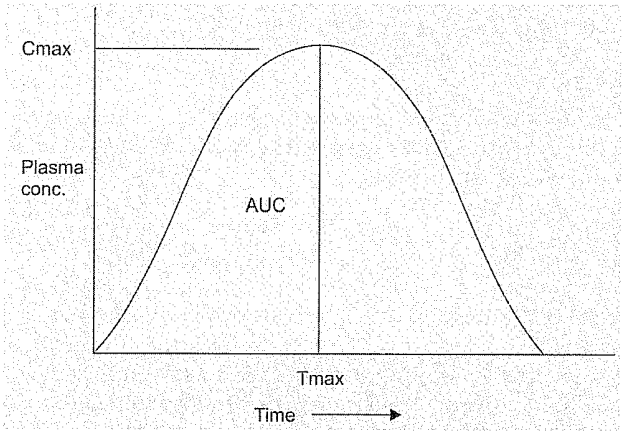



**Fig. 2.1: Plot between plasma concentration and time to calculate bioavailability**

## 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.**

**Drugs with high plasma protein binding**
- **Benzodiazepines**
  - Diazepam
  - Chlordiazepoxide
  - Midazolam
- **Chlorpropamide**
- **Tolbutamide**
- **Cyclosporine**
- **Fluoxetine**
- **Imipramine**
- **Verapamil**
- **Warfarin**

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.

**Dialysis in not effective in**
**A** - **A**mphetamines
**V** - **V**erapamil
**O** - **O**rganophosphates
- **O**pioids
**I** - **I**mipramine
**D** - **D**igitalis
**Dialysis** - **D**iazepam

### Dialysis in Drug Poisoning

Certain drugs can be removed by dialysis. However
- Dialysis does not filter proteins. Therefore, drugs having high plasma protein binding (e.g. diazepam) cannot be removed by dialysis
- Dialysis removes only those drugs which are present in sufficient free concentration in plasma. Thus, drugs having high volume of distribution [More in tissues but less in Plasma] are difficult to be removed by dialysis e.g. digoxin, imipramine, propanolol, verapamil etc.
- Thus, drugs having low $V_d$ and low PPB are good candidates of dialysis e.g. salicylates.

### Clinical Importance of Plasma Protein Binding

- Duration of action: Drugs with high PPB are usually long acting
- Distribution: High PPB drugs stay in plasma, thus have low $V_d$.
- Displacement: Highly PPB drug can be displaced by another highly bound drug
- Dialysis: It is not effective for drugs having high PPB

**PRODRUGS**

| | |
|---|---|
| P | - Prednisone |
| L | - Levo-dopa |
| A | - ACE inhibitors (except captopril and lisinopril) |
| S | - Sulfasalazine |
| M | - Mercaptopurine |
| A | - Acyclovir |
| Makes | - Methyldopa |
| Certain | - Cyclophosphamide, Clopidogrel, Carbimazole |
| Drugs | - Dipivefrine |
| Powerful | - Proguanil |

### 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.

$$V_d = \frac{\text{Dose administrated (i.v)}}{\text{Plasma concentratin } (C_o)}$$

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).

### 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 (e.g. diazepam, propanolol).

- 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.

**Enzyme Inducers**

| | |
|---|---|
| G | - Griseofulvin |
| P | - Phenytoin |
| R | - Rifampicin |
| S | - Smoking |
| Cell | - Carbamazepine |
| Phone | - Phenobarbitone |

**Enzyme Inhibitors**

| | |
|---|---|
| Vitamin | - Valproate |
| K | - Ketoconzole |
| Cannot | - Cimetidine |
| Cause | - Ciprofloxacin |
| Enzyme | - Erythromycin |
| Inhibition | - INH |

Glucuronidation is most common phase II metabolic reaction

### Drug Metabolizing Enzymes

These can be broadly divided into microsomal (present in smooth endoplasmic reticulum) and non-microsomal.

**Metabolic Reactions by**

**Microsomal Ezymes**
- Oxidations
  - Cytochrome $P_{450}$
  - Flavin Monoxygenases
- Glucuronide conjugation
- Reduction
- Hydrolysis

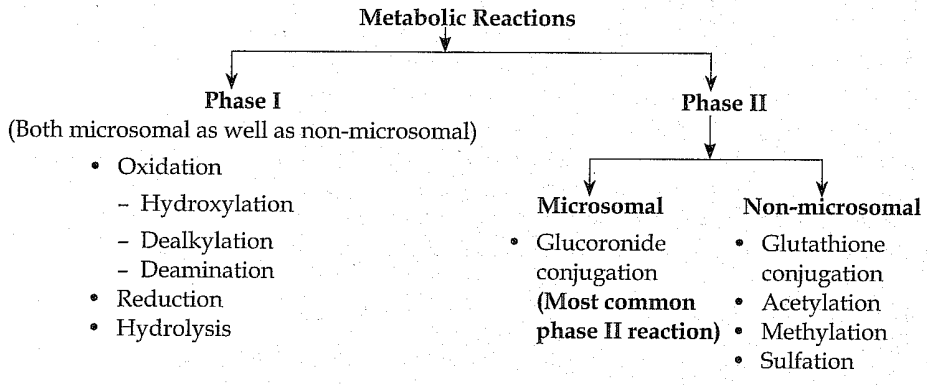
**Non-microsomal Enzymes**
- All phase II except glucuronidation
- Oxidation
- Reduction
- Hydrolysis

- 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.**
- **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.**

Glucoronide conjugation is catalyzed by microsomal enzymes but not by cytochrome p450 enzymes

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 reactins include oxidation, reduction, hydrolysis, cyclization and decyclization etc. whereas phase II reactions include glucuronidation, acetylation, methylation, sulfation and glycine conjugation etc.

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.




**Phase I reactions**
- *Oxidation*
- *Reduction*
- *Hydrolysis*
- *Cyclization*
- *Decyclization*

**Phase II reactions**
- *Glucuronidation*
- *Acetylation*
- *Methylation*
- *Sulfation*
- *Glycine conjugation*

| CYP | Substrate | Inducer | Inhibitor |
|---|---|---|---|
| 3A4 (Metabolizes 50% of drugs, most common) | • Astemizole<br>• Cisapride<br>• Terfenadine<br>• Cyclosporine<br>• Tacrolimus<br>• Calcium channel blockers<br>• Protease inhibitors<br>• Estrogens | Barbiturates<br>Rifampicin<br>Phenytion<br>Carbamazepine<br>St. John's wort | Erythromycin<br>Ketoconazole<br>Fluconazole<br>Grapefruit juice<br>Ritonavir |
| 2D6 (Metabolizes 20% drugs) | • Most antidepressants<br>– TCA<br>– SSRI<br>– MAO inhibitors<br>• Most beta blockers<br>• Most antiarrhythmics | No known inducer | Quinidine<br>Paroxetine |

| | | | |
|---|---|---|---|
| 2 C 19 | • Omeprazole<br>• Clopidogrel | Rifampicin<br>Barbiturates | Fluconazole |
| 2 C 9 | • Phenytion<br>• Tolbutamide<br>• Warfarin | Rifampicin<br>Barbiturates | Erythromycin<br>Cimetidine |
| 1 A 2 | • Theophylline<br>warfarin | Smoking<br>Rifampicin | Ciprofloxacin |
| 2 E 1 | • Acetaminophen<br>• Enflurane<br>• Halothane | Ethanol | Disulfiram |

### 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.

Glomerular filtration does not depend on the lipid solubility

Lithium, KI and rifampicin are secreted in saliva

Urine should be *alkalinized* for acidic drug poisoning whereas acidified for basic drug poisoning

#### Kinetics of Elimination

**Rate of Elimination** is the *amount of drug eliminated per unit time*. If it is seen as a function of plasma concentration, we derive an important parameter known as **clearance (CL)**

$$CL = \frac{\text{Rate of Elimination}}{\text{Plasma concentration}}$$

#### 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, {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. |

**Drugs showing zero/pseudo zero order kinetics**

| | |
|---|---|
| **Zero** | Zero order kinetics shown by |
| **W** | Warfarin |
| **A** | Alcohol and Aspirin |
| **T** | Theophylline |
| **T** | Tolbutamide |
| **Power** | Phenytoin |

**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 parameter; $V_d$ 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.

Half life is a *secondary pharmacokinetic parameter derived from two primary parameter; $V_d$ and CL*

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

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.

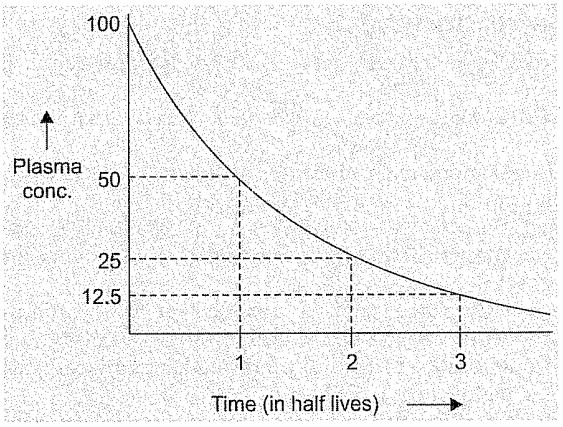



**Fig. 2.2: Plasma concentration time curve in first order kinetics when drug administration is stopped at steady state concentration**

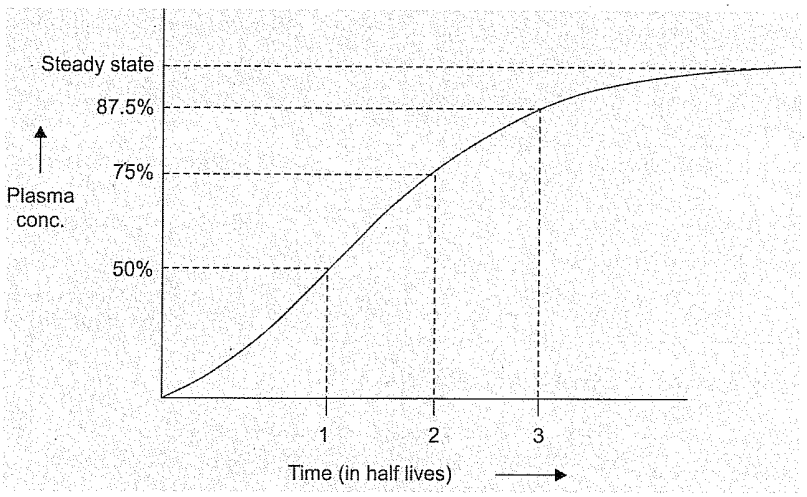



**Fig. 2.3: Plasma concentration time curve in first order kinetics with constant i.v. infusion**



## STEADY STATE

If fixed dose of a drug is administered after regular intervals, its plasma concentration starts increasing. However, as plasma concentration rises, rate of elimination also starts increasing. When rate of administration becomes equal to rate of elimination, plasma concentration stabilizes. This is called steady state.

1. Time to reach steady state depends on $t_{½}$. It takes approximately 5 half lives.
2. Steady state plasma concentration acheived depends on dose rate.
3. Variation between peak and trough concentration at steady state depends on dosing interval. However, average steady state plasma concentration remains same irrespective of dosing interval provided dose rate remains same.

### 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 $V_d$.

$$Loading\ dose = V_d \times Target\ plasma\ concentration$$

**Maintenance dose:** It is mainly dependent on CL.

$$Maintenance\ dose = CL \times Target\ plasma\ concentration$$

**TDM is required for**
- Digitalis
- Aminoglycosides
  e.g. gentamicin
- Lithium
- Antiepileptics
  e.g. phenytoin
- Immunomodulators
  e.g. Cyclosporine
  Tacrolimus

## 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 drug response or 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 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). Due to same reason, TDM is not indicated for anticoagulants (e.g. warfarin) or antidiabetics (e.g. metformin).
- 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.*

#### 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 result 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. Drugs with high affinity can be used in low concentrations.

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 $\beta_1$ 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.

> $K_m$ looks like kilometers, In competition one need to run more kilometers i.e. $K_m$ increases.

> Km is Michaelis Menton's constant and is calculated as amount of substrate required to produce half of the maximal velocity whereas $V_{max}$ is maximum reaction velocity.

> Competitive inhibitors increased $K_m$ and do not alter $V_{max}$ *whereas a non-competitive inhibitor* result in decrease in $V_{max}$ *but does not affect the* $K_m$

**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 $\beta_2$ 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.

Cyclic AMP, $IP_3$ and DAG act as second messengers

### G Protein Coupled Receptors (Metabotropic 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). 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. Activated α-subunit may result in one of the 3 actions:

1. **Activation (by Gs) or inhibition (by Gi) of enzyme adenyl cyclase**: It changes the concentration of cAMP that acts by activating protein kinases (e.g. protein kinase A). Latter produce action by phosphorylation of their substrates. Examples include β-receptors (increase cAMP) and somatostatin (works by decreasing cAMP).
2. **Activation of phospholipase C (by Gq)**: This enzyme converts $PIP_2$ to $IP_3$ and DAG. Final result is increase in intracellular calcium and thus action e.g. α-receptors, vasopressin $V_1$ receptors.
3. **Stimulation or inhibition of ion channels** e.g. $M_2$ receptors of ACh.

Cyclic AMP, $IP_3$ and DAG act as second messengers whereas $Ca^{2+}$ is a third messenger. After the action, the intrinsic GTPase activity of alpha subunit result in joining it with β-γ subunits and thus G-protein is available for action again.

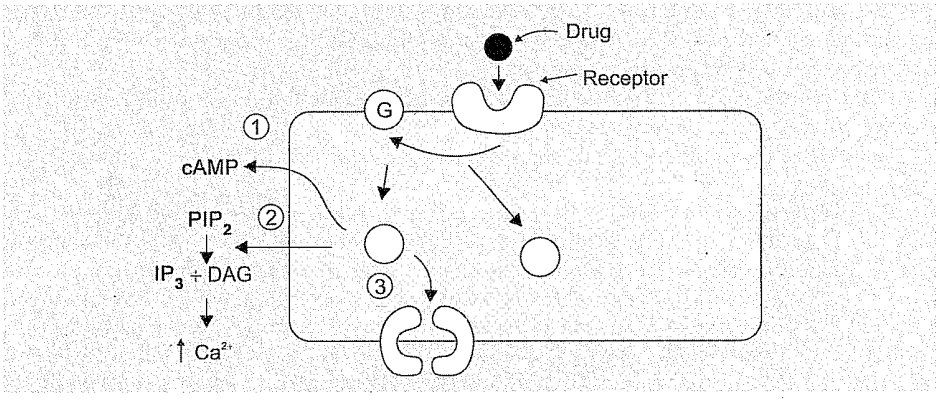



**Fig. 2.4: G-protein coupled receptor**

### Inotropic 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** (receptors of glutamate) and **$5\text{-}HT_3$** receptors.

> Inotropic receptors include **$GABA_A$, $N_M$, $N_N$, NMDA** (receptors of glutamate) and **$5\text{-}HT_3$** receptors.

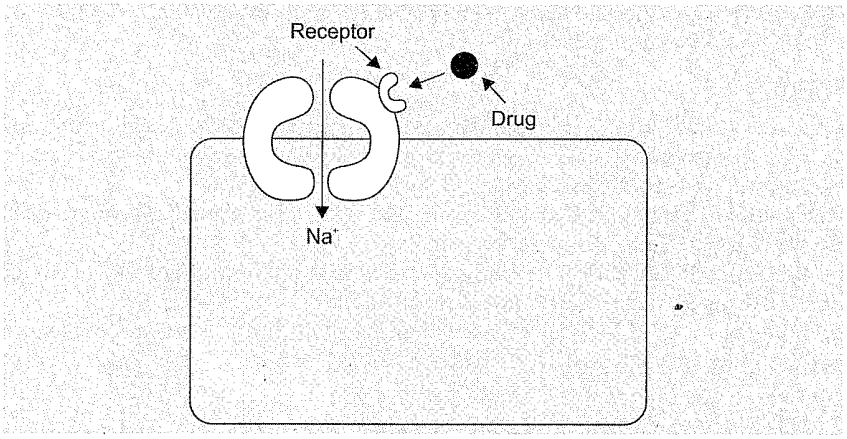



**Fig. 2.5: Ionotropic receptors**

### 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.

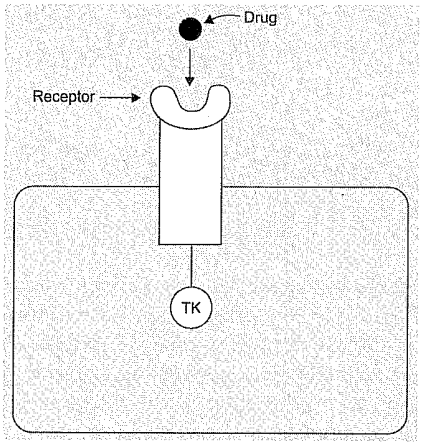



**Fig. 2.6: Enzymatic Receptors**

### 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).

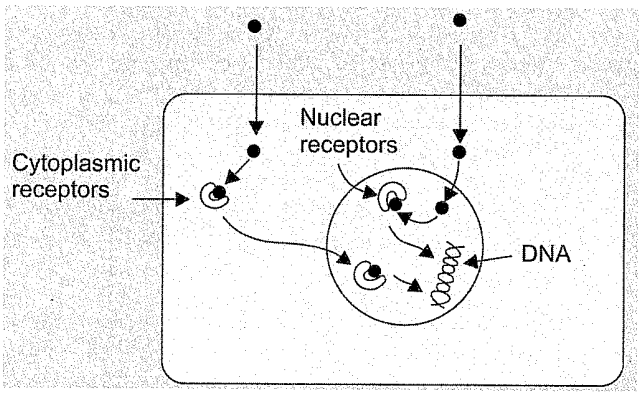



**Fig. 2.7: Intracellular receptors**

## 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 $LD_{50}$.

**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.

$$\text{T.I.} = \frac{LD_{50}}{ED_{50}}$$

### GRADED DRC

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

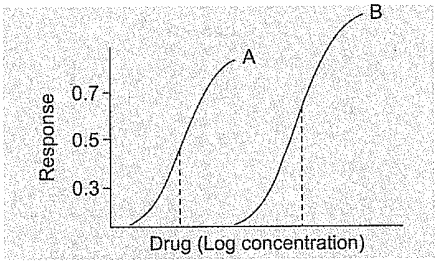



**Fig. 2.8: Log DRC of two drugs A and B**

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.

### 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. 1.8, drug A is more potent than drug B.

Efficacy is *clinically* more important than potency.

### 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. 1.8, drug B is more efficacious than drug A.

Drugs having steep DRC have narrow therapeutic index (like barbiturates) than those having less steep curves (e.g. benzodiazepines).

### 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).

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.*

In case of competitive inhibitor, dose response curve will shift to right whereas In case of non competitive inhibitor, there will be flattening of DRC.

### 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**)
   - Sulfonamides including dapsone and PAS
   - Hydralazine
   - Isoniazid
   - Procainamide

In phase 1 clinical trials, The drug is tested in **healthy human volunteers and** we **cannot determine efficacy** in this phase.

Ethical clearance is not necessary in phase 4 clinical trials.

**Note:**
- All SHIP drugs can also cause lupus erythematosis.
- Other drugs 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.**

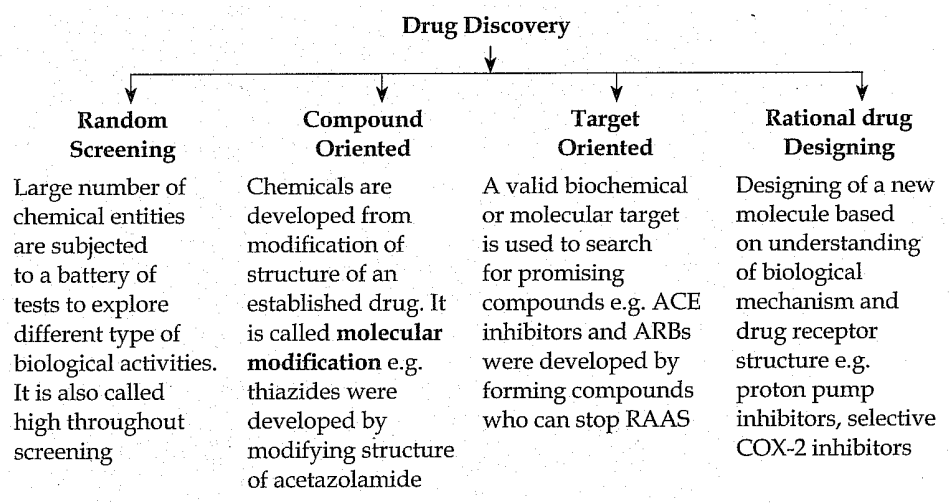
*Recently, Phase O trial has also been added and is known as microdosing studies. This is added to expedite the marketing of the drug.*

## NEW DRUG DEVELOPMENT

Drug development process is broadly divided into
- Drug discovery phase
- Preclinical studies
- Clinicial trials

### Drug Discovery Phase

Most new drugs are discovered through random screening, compound oriented approach, target oriented approach or rational drug designing.




These all approaches result in selection of several compounds (process called **lead finding**). These are then subjected to various procedures to identify one or two drug candidates (now called **lead compounds**) suitable for further investigations. (This process is called **lead optimization**). These lead compounds are then evaluated in preclinical phase.

### Pre-Clinical Studies

The lead compounds are tested on animals to know the whole pharmacological profile. Tests are first performed on small animals (mice, rat, guinea pig etc. and then on large animal (like cat, dog, monkey etc). All studies like pharmacokinetics, pharmacodynamics, toxicology, therapeutic index etc. are performed and promising compounds are selected that can be evaluated in humans.

### 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** (extremes 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.

**Pharmacovigilance** is the science and activities realting to the detction, assessment, understanding and prevention of adverse effects or any other possible drug-related problems

An **orphan drug** is a pharmaceutical agent that has been developed specifically to treat a rare medical condition (affecting fewer than 200,000 people)

**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.

## SUMMARY OF CLINICAL TRIALS

| Phase | Name | Conducted on | Blinding and control | Purpose |
|---|---|---|---|---|
| I | Human Pharmacology and safety | Healthy volunteers (20 – 100) | OPEN LABEL (No blinding) | – To know maximum tolerable dose (MTD)<br>– Safety and tolerability |
| II | Therapeutic exploratory | 100 – 150 Patients (homogenous population) | Single blind Controlled | – To establish therapeutic efficacy<br>– Dose ranging and ceiling effect |
| III | Therapeutic confirmatory | Upto 5000 patients from several centres (heterogenous population) | Double blind Randomized Controlled | – To confirm therapeutic efficacy<br>– To establish the value of drug in relation to existing therapy |
| IV | Post marketing surveillance | Large number of patients being treated by practicing physicians | — | – To know rare and long-term adverse effects<br>– Special groups like children, pregnancy etc can be tested |
| O (Zero) | Microdosing studies | Healthy volunteers (small number) | — | – Very low dose 1/100th of human dose; max 100 μg) of drug is administered to know pharmacokinetics. This could avoid costly phase I studies for candidate drugs with unsuitable pharmacokinetics. |

### Adverse Drug Reactions

These are noxious or unintended effects produced by drugs. These may be classified as

- **Type A:** Augmented pharmacologic effects - Dose dependent and predictable e.g. hypoglycemia caused by anti-hyperglycemic drugs like sulfonylureas
- **Type B:** Bizarre effects (or idiosyncratic) - Dose independent and unpredictable e.g. allergic reactions caused by penicllins
- **Type C:** Chronic effects e.g. peptic ulcer caused by chronic use of NSAIDs
- **Type D:** Delayed effects e.g. teratogenicity caused by thalidomide
- **Type E:** End-of-treatment effects e.g. withdrawal response to morphine
- **Type F:** Failure of therapy

### 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.