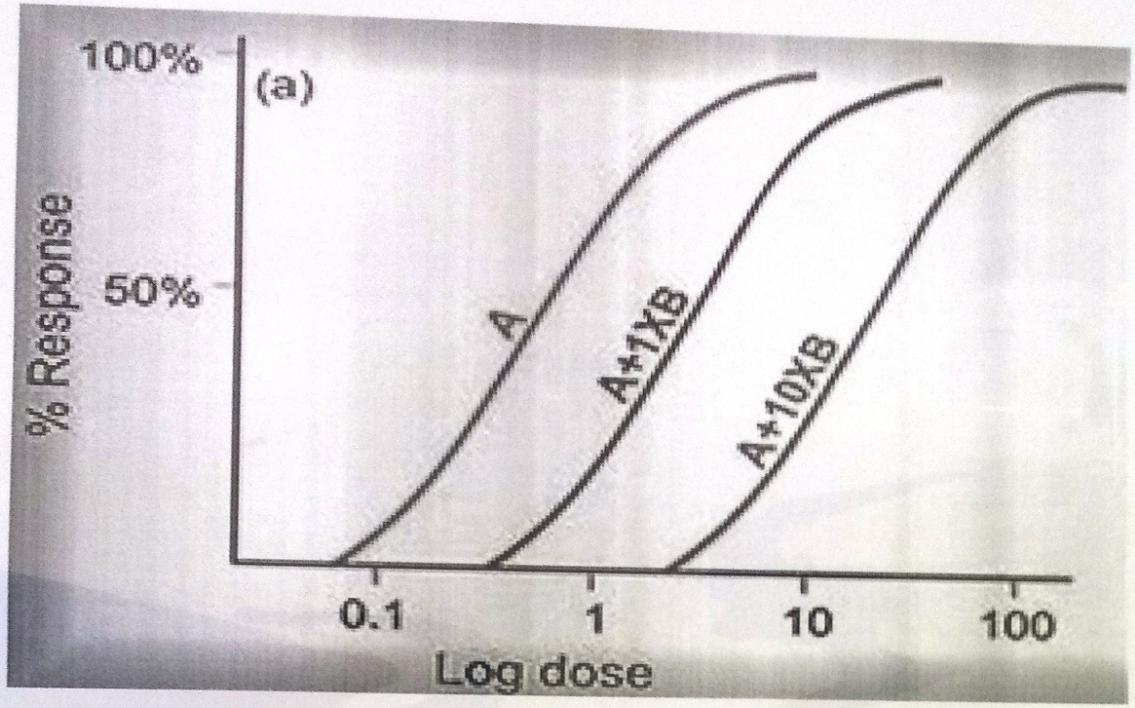
GENERAL PHARMACOLOGY CHARTS

CHART - 1



A.LDR curve for agonist alone.

A+1XB, A+10XB.LDR curves for agonist in presence of increasing concentration of antagonist (B).

1) **What changes do you observe on LDR curve for agonist in presence of antagonist?**

2) **Give two examples of above mentioned antagonism, (one at receptor level and one at enzyme level)?**

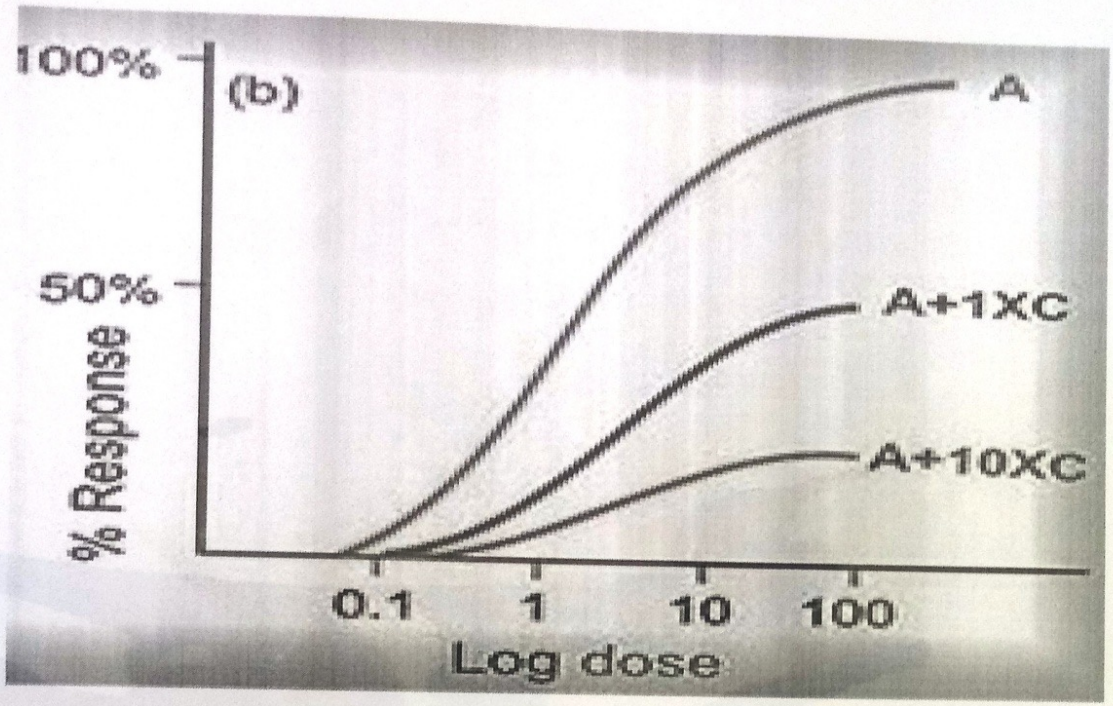
CHART - 1

1) The LDR curve is shifted parallelly towards right. Efficacy remains the same. Potency decreases. The same maximal response attained by increasing the dose of agonist.

2) Receptor level – Atropine and Acetyl choline on muscarinic receptor

   Enzyme level – Physostigmine and Acetyl choline on Acetylcholine esterase

CHART - 2



A.LDR curve for agonist alone.

A+1XC, A+10XC.LDR curves for agonist in presence of increasing concentration of antagonist (C).

1) **Note and record the changes on the LDR curves on increasing the concentration of the antagonist?**
2) **Give two examples of above mentioned antagonism?**
3) **What is the effect of prolonged exposure to antagonist? What is its significance?**

CHART - 2

1) **Progressive flattening of LDR curve .Efficacy decreases. Maximal response is suppressed by increasing the dose of the antagonist.The same maximal response cannot be attained by increasing the dose of the agonist. Potency remains the same.**

2) **Receptor level → GABA receptor - Flumazenil**

   Enzyme level → Aldehyde dehydrogenase and Disulfiram, Cyclooxygenase and Aspirin

3) **Upregulation of receptors**

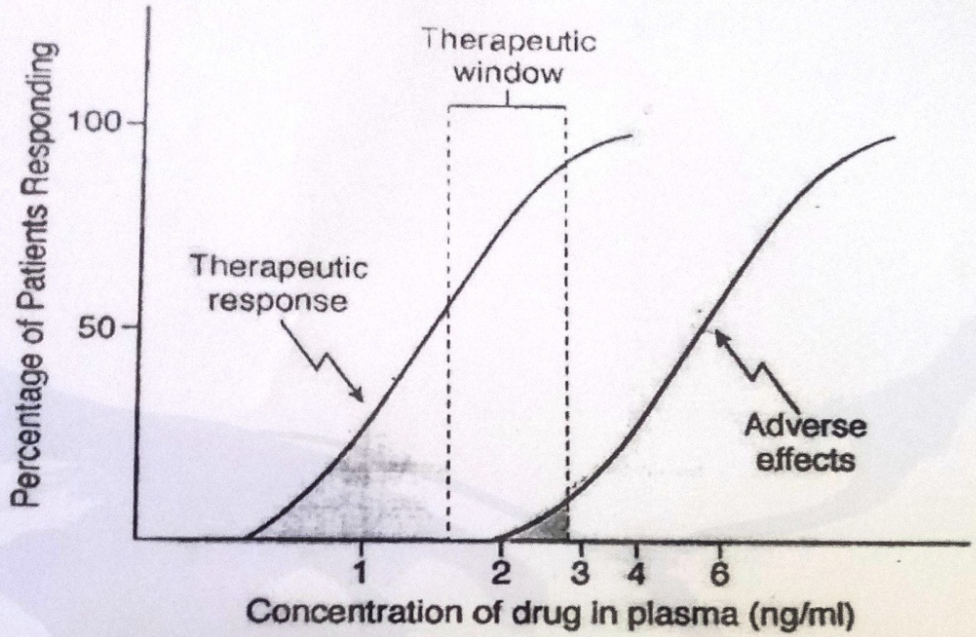
   Supersensitivity of receptors

   Prolonged exposure of antagonist followed by sudden withdrawal can result in - Rebound increase in original symptoms.

   Eg: Sudden withdrawal of Propranolol → Rise in BP

CHART - 3

DRC FOR THERAPEUTIC AND ADVERSE EFFECT OF THE SAME DRUG



1) Define therapeutic index. Give examples for,
   a. Drugs with high therapeutic index.
   b. Drugs with low therapeutic index.

2) What is the significance of knowing therapeutic index?
3) What is therapeutic window phenomenon? Give two examples?
4) Significance of risk-benefit ratio?

CHART - 3

1) **The gap between the therapeutic effect DRC and the adverse effect DRC defines the safety margin or the therapeutic index of a drug. It is often calculated as :**

$$\text{Therapeutic index} = \frac{\text{Median lethal dose}}{\text{Median effective dose}}$$

$$\text{or } \frac{\text{LD50}}{\text{ED50}}$$

Median effective dose (ED50) → Dose which produces specified effect in 50% individuals.

Median lethal dose (LD50) → Dose which kills 50% of the recipients.

a) High therapeutic index → Penicillin, Benzodiazepines

b) Low therapeutic index → Lithium, Digoxin, Theophylline

CHART – 3 (Contd..)

2) **Therapeutic index is an index of drug safety. Higher the value of therapeutic index, safer is the drug.**

3) **Therapeutic window is the range of plasma concentrations below which the drug is ineffective and above which toxicity appears.**

   Optimal therapeutic effect is shown by only a narrow range of plasma concentration.

   Below and above this range – Suboptimal response

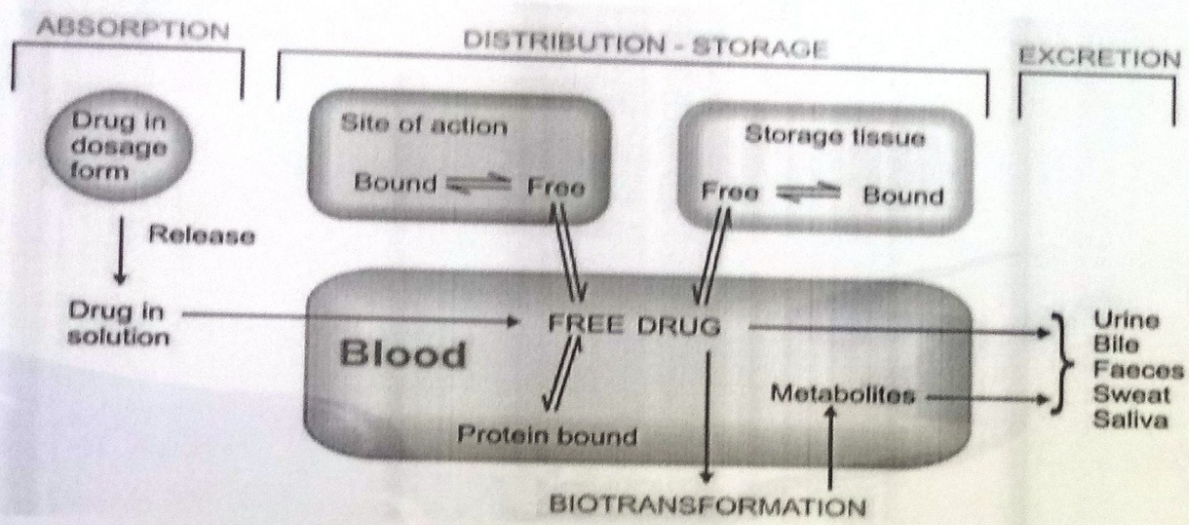
   Eg: Clonidine 0.2 – 2 ng/ml, Imipramine 50 – 150 ng/ml

4) **Risk-benefit ratio conveys a judgement on the estimated harm (adverse effects, cost, inconvenience) vs expected advantages (relief of symptoms, cure, reduction of complications/mortality, improvement in quality of life).**

   A drug should be prescribed only when the benefits outweigh the risks.

CHART - 4

PHARMACOKINETICS



1) Which route of drug administration produces the most rapid onset of action?
2) From which part of the GIT is Aspirin absorbed? Why ?
3) What is V_d of drugs retained in the vascular compartment? Give 2 examples?
4) How will Tolbutamide administration affect a person who is stabilized on Warfarin?
5) How will you enhance the renal elimination of Phenobarbitone? Give the rationale?

CHART – 4

1) **Intravenous route**

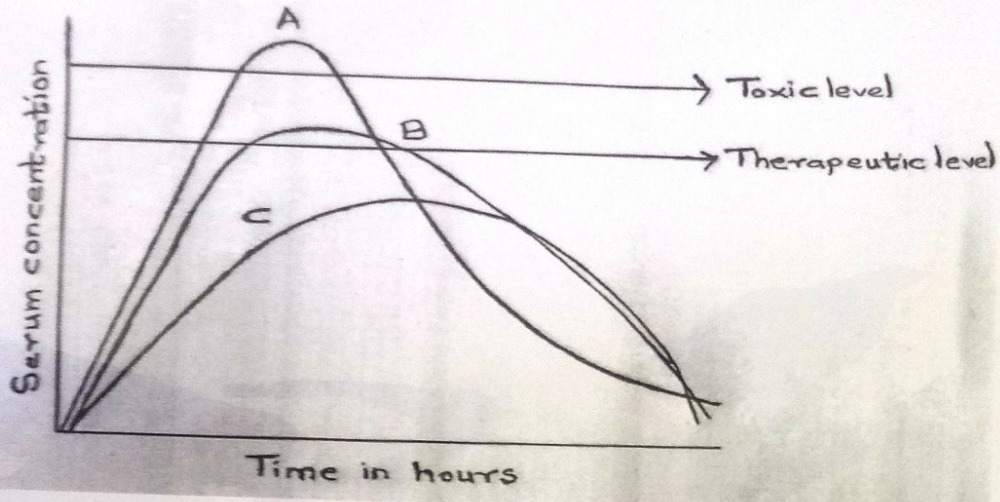
2) **Aspirin is rapidly absorbed from the stomach. Aspirin is an acidic drug; became unionized in acidic pH of stomach and hence are rapidly absorbed.**

3) **Have low values of V_d. Drugs having very large molecular weight or binds extensively to plasma proteins are largely restricted within the vascular compartment. Examples : Warfarin, Heparin, etc**

4) **Warfarin displaces Tolbutamide from plasma protein binding sites → Free drug concentrations of Tolbutamide ↑ses → Hypoglycemia**

5) **Through alkalinisation of urine by giving NaHCO3. Phenobarbitone is an acidic drug. Acidic drugs ionise in alkaline pH. No reabsorption of Phenobarbitone from glomerular filtrate. Enhance elimination through urine.**

CHART - 5



1. Which drug among the above graph has the quickest onset of action?
2. What is the disadvantage of drug A?
3. Which drug will you choose for clinical use?
4. Comment on drug C.
5. What information will you get from AUC?
6. AUC (Oral) of a drug is 25 cm2 and AUC (I/V) is 500 cm2. Calculate its bioavailability.
7. Which route is preferred for the above drug?

CHART – 5

1) **Drug A has the quickest onset of action. It can be given in emergency situation.**

2) **Disadvantage → It crosses the toxicity level.**

3) **Drug B is appropriate for clinical use because its concentration attains the therapeutic level and it does not crosses the toxicity level.**

4) **Drug C is therapeutically ineffective as its concentration does not attain the therapeutic level.**

CHART – 5(Contd..)

5) **AUC is area under the curve. It is a measure of bioavailability. It provides information regarding the rate of absorption, extent of absorption and the time taken to attain maximum concentration.**

6) **Bioavailability = $\frac{\text{AUC (Oral)}}{\text{AUC (IV)}} \times 100 = \frac{25}{500} \times 100 = 5\ \%$**

7) **Intravenous route is preferred.**

CHART - 6

DRUG	Oral bioavailability (%)	Plasma protein binding (%)	V_d (L/70Kg)	$t_{1/2}$ (hours)	Urinary excretion (%)
Amikacin	---	4	19	2.3	98
Chloroquine	89	61	13000	214	61
Diazepam	<100	99	77	43	1
Lithium	<100	0	55	22	95
Phenytoin	90	89	45	Conc dependent	2
Tolbutamide	93	96	7	6	0

1) Compare the bioavailabilities of Amikacin and Diazepam?
2) Which is the best route for Amikacin?
3) Which drug has the highest Vd? What is its clinical significance?
4) Compare the urinary excretions of Lithium and Tolbutamide?
5) Comment on the $t_{1/2}$ of Phenytoin?
6) Drugs like Sulfonamides can compete with other drugs for their plasma protein binding sites,
   What will happen to the plasma concentration of Tolbutamide when sulfonamides are given concomitantly?
7) What change is produced to the serum concentration of Lithium if Diuretics are given concomitantly?

CHART – 6

1) **Oral bioavailability of Diazepam is higher than that of Amikacin.Amikacin is a highly ionized drug. Hence it is not absorbed in the GIT and excreted unchanged in urine.**

2) **Intravenous route is preferred.**

3) **Chloroquine has the highest V_d(13000). Clinical significance → A large value of V_d indicates that larger quantity of drug is present in extravascular tissue. Drugs sequestrated in other tissues may have, V_d much more than the total body water or even body mass and plasma concentration is low.**

   Therefore, in case of poisoning, drugs with large volumes of distribution are not easily removed by haemodialysis.

CHART – 6 (Contd..)

4) **Urinary excretion of Lithium is higher than that of Tolbutamide.**

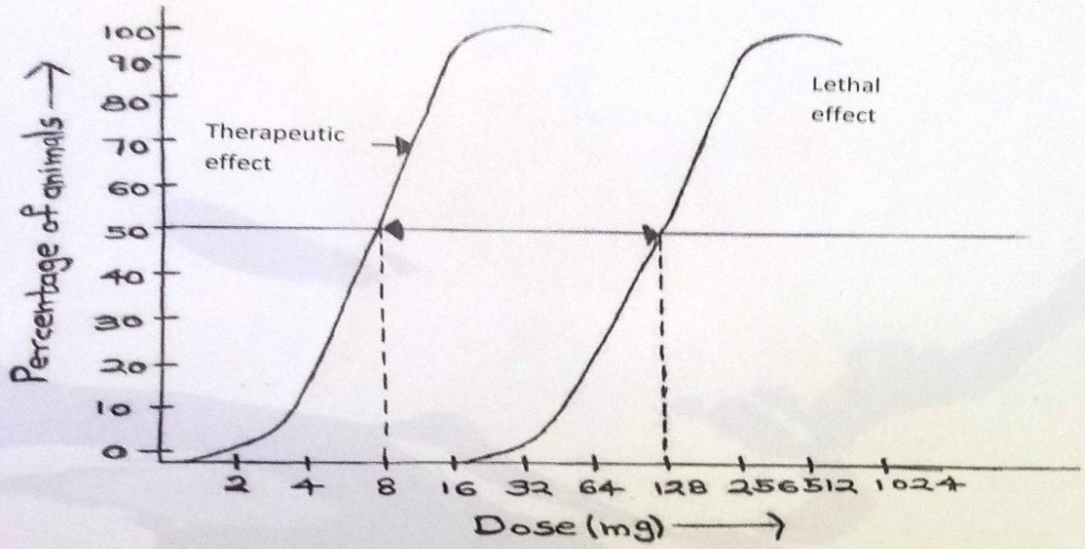
5) **Plasma $t_{1/2}$ of Phenytoin is concentration dependent. It obeys saturation kinetics. Kinetics changes from first order to zero order over the therapeutic range. As a result small increments in dose produce disproportionately high plasma concentrations and larger $t_{1/2}$.**

6) **Sulfonamides will displace Tolbutamide from its plasma protein binding sites when both are given concomitantly. Free plasma drug levels of Tolbutamide will rise and can cause hypoglycemia.**

7) **Diuretics by causing Na^+ loss promote proximal tubular reabsorption of Na^+ as well as Li^+ → Plasma levels of Lithium rise → Lithium toxicity.**

CHART - 7

THERAPEUTIC INDEX



1. Define Therapeutic index (TI).

2. Calculate the therapeutic index from the above graph.

3. Give 2 examples for drugs with
   a. High therapeutic index
   b. Low therapeutic index

4. What is the significance of knowing therapeutic index ?

CHART - 7

1) The gap between the therapeutic effect DRC and the adverse effect DRC defines the safety margin or the therapeutic index of a drug. It is often calculated as :

$$\text{Therapeutic index} = \frac{\text{Median lethal dose}}{\text{Median effective dose}}$$

$$\text{or } \frac{\text{LD50}}{\text{ED50}}$$

Median effective dose (ED50) → Dose which produces specified effect in 50% individuals.

Median lethal dose (LD50) → Dose which kills 50% of the recipients.

2) Therapeutic index is calculated as : $TI = \frac{LD50}{ED50}$

$$= \frac{128 \text{ mg}}{8 \text{ mg}}$$

$$= 16$$

CHART - 7

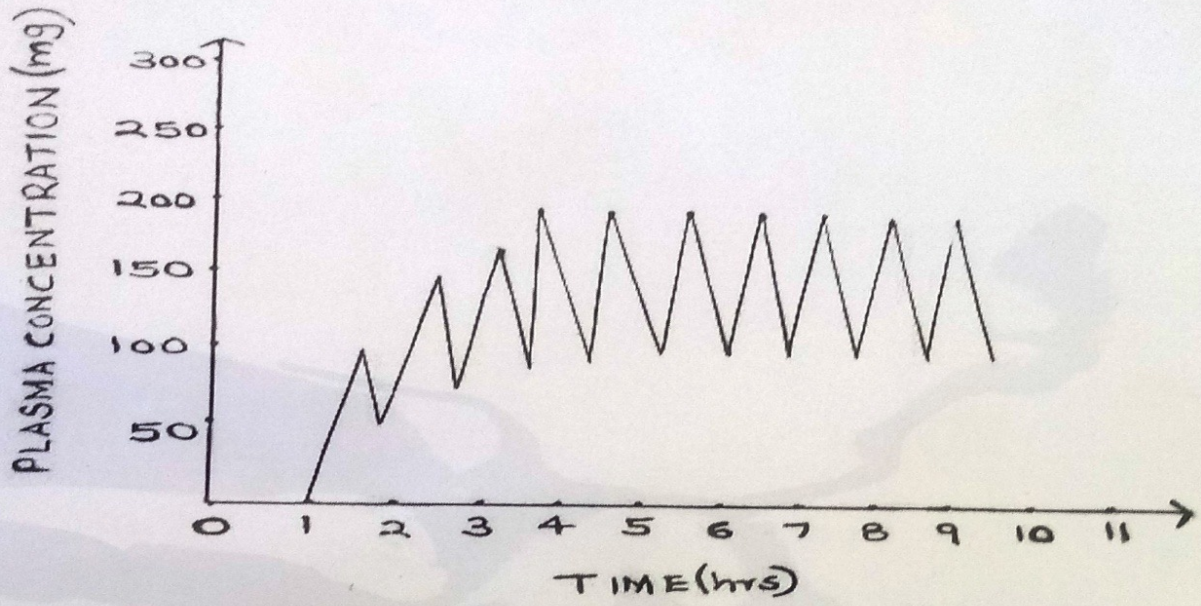
3) a) Drugs with high therapeutic index → Penicillin, Benzodiazepines

b) Drugs with low therapeutic index → Lithium, Digoxin, Theophylline

4) Therapeutic index is an index of drug safety. Higher the value of therapeutic index, safer is the drug.

CHART - 8

PLASMA HALF LIFE



1) Explain the graph.

2) Define plasma half life. What is its significance ?

3) Give 2 examples for drugs having
   a. Long $t_{1/2}$
   b. Short $t_{1/2}$

4) What do you mean by steady state plasma concentration ?

CHART – 8

1) This graph shows the concept of steady state plasma concentration.
   If fixed dose of a drug is administered after regular intervals, its plasma concentration starts increasing.
   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.

2) The Plasma half life ($t_{1/2}$) of a drug is the time taken for its plasma concentration to be reduced to half of its original value.
   It is a secondary pharmacokinetic parameter derived from two primary parameter; V_d and CL.

$$t1/2 = \frac{0.693 \times V_d}{CL}$$

CHART - 8

2) Significance of Plasma half life ($t_{1/2}$) :

- It determines the dosing interval and time required to reach the steady state.
- 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.
- For drugs eliminated by 1st order kinetics → $t_{1/2}$ remains constant because V_d and CL do not change with dose.
- For drugs eliminated by zero order kinetics → $t_{1/2}$ gets prolonged with dose because CL progressively decreases as dose is increased.

CHART - 8

3) Drugs with long $t_{1/2}$: Amiodarone, Digitoxin, etc

   Drugs with short $t_{1/2}$: Adenosine, Penicillin - G, etc

4) When constant 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.

   Time to reach steady state depends on $t_{1/2}$. It takes approximately 5 half lives.

CHART - 10

4) **Steady state plasma concentration achieved depends on dose rate.**

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.