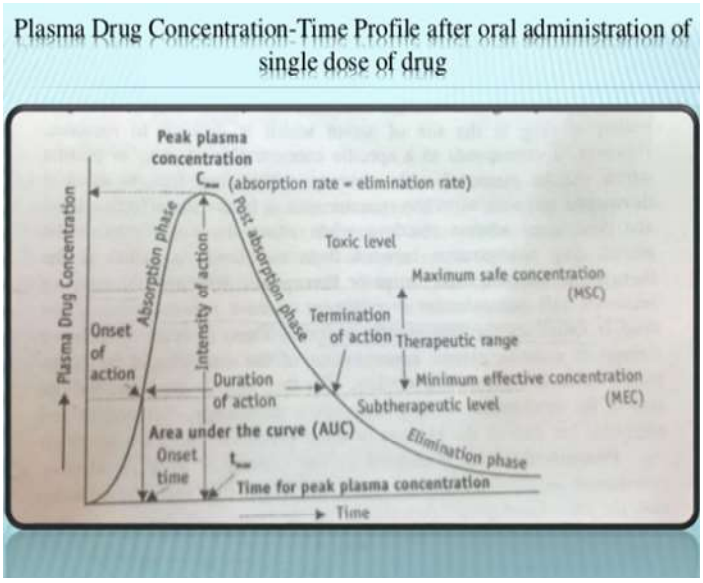
Unit III & IV

Basics of Pharmacokinetics

- Duration of drug therapy ranges from a single dose of drug for acute conditions to drugs taken lifelong for cronic conditions.
- Frequency of administration of drug in a particular dose is called as dosage regimen
- Kinetics of drug absorption, distribution, metabolism and excretion and their relationship with pharmacological, therapeutic or toxicological response in men and animals ------ Pharmacokinetics



Two categories can be evaluated from a plasma concentration time profile-

1. Pharmacokinetic Parameters
2. Pharmacodynamic Parameters

1. **Pharmacokinetic Parameters-**

- **Peak plasma concentration (C_{max})** – It is expressed in mcg/ml. It gives the rate of drug absorption. It depends upon-
  -dose administered
  -rate of absorption
  -rate of elimination
- **Time of peak concentration (t_{max})** - It is expressed in hours. It gives the rate of drug absorption. Onset time and onset of action is dependent on t_{max}.
- **Area under the curve (AUC)** – It is expressed in mcg/ml*hours. It gives the extent of absorption. It is the important parameter in evaluating the bioavailability of drug from its dosage form.

2. **Pharmacodynamic Parameters-**

- **Minimum effective concentration (MEC)**
- **Maximum safe concentration (MSC)**
- **Onset of action**
- **Onset time**
- **Duration of action**
- **Intensity of action**
- **Therapeutic range**
- **Therapeutic index** - The ratio of maximum safe concentration to minimum effective concentration of the drug is called as the therapeutic index i.e. MSC/MEC.

- **Order of a reaction** - The manner in which the concentration of drug influences the rate of reaction or process is called as the order of reaction.

- For a general reaction,
  $dC/dt = -KC^n$
  K= rate constant
  n = order of reaction
  n = 0, zero order kinetics
  n = 1, first order kinetics

- Basically three types of kinetics are encountered-
  - Zero order kinetics
  - First order kinetics
  - Mixed order kinetics

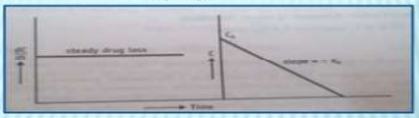
- **Zero order kinetics (constant rate process)**

$$dC/dt = -K_0C^0 = -K_0$$

K_0=zero order rate constant in mg/min

After rearrangement and integration the comes out to be,

$$C = C_0 - K_0t$$



- Zero order half life

$$T_{1/2} = C_0/2K_0$$

- The half life of zero order is proportional to the initial concentration of drug C_0 and inversely proportional to K_0
- Examples of zero order-
  - Controlled drug delivery such as that from i.m. implants or osmotic pumps
  - Administration of a drug as a constant rate i.v. infusion

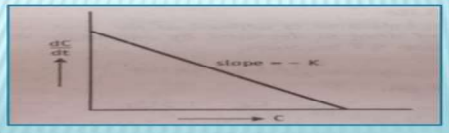
First order Kinetics (Linear kinetics)

If n=1,

$$dC/dt = -KC$$

K=first order rate constant, in $time^{-1}$ or per hour

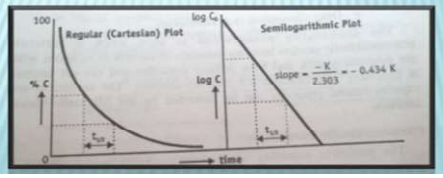
- The rate of a first order reaction is directly proportional to the concentration of drug undergoing reaction i.e. greater the concentration, faster the reaction.



- After rearrangement and integration the equation will give

$$C = C_0e^{-Kt} \quad \text{or, } \log C = \log C_0 - Kt/2.303$$

- First order process is also called as mono-exponential rate process.
- A semilogarithmic plot of above equation gives a straight line with slope = -K/2.303 and y-intercept = $\log C_0$



- First order half life

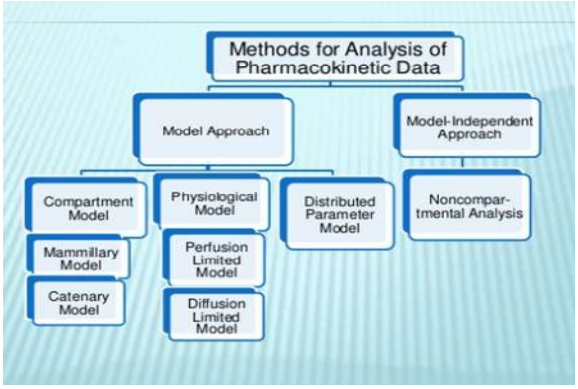
$$t_{1/2} = 0.693/K$$

- The half life of first order process is a constant and independent of initial drug concentration.
- Most pharmacokinetic processes like absorption, distribution and elimination follow first order kinetics.

- **Mixed order kinetics (Nonlinear Kinetics)**
  Sometimes the kinetics of the pharmacokinetic processes fluctuates from predominantly first order to predominantly zero order, therefore such kind of kinetics is called mixed order kinetics. Mixed order kinetics is called dose dependent kinetics or nonlinear kinetics.

- Example-
  Drug absorption of vitamin C
  Drug distribution of naproxen
  Drug elimination of riboflavin

- Nonlinearity is usually seen when the pharmacokinetic processes involves carriers or enzymes which are substrate specific, which gets saturated at high drug concentration i.e. capacity limited. Such capacity limited processes is described by Michaelis-Menten kinetics.



REFERENCES

- Shargel Leon, Andrew Yu B.C., "*Applied biopharmaceutics and pharmacokinetics*" , 5th edition, published by Mc Graw Hill ,page no. 185 .207,613-625.
- Gibaldi M., "*Biopharmaceutics And Clinical Pharmacokinetics*" 4th edition, Pulished by Pharma Med Press,Page no.345.
- Notari Robert E., "*Biopharmaceutics & clinical* pharmacokinetics.", Fourth Edition, published by Marcell Dekker, page no.351-397.