UNIT- IV 08 Hours

Multicompartment models: Two compartment open model. IV bolus Kinetics of multiple dosing, steady state drug levels, calculation of loading and mainetnance doses and their significance in clinical settins.

Multi compartment models (Delayed distribution models)

- One compartment is described by mono-exponential term i.e. elimination.
- For large class of drugs this terms is not sufficient to describe its disposition.
- It needs a bi- or multi- exponential terms.
- This is because the body is composed of a heterogeneous group of tissues each with different degree of blood flow and affinity for drug and therefore different rates of elimination.
- The no. of exponentials required to describe such a plasma level-time profile determines the no. of kinetically homogeneous compartments into which a drug will distribute.
- The simplest and commonest is the two compartment model which classifies the body tissues in two categories :

1. Central compartment or Compartment 1
2. Peripheral or Tissue Compartment or Compartment 2.

Compartment 1 comprises of blood and highly perfused tissues like liver, lungs, kidneys, etc. that equilibrate with the body rapidly.

1. Elimination usually occurs from this compartment.
2. Compartment 2 comprises of poorly perfused and slow equilibrating tissues such as muscles, skin, adipose, etc.
3. Considered as a hybrid of several functional physiologic units.

Depending upon the compartment from which the drug is eliminated, the 2 compartment model can be further categorized into :

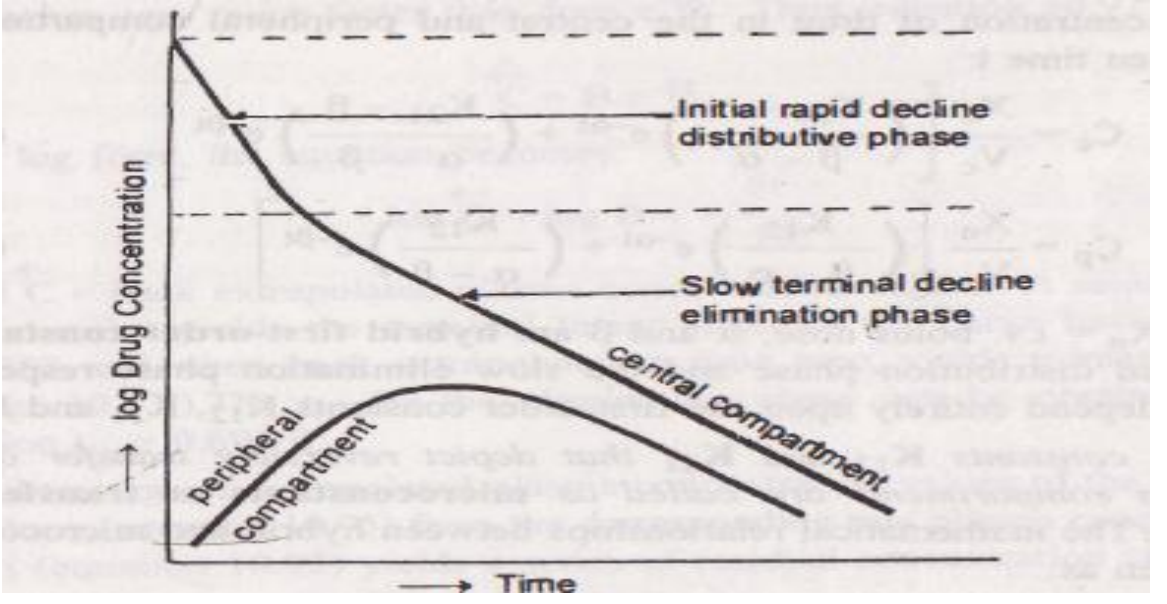
- With elimination from Central compartment
- With elimination from peripheral compartment
- With elimination from both the compartments

In the absence of information, elimination is assumed to occur exclusively from the central compartment.

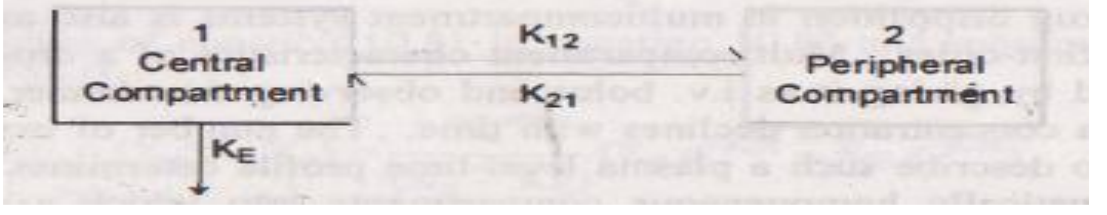
Two compartment Open model-iv bolus administration:

Elimination from central compartment:

- After the iv bolus of a drug the decline in the plasma conc. is bi-exponential.
- Two disposition processes- distribution and elimination.
- These two processes are only evident when a semilog plot of C vs t is made.
- Initially, the conc. of drug in the central compartment declines rapidly, due to the distribution of drug from the central compartment to the peripheral compartment. This is called Distributive phase.
- A pseudo-distribution equilibrium occurs between the two compartments following which the subsequent loss of drug from the central compartment is slow and mainly due to elimination.
- This second, slower rate process, is called as the post-distributive or elimination phase.



- In contrast to this compartment, the conc of drug in the peripheral compartment first increases and reaches its max.
- Following peak, the drug conc declines which corresponds to the post-distributive phase.



$$\frac{dC_c}{dt} = K_{21}\, C_p - K_{12}\, C_c - K_E\, C_c$$

Extending the relationship $X = V_d\, C$

$$\frac{dC_c}{dt} = \frac{K_{21}\,X_P}{V_p} - \frac{K_{12}\,Xc}{Vc} - \frac{K_E\,Xc}{Vc}$$

X=amt. of drug in the body at any time t remaining to be eliminated

C=drug conc. in plasma

V_d =proportionality const app. volume of distribution

X_c and X_p=amt of drug in C1 and C2

V_c and V_p=apparent volumes of C1 and C2

The rate of change in drug conc. in the peripheral component is given by:

$$\frac{dC_p}{dt} = K_{12}\,C_c - K_{21}C_p$$

$$= \frac{K_{12}\,Xc}{Vc} - \frac{K_{21}\,X_P}{V_p}$$

On integration equation gives conc. of drug in central and peripheral compartments at any given time t :

$$C_c = \frac{X_o}{V_c}\left[\left(\frac{K_{21}-\alpha}{\beta-\alpha}\right)e^{-\alpha t} + \left(\frac{K_{21}-\beta}{\alpha-\beta}\right)e^{-\beta t}\right]$$

$$C_p = \frac{X_o}{V_p}\left[\left(\frac{K_{12}}{\beta-\alpha}\right)e^{-\alpha t} + \left(\frac{K_{12}}{\alpha-\beta}\right)e^{-\beta t}\right]$$

Xo = iv bolus dose

a and b = hybrid first order constants for rapid dissolution phase and slow elimination phase, which depend entirely on 1st order constants K12, K21, KE

The constants K12 and K21 that depict the reversible transfer of drug between the compartments are called micro or transfer constants.

The relation between hybrid and micro constants is given as :

$\alpha + \beta = K_{12} + K_{21} + K_E$

$\alpha\beta = K_{21}\,K_E$

$Cc = A\,e^{-\alpha t} + Be^{-\beta t}$

Cc=distribution exponent + elimination exponent

A and B are hybrid constants for two exponents and can be resolved by graph by method of residuals.

$$A = \frac{X_o}{V_c}\left[\frac{K_{21} - \alpha}{\beta - \alpha}\right] = C_o\left[\frac{K_{21} - \alpha}{\beta - \alpha}\right]$$

$$B = \frac{X_o}{V_c}\left[\frac{K_{21} - \beta}{\alpha - \beta}\right] = C_o\left[\frac{K_{21} - \beta}{\alpha - \beta}\right]$$

C_o = plasma drug conc immediately after i.v. injection

Method of residuals : the biexponential disposition curve obtained after i. v. bolus of a drug that fits two compartment model can be resolved into its individual exponents by the method of residuals.

$$C = A\, e^{-\alpha t} + Be^{-\beta t}$$

From graph the initial decline due to distribution is more rapid than the terminal decline due to elimination i.e. the rate constant a >> b and hence the term e^{-at} approaches zero much faster than e^{-bt}

$$\overleftarrow{C} = B\, e^{-\beta t}$$

$$\log \overleftarrow{C} = \log B - \frac{\beta t}{2.303}$$

$\overleftarrow{C}$ = back extrapolated pl. conc

A semilog plot of C vs t yields the terminal linear phase of the curve having slope –β/2.303 and when back extrapolated to time zero, yields y-intercept log B. The $t^{1/2}$ for the elimination phase can be obtained from equation $t^{1/2} = 0.693/\beta$.

Residual conc values can be found as-

$$C_r = C - \overleftarrow{C} = A\, e^{-\alpha t}$$

$$\log C_r = \log A - \frac{\alpha t}{2.303}$$

A semi log plot Cr vs t gives a straight line.

$$C_0 = A + B$$

$$K_E = \frac{\alpha \beta C_o}{A\beta + B\alpha}$$

$$K_{12} = \frac{A B (\beta - \alpha)^2}{C_o (A\beta + B\alpha)}$$

$$K_{21} = \frac{A\beta + B\alpha}{C_o}$$

For two compartment model, KE is the rate constant for elimination of drug from the central compartment and β is the rate constant for elimination from the entire body. Overall elimination t1/2 can be calculated from β.

Area under (AUC) the curve $AUC = \frac{A}{\alpha} + \frac{B}{\beta}$

App. volume of Central compartment = $\frac{X_o}{C_o} = \frac{X_o}{K_E(AUC)}$

App. volume of Peripheral compartment = VP = $\frac{V_C K_{12}}{K_{21}}$

Apparent volume of distribution at steady state or equilibrium

$$V_{d,ss} = V_C + V_P$$

$$V_d, \text{ area} = \frac{X0}{\beta AUC}$$

Total systemic Clearence= $Cl_T = \beta V_d$

Renal Clearence= $Cl_R = \frac{dX_u}{dt} = K_E V_C$

The rate of excretion of Unchanged drug in urine can be represented by :

$$\frac{dX_u}{dt} = K_E A e^{-\alpha t} + K_E B e^{-\beta t}$$

The above equation can be resolved into individual exponents by the method of Residuals.

Two – Compartment open model- I.V. Infusion

The plasma or central compartment conc. of a drug when administered as constant rate (0 order) i.v. infusion is given as:

$$C = \frac{R_o}{V_c K_E}\left[1 + \left(\frac{K_E - \beta}{\beta - \alpha}\right) e^{-\alpha t} + \left(\frac{K_E - \alpha}{\alpha - \beta}\right) e^{-\beta t}\right]$$

At steady state (i.e.at time infinity) the second and the third term in the bracket becomes zero and the equation reduces to:

$$Css = \frac{Ro}{V_C K_E}$$

Now $V_C K_E = V_d \beta$

$$CSS = \frac{R0}{Vd\beta} = \frac{Ro}{Cl_t}$$

The loading dose X_0,L = Css V_c = $\frac{Ro}{K_E}$

MULTIPLE DOSING

Dosage regimen is defined as the manner in which a drug is taken. For some drugs like analgesics, hypnotics, anti-emetics etc. A single dose is sufficient to provide effective treatment. In cases where illness is longer than the therapeutic effect produced by a single dose drugs should be taken repeatedly for a specific period of time. This is called as multiple dosage regimen. E.g.- Antibacterial, Anticonvulsants, Cardio tonics, Hormones.

OBJECTIVES OF MULTIPLE DOSING

- To prolong the therapeutic activity of the drug.
- To achieve maximum efficacy.

PARAMETERS TO BE ADJUSTED IN DEVELOPING A DOSAGE REGIMEN

1. Size of the drug dose.
2. Frequency of drug administration that is the time interval between the doses (T).
3. ajustement of both dose size & dose interval.

MULTIPLE IV BOLUS

After a single dose administration, we assume that there is no drug in the body before the drug is administrated and that no more is going to be administered. However, in the case of multiple dose administration we are expected to give second dosage and also subsequent doses before the drug is completely eliminated. Thus accumulation of drug of the drugs should be considered. On repeated drug administration,

the plasma concentration will be added upon for each dose interval giving a plateau or steady state with the plasma concentration fluctuating between a minimum and a maximum.

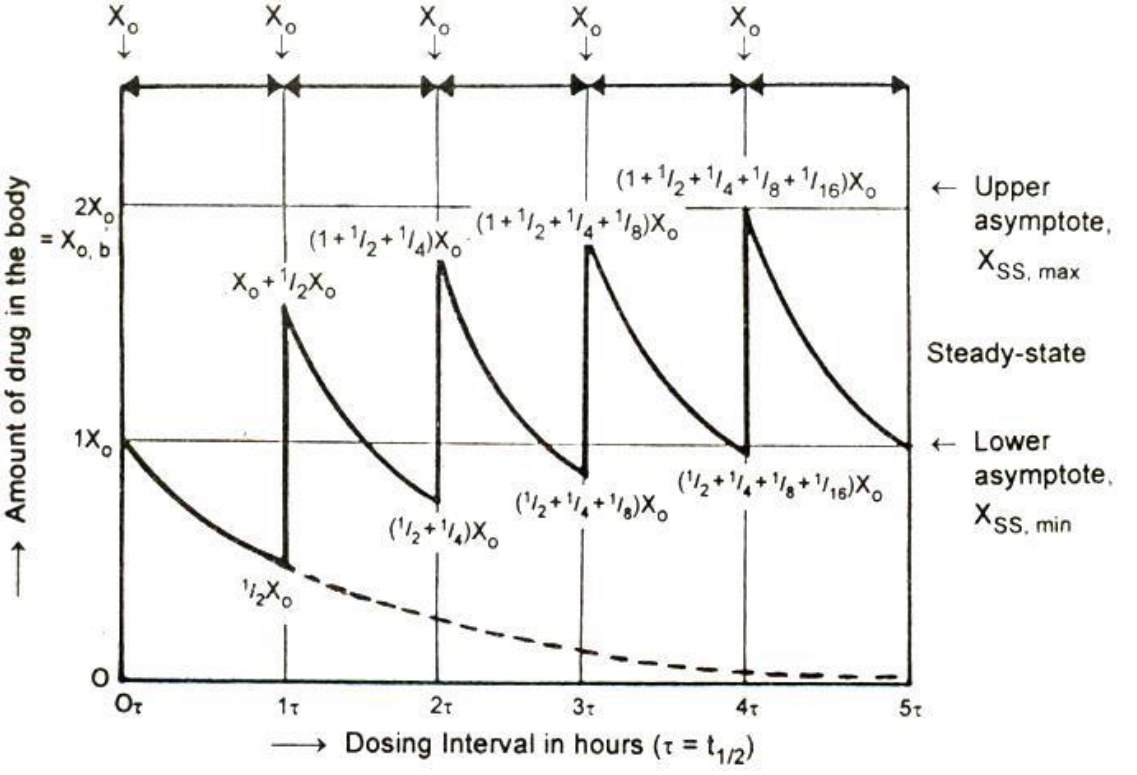
If the doses are given far enough apart then the concentration will have fallen to approximately zero before the next dose. There will then be no accumulation of drug in the body.

ACCUMULATING DOSES

After administration of first dose Xo at τ =0, the amount of drug in the body will be X=1Xo.

- At the next dosing interval when X=1/2Xo the amount of drug remaining in the body content to X=Xo +1/2Xo
- Accumulation occurs because drug from previous doses has not been removed completely.
- As the amount of drug in the body rises gradually due to accumulation.

When τ< t1/2, the degree of accumulation is greater and vice versa. Thus the extent to which a drug accumulates in the body during multiple dosing is a function of dosing interval and elimination half-life an is independent of dose size. The extent to which a drug will accumulate with any dosing interval in a patient can be derived from information obtained with a single dose and is given by accumulation index.



TIME TO REACH STEADY STATE DURING MULTIPLE DOSING

The time required to reach steady state depends primarily upon the half-life of the drug. Provided Ka >> KE, the plateau principle is reached in approximately 5 half- lives. This is called as plateau principle. It also means that the rate at which the multiple dose steady-state is reached is determined only by KE. The time taken to reach steady-state is independent of dose size, dosing interval and number of doses.

ACCUMULATION INDEX

The extent to which a drug will accumulate relative to the first dose can be quantified by an accumulation factor R.

The amounts of drug at steady sate are compared to the corresponding values at time t after the first dose i.e.

$$\frac{\text{Ass max}}{\text{Amax,1}} = \frac{\text{Ass, av}}{\text{Aav,1}} = \frac{\text{Ass min}}{\text{Amin,1}} = \frac{1}{1\text{-e-k}\,\tau}$$

Therefore $R = \frac{1}{1\text{-e-ke}\,\tau}$

R is an index of extent of accumulation

Also $R = 1/\ 1\text{-e-}(0.693/\ t1/2)\,\tau$

R is dependent on the dosing interval τ and half-life.

AVERAGE AMOUNT OF DRUG AT STEADY STATE

The average drug concentration at steady state Css av is a function of maintenance dose Xo, the fraction of dose absorbed F, the dosing interval τ and clearance CLT of drug.

Average rate in = Average rate out

Average rate in = F × Dose/ τ

Average rate out = K. Ass av

Where Ass av is the average amount of drug in the body over dosing interval at plateau.

Therefore F × Dose/ τ = K. Ass av---------- (6)

F × Dose/ τ = K V Ass av ---------- (7)

F × Dose/ τ = CL Css av ---------- (8)

Where Css av = average plasma concentration at steady state.

F × Dose/ τ = 0.693 Ass av/ t1/2---------- (9)

Ass av = 1.44 F X Dose t1/2/ τ ---------- (10)

From equation 8 we can write the following equ for Css av.

Css av = F Dose (Xo)/CL τ

Thus the average amount of drug in the body at steady state depends on rate of administration, bioavailability and half-life and plasma drug concentration depends on also clearance apart from dose, bioavailability and dosing interval.

Average drug concentration can also be defined as

Css av = AUC/ τ

AUC is the area under the curve following a single maintenance dose.

LOADING AND MAINTENANCE DOSES

 A drug does not show therapeutic activity unless it reaches the desired steady- state.

 It takes about 5 half-lives to attain it and therefore the time taken will be too long if the drug has a long half-life.

 Plateau can be reached immediately by administering a dose that gives the desired steady-state instantaneously before the commencement of maintenance doses Xo.

 Such an initial or first dose intended to be therapeutic is called as primary dose or loading dose Xo,L .

Xo,L = Css av Vd F ---------- (1)

 After e.v administration, Cmax is always smaller than that after iv administration and loading dose is proportionally smaller.

 When Vd is not known, loading dose may be calculated by following equation.

$$\frac{Xo,L}{Xo} = \frac{1}{(1-e^{-k a\tau})(1-e^{-ke\tau})}$$

The above equation applies when Ka>> KE and drug is distributed rapidly. When the drug is given IV, the absorption phase is neglected and the above equation reduces to.

$$\frac{Xo,L}{Xo} = \frac{1}{(1-e^{-ke\tau})} = Rac$$

Xo,L is called as dose ratio.

As a rule, when $\tau = t1/2$ dose ratio should be equal to 2 but must be smaller than 2 when $\tau > t1/2$ and greater when $\tau < t1/2$. Fig shows that if loading dose is not optimum, either too low or too high, the steady-state is attained within approximately 5 half-lives.

MULTIPLE ORAL DOSE ADMINISTRATION:

 Oral multiple dosing regimen is initiated plasma concentrations will increases, reach a maximum and begin to decline.

 A second dose will be administered before all of the absorbed drug from the first dose is eliminated.

 Plasma concentration resulting from the second dose will be higher than those from the first dose.

 This increase in concentration with dose will continue to occur until a steady state is reached at which the rate of drug entry into the body will equal the rate of exit.

 Hence the concentration at any time during a dosing interval should be the same from dose to dose. Plasma concentration achieved following a single dose can be given by

$$C = \frac{F.\ Dose\ .\ Ka}{Vd\ (Ka-K)} \left[e^{-k\tau} - e^{-k\ a\tau}\right] \quad \text{---------- (1)}$$

Ka is the absorption rate constant and K is the elimination rate constant

During a multiple dose regimen for a constant dose and dose interval can be determined from the following equation.

$$C = \frac{F.\ Dose\ .\ Ka}{Vd\ (Ka-K)} \cdot \frac{1- e^{-nk\tau}}{1- e^{-k\tau}} \cdot e^{-k\tau} -- \frac{1- e^{-k\tau}}{1- e^{-k\tau}} \cdot e^{-kat} \quad \text{---------- (2)}$$

Where n = number of doses

τ = dosing inteval

t = time after administration of n doses

F = fraction of the dose absorbed

Equation 2 is a general equation.

There is accumulation of the drug in the body to some plasma concentrations fluctuate between a minimum and a maximum value.

The mean plasma level at steady state,

$$Css\ av = \frac{F.\ Dose}{Vd.\ K.\ \tau} \quad \text{---------- (3)}$$

Also

$$Css\ av = \frac{F.\ Dose}{CL\ .\ \tau} \quad \text{---------- (4)}$$

Css av can also be calculated from the equation

$$Css\ av = \frac{[AUC]^{\infty}_{0}}{\tau} \quad \text{---------- (5)}$$

where $[AUC]^{\infty}_{0}$ is the area under plasma concentration

Vs time curve from t=0 to t=∞ following a single maintenance dose.

We get the same average plasma concentration whether the dose is given as a single dose every t dosing. Eg: 300mg given every 12hr or 100mg every 4hr

At steady-state, the drug concentration at any time can be determined by letting n=∞. Therefore $e^{-nk\tau}$ becomes zero equation (2) can be written as

$$Css = \frac{F.\ Dose\ .\ Ka}{Vd\ (Ka-K)} \cdot e^{-kt} - \frac{e^{-kat}}{1- e^{-k\tau}} \cdot \frac{}{1- e^{-ka\tau}} \text{ ------- (6)}$$

If we assume that the subsequent doses are given after the plasma concentration has peaked e-kaτ = 0. That is the next dose is given after the absorption phase is complete.

Cmin at t = t is

$$C_{min} = \frac{F \cdot Dose \cdot Ka}{Vd\,(Ka-K)} \cdot \frac{e^{-kt}}{1-e^{-k\tau}} \quad \text{---------- (7)}$$

LOADING DOSE

Loading dose = maintenance dose / 1- e-kτ -------- (12)

From equation 3

Dm (maintenance dose) = Css,av Vd τ / 1.44 F t1/2

Considering equation 8

Ka>> K then (Ka-K) is approximately equal to Ka and thus

[Ka/ (Ka-K)] = 1

Therefore equation 8 can be written as

$$C^{ss}_{min} = \frac{F \cdot Dose \cdot Ka}{Vd\,(Ka-K)} \cdot \frac{e^{-kt}}{1-e^{-k\tau}} \quad \text{---------- (13)}$$

or Cmin = Cmax e-kt ---------- (14)

$$C_{max} = \frac{C_{min}}{e^{-kt}} \quad \text{---------- (15)}$$

Applications of pharmacokinetics:

The knowledge of pharmacokinetics is implemented in the following:

i. Dosage regimens:

Dosage regimen is a systematized dosage schedule having two variables, the size of each dose and the frequency of dose.

Dosage regimen estimation is based on the specific patient consideration and is known as individualization or optimization. This is required on the basis of age, weight, sex, disease state, liver function, pregnancy etc.

So, pharmacokinetics is used to calculate dosage regimen.

ii. Drug switching:

During a therapy course, a patient is switched over from one brand of drug or from one route to another (i.e. from IV to IM). This conversion may cause fluctuations in the drug concentration in body.

Pharmacokinetics study helps to reduce the fluctuation.

iii. Determination of route of administration:

Route of administration may affect drug pharmacokinetics.

A drug administered through oral route may demonstrate first pass effect.

A drug administered via IM route may demonstrate erratic drug release.

A drug administered via IV may precipitate at injection site.

So, the pharmacokinetic evaluation is required in determination of route.

iv. Calculation of dose:

The pharmacokinetics also helps in choosing the loading dose (a large initial dose given to achieve the effective plasma concentration) and maintenance dose (Dose of a drug at regular and fixed time intervals to maintain its effective concentration in body).

v. Prediction of drug interaction:

Pharmacokinetics studies are helpful in assessment of drug-drug and food-drug interactions that interfere at drug absorption, distribution, metabolism and excretion.

vi. Prediction of drug accumulation:

Pharmacokinetics studies are implemented in the assessment of rate and extent of drug accumulation (protein binding).

vii. Identification of pharmacokinetics variables:

Pharmacokinetics is employed to identify various patients, physiologic and disease variables that could alter clinical response i.e. liver function.

viii. Bioequivalence study:

The bioequivalence studies evaluate differences in the availability between formulations. These studies are based on pharmacokinetic evaluation of formulations.