Compartment Modeling

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Introduction

Introduction

- The time course of drug concentration determined after its administration can be satisfactorily explained by assuming the body as a single well-mixed compartment with first-order disposition processes.
- In case of other drug, two or more body compartment may be postulated to describe mathematically the data collected.
- The one compartment open model treats the body as one homogeneous volume in which mixing is instantaneous input and output are from this one volume.

One – Compartment Open Model (Instantaneous Distribution Model)

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- The one- compartment open model is the simplest model. Owing to its simplicity, it is based on following assumption

1) The body is considered as a single, kinetically homogeneous unit that has no barriers to the movement of drug.
2) Final distribution equilibrium between the drug in plasma and other body fluid (i.e. mixing) is attained instantaneously & maintained at all times. This model is followed by only those drugs that distribute rapidly throughout the body.
3) Drugs move dynamically, in (absorption) & out (elimination) of this compartment.
4) Elimination is a first order (monoexponential) process with first order rate constant.
5) Rate of input (absorption) > rate of output (elimination).

One – Compartment Open Model (Instantaneous Distribution Model)

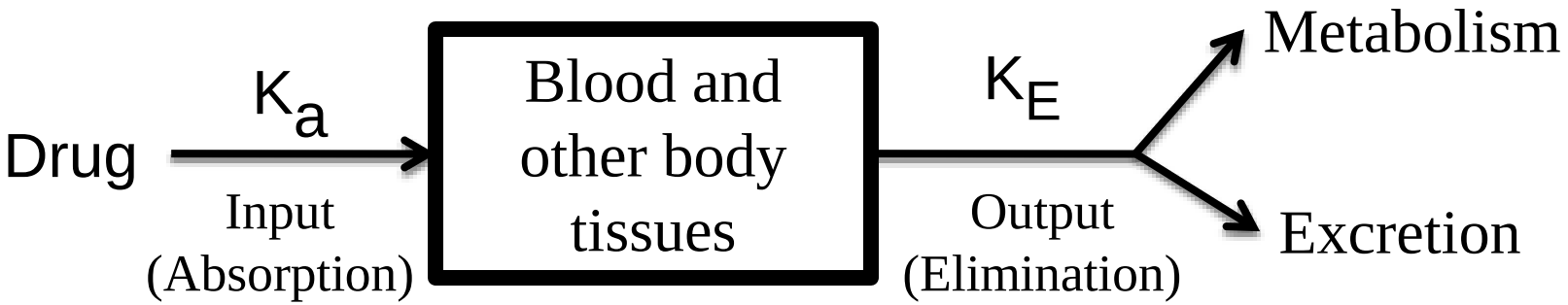


FIG: One-compartment open model showing input and output processes

One – Compartment Open Model (Instantaneous Distribution Model)

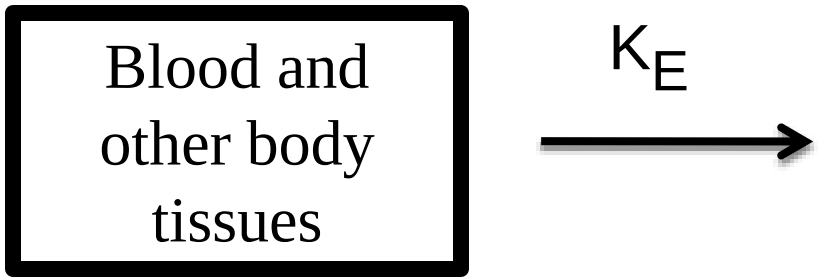
- Depending on rate of input, several one compartment open models are :

1. One compartment open model, i.v. bolus administration
2. One compartment open model, continuous i.v. infusion.
3. One compartment open model, e.v. administration, zero order absorption.
4. One compartment open model, e.v. administration, first order absorption

One-compartment Open Model: Intravenous Bolus Administration

One-compartment Open Model: Intravenous Bolus Administration

- The drug is rapidly distributed in the body when given in the form of intravenous injection (i.v. bolus or slug). It takes about one to three minutes for complete circulation & therefore the rate of absorption is neglected in calculation.



One-compartment Open Model: Intravenous Bolus Administration

- The general expression for rate of drug presentation to the body is:

$$\frac{dX}{dt} = \text{Rate in (availabity)} - \text{Rate out (elimination)} \qquad \ldots(1)$$

- Since rate in or absorption is absent, the equation becomes:

$$\frac{dX}{dt} = - \text{Rate out} \qquad \ldots(2)$$

- If the rate out or elimination follows first-order kinetics, then:

$$\frac{dX}{dt} = - K_E X \qquad \ldots(3)$$

- where K_E = first-order elimination rate constant, and

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

- Negative sign indicates that the drug is being lost from the body.

Estimation of pharmacokinetic parameters – IV bolus administration

- Elimination phase can be characterized by 3 parameters -

1) Elimination rate constant
2) Elimination half life
3) Clearance

Elimination Rate Constant

Elimination Rate Constant:

- Integration of equation (3) yields:

$$\ln X = \ln X_0 - K_E t \quad \ldots(4)$$

- Where, X_0 = amount of drug at time

  t = zero i.e. the initial amount of drug injected.

- Equation (4) can also be written in the exponential form as:

$$X = X_0 e^{-K_E t}$$

- This equation shows one compartment kinetics is monoexponential. …(5)

Elimination Rate Constant

- Transforming equation (4) into common logarithms (log base 10) we get:

$$\log X = \log X_0 - \frac{K_E t}{2.303} \qquad \ldots(6)$$

- Since it is difficult to determine directly the amount of drug in the body X, advantage is taken of the fact that a constant relationship exists between drug concentration in plasma C and X, thus

$$X = V_d\, C \qquad \ldots(7)$$

where, V_d = proportionality costant popularly known as the *apparent volume of distribution.*

Elimination Rate Constant

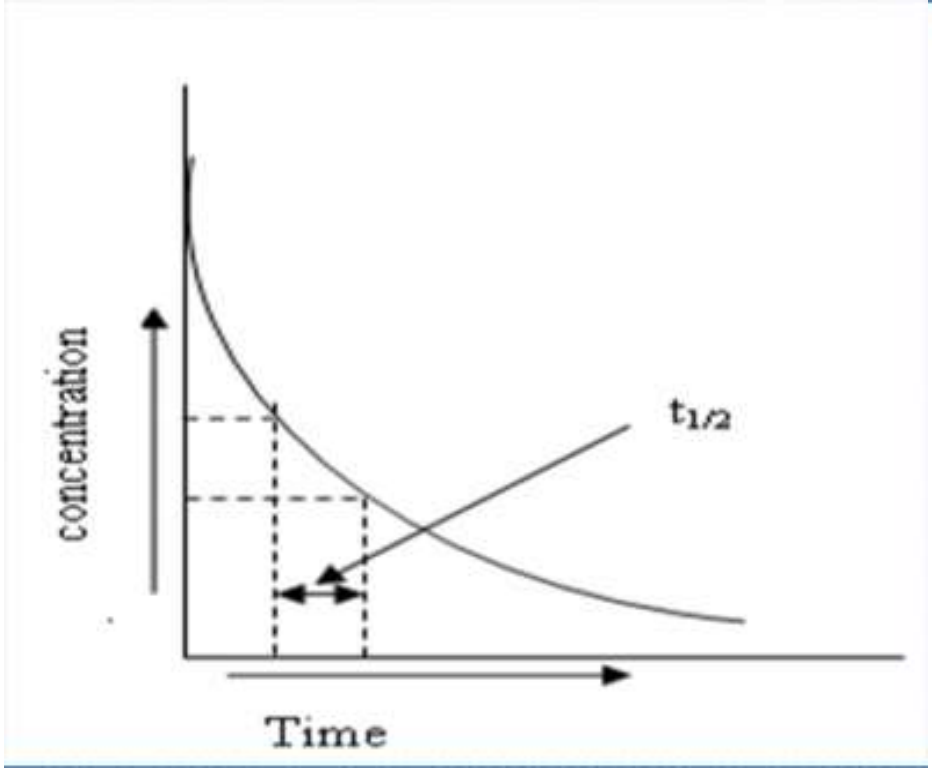
- It is a pharmacokinetic parameter that permits the use of plasma drug concentration in place of total amount of drug in the body by equation (6) therefore becomes:

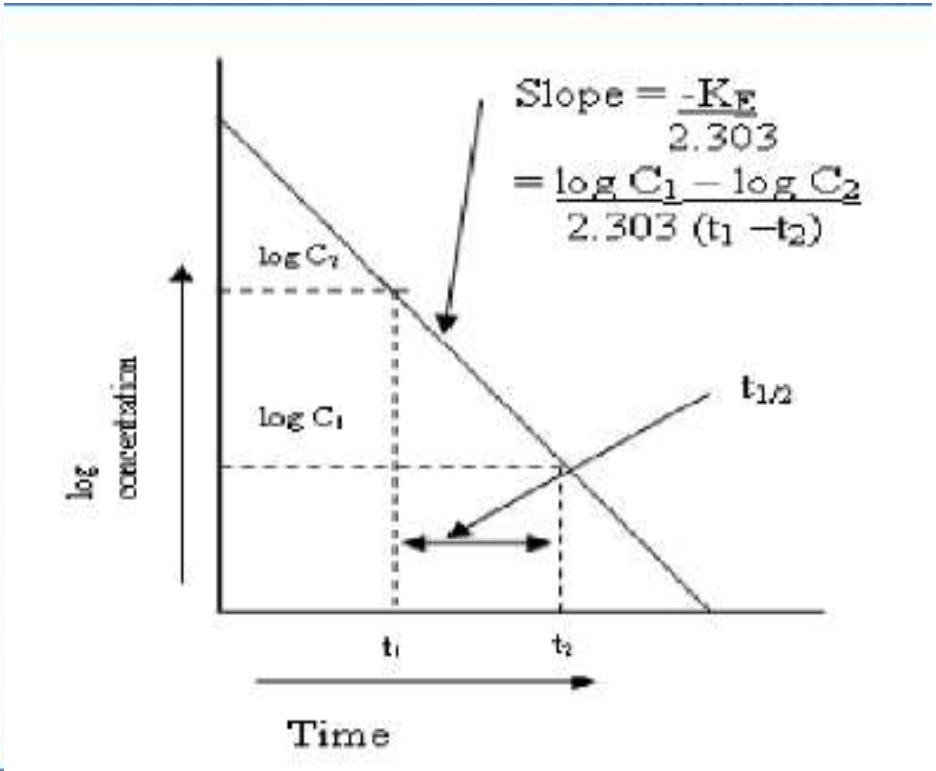
$$\log C = \log C_0 - \frac{K_E t}{2.303} \qquad \ldots(8)$$

where C_0 = plasma drug concentration immediately after i.v. injection.

- Equation (8) is that of a straight line and indicates that semi logarithmic plot of log C vs t, will be linear with Y-intercept as log C_0

Elimination Rate Constant





a) Cartesian plot of drug that follows one-compartment kinetics and given by rapid injection

b) Semi logarithmic plot for the rate of elimination in a one-compartment model

Elimination Rate Constant

- The elimination or removal of drug from the body is the sum of urinary excretion, metabolism, biliary excretion, pulmonary excretion and other mechanisms involved therein.
- Thus, K_E is an additive property of rate constant for each of this processes and better called as **overall elimination rate constant**.

$$K_E = K_e + K_m + K_b + K_1 + ... \quad \ldots(9)$$

- The fraction of drug excreted unchanged in urine F_e and fraction of drug metabolized F_m can be given as

$$F_e = \frac{K_e}{K_E} \quad \ldots(10)a$$

$$F_m = \frac{K_m}{K_E} \quad \ldots(10)b$$

Elimination Half - Life

Elimination Half - Life

- Elimination half life : Also called as biological half life.
- The time taken for the amount of drug in the body as well as plasma concentration to decline by one- half or 50% its initial value.
- It is expressed in hours or minutes.
- Half life expressed by following equation:

$$t_{1/2} = \frac{0.693}{K_E} \qquad \ldots(11)$$

- The half – life is a secondary parameter that depends upon the primary parameter clearance & apparent volume of distribution.
- According to following equation:

$$t_{1/2} = \frac{0.693 V_d}{Cl_T} \qquad \ldots(12)$$

Apparent Volume of Distribution

Apparent Volume of Distribution

- The two separate & independent pharmacokinetic characteristics of a drug distribution of a drug .since, they are closely related with the physiological mechanism of body, they are called as primary parameters.

- Modification of equation (7) defined apparent volume of distribution :

$$V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}} = \frac{X}{C} \qquad \ldots(13)$$

- The best and the simplest way of estimating V_d of a drug is administering it by rapid i.v. injection, determining the resulting plasma concentration immediately by using the following equation:

$$V_d = \frac{X_0}{C_0} = \frac{i.v.\text{bolus dose}}{C_0} \qquad \ldots(14)$$

Apparent Volume of Distribution

- A more general, a more useful non-compartmental method that can be applied to many compartment models for estimating the V_d is:
- For drugs given as i.v. bolus,

$$V_{d(area)} = \frac{X_0}{K_E AUC} \qquad \ldots(15)a$$

- For drugs administered extravascularly (e.v.),

$$V_{d(area)} = \frac{FX_0}{K_E AUC} \qquad \ldots(15)b$$

X_0 = dose administered

F = fraction of drug absorbed into the systemic circulation.

Clearance

Clearance

- **Clearance** : Clearance is the most important parameter in clinical drug applications & is useful in evaluating the mechanism by which a drug is eliminated by the whole organisms or by a particular organ.
- Clearance is a parameter that relates plasma drug concentration with the rate of drug elimination according to following equations-

$$clearance = \frac{\text{rate of elimination}}{\text{plasma drug concentration}} \qquad \ldots(16)$$

Or

$$Cl = \frac{d_x/d_t}{c}$$

- Clearance is defined as the theoretical volume of body fluid containing drug from which the drug is completely removed in a given period of time. It is expressed in ml/min or lit/hr.

Total Body Clearance

- Clearance at an individual organ level is called as organ clearance.
- It can be estimated by dividing the rate of elimination by each organ with the concentration of drug presented to it. Thus,
- Renal clearance

$$Cl_R = \frac{Rate\ \text{of elimination by kidney}}{C} \quad \ldots(17)$$

- Hepatic clearance

$$Cl = \frac{\text{Rate of elimination by liver}}{C} \quad \ldots(18)$$

- Other organ clearance

$$Cl = \frac{\text{Rate of elimination by other organs}}{C} \quad \ldots(19)$$

Total Body Clearance

- The total body clearance, $Cl_T = Cl_R + Cl_H + Cl_{other}$
- Clearance by all organs other than kidney is some times known as nonrenal clearance Cl_{NR}
- It is the difference between total clearance and renal clearance according to earlier an definition (equation 17)

$$Cl_T = \frac{dx/dt}{C} \qquad \ldots(20)$$

Substituting $dX/dt = K_E X$ from equ.3 in above equ.we get

$$Cl_T = \frac{K_E X}{C} \qquad \ldots(21)$$

Since X/C = Vd (from equation 13) the equ. (21) can be written as

$$Cl_T = K_E v_d \qquad \ldots(22)$$

Total Body Clearance

- Parallel equation can be written for renal and hepatic clearance as:

$$Cl_R = Ke\ V_d$$

$$Cl_H = Km\ V_d$$

Since, $K_E = 0.693/t1/2$ (from equa. 11), clearance can be related to half life by the following equation

…(23)

$$Cl_T = \frac{0.693 v_d}{t_{1/2}}$$

One-Compartment Open Model

Extravascular Administration

One-Compartment Open Model

Extravascular Administration

- When a drug is administered by extravascular route ,the rate of absorption may be described by mathematically as a zero or first order process.
- A large number of plasma concentration time profile can be described by a one compartment model with first order absorption & elimination.
- Difference between zero- order and first- order kinetics are given in fig.

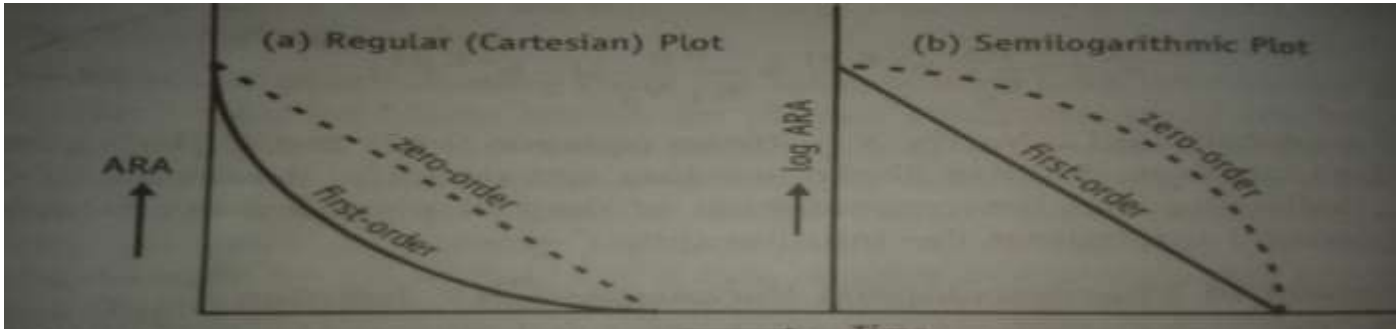


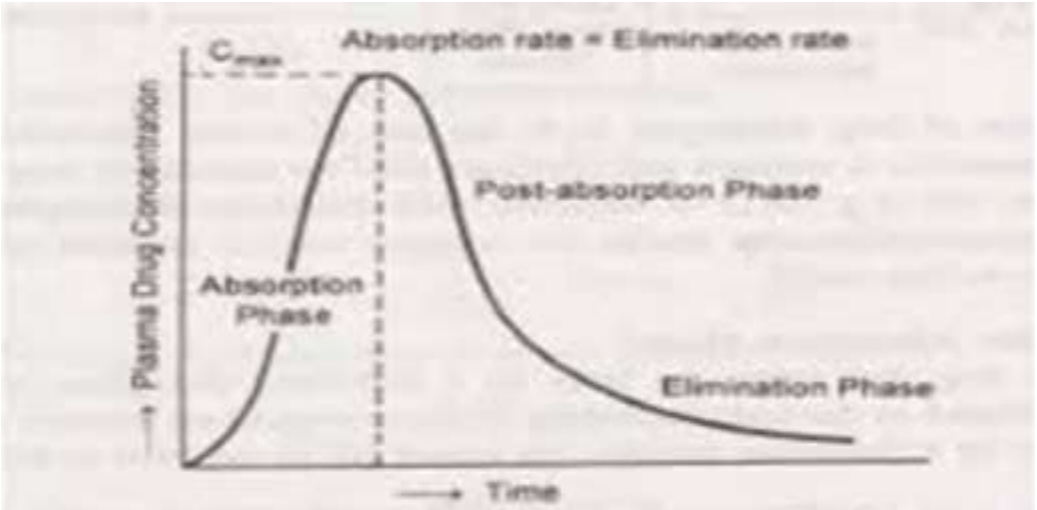
Fig. 9.6 Distinction between zero-order and first-order absorption processes. *Figure a* is regular plot, and *Figure b* a semilog plot of amount of drug remaining to be absorbed (ARA) versus time t.

One-Compartment Open Model

Extravascular Administration

- Zero order absorption is characterized by a constant rate of absorption .
- After e.v. administration , the rate in the change of amount of drug in the body dx/dt is difference between the rate of input (absorption) dx_{ev}/dt and rate of output(elimination) dx_E/dt .
- dx /dt = rate of absorption – rate of elimination

$$\frac{dx}{dt} = \frac{dx_{ev}}{dt} - \frac{dx_E}{dt} \quad \ldots(1)$$



ig. 10.7 The absorption and elimination phases of the plasma concentration-time profile obtained after extravascular administration of a single dose of a drug.

One-Compartment Open Model
Extravascular Administration

- During the absorption phase, the rate absorption is greater than the rate of elimination

$$\frac{dx_{ev}}{dt} > \frac{\mathrm{dx_E}}{\mathrm{dt}} \qquad \ldots(2)$$

- At peak plasma concentration , the rate of absorption equals the rate of elimination and the change in amount of drug in the body is zero

$$\frac{dx_{ev}}{dt} = \frac{\mathrm{dx_E}}{\mathrm{dt}} \qquad \ldots(3)$$

- The plasma level time curve is characterized only by the Elimination phase.

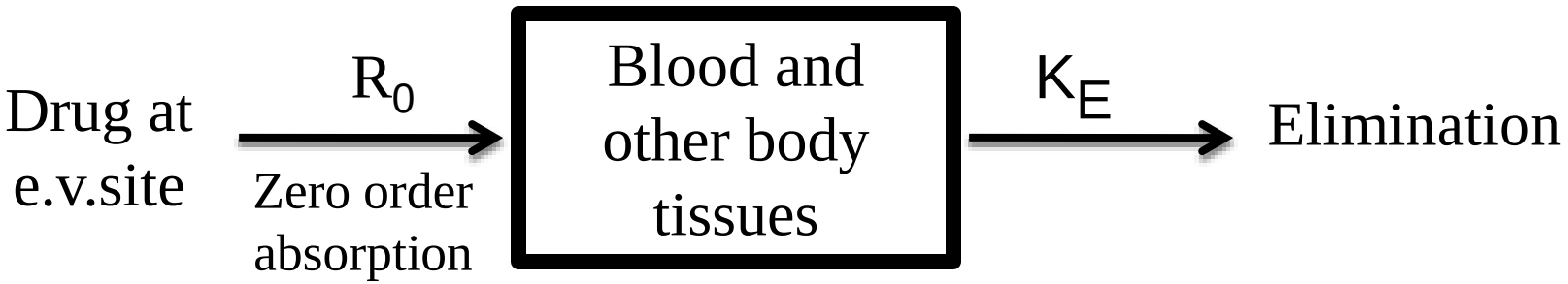
$$\frac{dx_{ev}}{dt} < \frac{\mathrm{dx_E}}{\mathrm{dt}} \qquad \ldots(4)$$

Zero- Order Absorption Model

Extravascular Administration

Zero - Order Absorption Model
Extravascular Administration

- This model is similar to that for constant rate infusion.

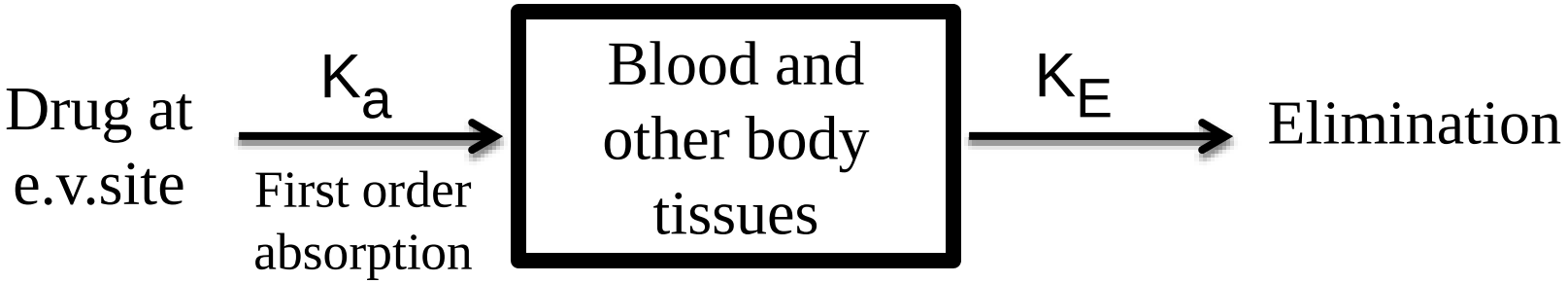


- All equation that explain the plasma concentration – time profile for constant rate i.v. infusion are also applicable to this model.

First order Absorption Model Extravascular Administration

First order Absorption Model Extravascular Administration

- A drug that enters the body by a first order absorption process gets distributed in the body according to one - compartment kinetics and is eliminated by a first - order process, the model can be depicted as follows



- The differential form of the drug the eque. (1)

$$\frac{dx}{dt} = k_a x_a - k_E x \qquad \ldots(5)$$

- Ka = first order absorption rate constant
- Xa = amount of drug at the absorption site remaining to be absorbed i.e. ARA.

First order Absorption Model Extravascular Administration

- Integration of eque. (5)

$$C = \frac{K_a F X_0}{K_a - K_E} [e^{-k_E t} - e^{-k_a t}] \quad \ldots(6)$$

Transforming in to concentration terms, the eque. Becomes

$$C = \frac{K_a F X_0}{Vd(K_a - K_E)} [e^{-k_E t} - e^{-k_a t}] \quad \ldots(7)$$

Where, F= fraction of drug absorbed systemically after e.v. administration .

Assessment of Pharmacokinetic Parameters

Extravascular administration

Assessment of Pharmacokinetic Parameters

Extravascular administration

- C_{max} and t_{max} : At peak plasma concentration , the rate of absorption equals rate of elimination i.e. $K_aX_a = K_EX$ and the rate of change in plasma drug concentration dc/dt = zero . Differntiating equation(7)

$$\frac{dc}{dt} = \frac{K_a F X_0}{Vd(K_a - K_E)}[-K_E e^{-k_E t} + K_a e^{-k_a t}] = \text{Zero} \qquad \ldots(8)$$

- On simplifying ,the above eque. Becomes:

$$K_E e^{-k_E t} = K_a e^{-k_a t} \qquad \ldots(9)$$

- Converting to logarithmic form,

$$\log k_E - \frac{k_E t}{2.303} = \log k_a - \frac{k_a t}{2.303} \qquad \ldots(10)$$

Assessment of Pharmacokinetic Parameters

Extravascular administration

- Where t is t_{max} . Rearrangement of above eque. yield.

$$T_{max} = \frac{2.303 \log \ (K_a/K_E)}{K_a - K_E} \quad \ldots(11)$$

- C_{max} can be obtained by substituting eque. (11) in eque (7), simpler eque for the same is:

$$C_{max} = \frac{FX_0}{V_d} e^{-k_E t_{max}} \quad \ldots(12)$$

- It has been shown that at C_{max}, when $K_a = K_E$, $t_{max} = 1/K_E$. Hence the above eque. Further reduced to:

$$C_{max} = \frac{FX_0}{V_d} e^{-1} = \frac{0.37 \ FX_0}{V_d} \quad \ldots(13)$$

Since, FX_0/V_d represent C_0 .

Elimination Rate Constant

Elimination Rate Constant

- The parameter can be computed from the elimination phase of the plasma level time profile.
- For most drugs administered e.v., absorption rate is significantly greater than the elimination rate.
- At such a stage, when absorption is complete, the change in plasma conc. Is depend only on elimination rate and eque. (7) reduces to

$$C = \frac{K_a F X_0}{V_d (K_a - K_E)} e^{-k_{E^t}} \qquad \ldots(14)$$

- Transforming into log form, the eque. Becomes ,

$$\log C = \log \frac{K_a F X_0}{V_d (K_a - K_E)} - \frac{K_{E^t}}{2.303} \qquad \ldots(15)$$

Absorption Rate Constant

Absorption Rate Constant

- It can be calculated by the method of residuals.
- For a drug that follow one compartment kinetics & administered e.v., the concentration of drug in plasma is expressed by a biexposnential equation (7)

$$C = \frac{K_a F X_0}{V_d (K_a - K_E)} [e^{-K_E t} - e^{-K_a t}] \quad \ldots(14)$$

if $K_a F X_0 / V_d (K_a - K_E) = A$, a hybrid constant then :

- $$C = Ae^{-k_E t} - Ae^{-k_a t} \quad \ldots(15)$$
- During the elimination phase, when absorption is almost over, Ka>KE value of second exponential e-K_at is zero. Whereas the exponential e-^{K_E}t retaines some finite value. at this time the eque.(15) reduced to:

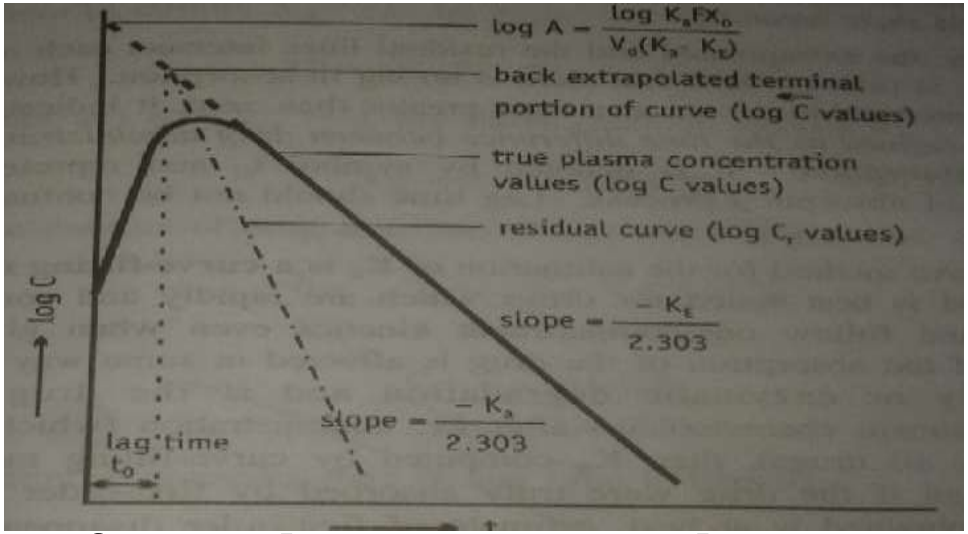
$$\overleftarrow{C} = Ae^{-K_E t} \quad \ldots(16)$$

- In log form, the above equation is:

$$\log \overleftarrow{C} = \log A - \frac{K_E t}{2.303} \quad \ldots(17)$$

Absorption Rate Constant

- Where, $\overleftarrow{C}$ represents the back extrapolation plasma concentration value.



- Substraction of true plasma conc. Values i.e. equa.(15) from the extrapolated plasma concentration values C_r

$$(\overleftarrow{C} - C) = C_r = Ae^{-K_a t} \qquad \ldots(18)$$

Absorption Rate Constant

- In log form, the eque.is

$$\log C_r = \log A - \frac{K_a t}{2.303} \qquad \ldots(19)$$

- A plot of log Cr vs t yields a straight line with –Ka/2.303 & y intercept log A
- In some instance , the KE obtained after i.v. bolus of some of the drug is very larger than the Ka obtained by recidual method and KE/Ka> 3,

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THANK YOU