UNIT

XVII

ONE-COMPARTMENT OPEN MODEL (E.V. ADMINISTRATION)

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INTRODUCTION

Absorption is required for therapeutic efficacy when a drug is supplied by an extravascular route (e.g., oral, intramuscular, rectal, etc.).

After e.v. administration, the rate of drug input (absorption) minus the rate of drug output (elimination) equals the **net rate of drug accumulation in the body** at any given time:

$$\frac{dX}{dt} = \frac{dX_{ev}}{dt} - \frac{dX_E}{dt}$$

where X_{ev} is the amount of drug in the gastrointestinal tract and

X_E is the amount of drug eliminated

When a drug is administered by extravascular route (e.g., oral, intramuscular, rectal, etc.), it absorb either by zero order kinetics or first order kinetics.

ZERO-ORDER ABSORPTION MODEL

The medication X_{ev} in the gastrointestinal tract is absorbed systemically at a constant rate, R_0, in this scenario. A first-order rate process characterised by a first-order rate constant, KE, eliminates the drug from the body instantaneously and quickly. This concept is similar to how a medicine is administered via intravenous infusion.

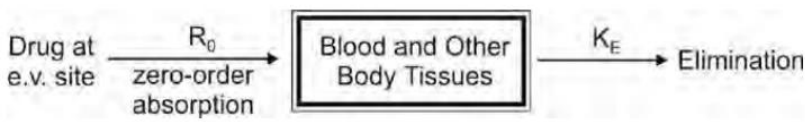

Figure 17.1: Block diagram showing drug movement after e.v. administration with zero order drug absorption in a one compartment open model.

At each given moment, the rate of first-order elimination equals K_EX. The input rate is just R_0. As a result, the net change in the body per unit time can be stated as:

$$\frac{dX}{dt} = R_0 - K_E X \qquad (1)$$

When V_dC is substituted for X in this equation, the result is:

$$C = \frac{R_0}{V_d K_E}\,(1 - e^{-K_E t})$$

Until the amount of drug in the gut, X_{ev}, is depleted, the rate of drug absorption remains constant. X_{ev} /R_0 is the time required for full medication absorption. The medicine is no longer available for absorption from the intestines after this time. A first-order elimination rate process then causes the drug concentration in the plasma to decrease.

FIRST-ORDER KINETIC ABSORPTION MODEL

Absorption is required for a drug's therapeutic efficacy when it is given by an extravascular route (e.g., oral, intramuscular, rectal, etc.). The following model can be used to represent a drug that enters the body through a first-order absorption process:

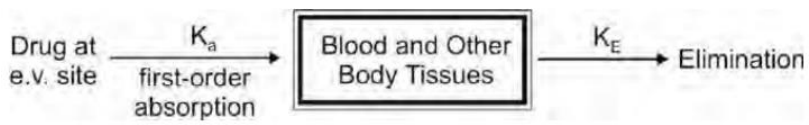

Figure 17.2: Block diagram showing drug movement after e.v. administration with first order drug absorption in a one compartment open model.

The rate of drug change in the body, dX/dt:

$$\frac{dX}{dt} = rate\ of\ in\ (absorption) - rate\ of\ out(elimination)$$

$$\frac{dX}{dt} = K_a F X_{ev} - K_E X$$

Where, K_a = first-order absorption rate constant from the GI tract,

F = fraction absorbed, and

X_{ev} = amount of drug in solution in the GI tract at any time t.

K_E = First order elimination rate constant

X = Amount of drug in body at time 't'

Since the drug in the gastrointestinal tract also follows a first-order decline, the amount of drug in the gastrointestinal tract (X_{ev}) at any time t is equal to $X_0 e^{-K_a t}$

$$\frac{dX}{dt} = K_a F X_0 e^{-K_a t} - K_E X$$

As illustrated below, this equation can be combined to produce the general oral absorption equation (bi-exponential) for calculating the drug concentration (C) in the plasma at any time t.

$$C = \frac{F K_a X_0}{V_d (K_a - K_E)} (e^{-K_E t} - e^{-K_a t})$$

Initially, absorption rate is significantly greater than the elimination rate i.e. $K_a t >> K_E t$. Hence, one can say that $e^{-K_a t}$ approaches zero much faster than $e^{-K_E t}$, or $e^{-K_a t} \longrightarrow 0$. Above equation reduces to

$$C = \frac{K_a F X_0}{V_d (K_a - K_E)} e^{-K_E t}$$

Transforming into log form, the equation becomes:

$$\log C = \log \frac{K_a F X_0}{V_d (K_a - K_E)} - \frac{K_E t}{2.303}$$

If $\frac{K_a F X_0}{V_d (K_a - K_E)} = A$, a hybrid constant, then:

$$\log C = \log A - \frac{K_E t}{2.303}$$

A plot of log C versus t yields a straight line with slope $-K_E/2.303$. **Elimination Half-Life (= Biological half-life, $t_{1/2}$)** can then be computed from K_E; $t_{1/2} = 0.693/K_E$

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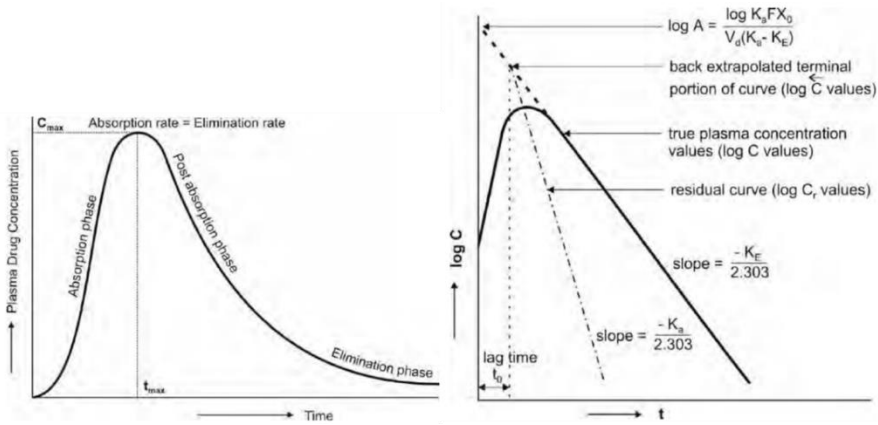

Figure 17.3: Drug-plasma profile e.v. administration in a one compartment open model, (a) normal plot, (b) semi-log plot.

Rate of absorption The method of residuals (also known as feathering, peeling, and stripping method) can be used to compute the constant of a medicine that is expressed by a bi-exponential equation. The residual method is a pharmacokinetics technique for breaking down a multi-exponential curve into its separate components. The following approach yields the value of Ka**:**

1. Back extrapolate the straight line of bi-exponential curve to time zero to obtain extrapolated plasma concentration ($\tilde{C}$). Here y-intercept is equal to log A.

$$\tilde{C} = Ae^{-K_E t}$$

2. The residual concentration values Cr are obtained by subtracting real plasma concentration (C) values from estimated plasma concentration (C) values.

$$\tilde{C} - C = C_r = Ae^{-K_a t}$$

In log form, the equation is:

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

A straight line with slope –Ka/2.303 and Y-intercept log A emerges from a plot of log Cr versus t. The relation 0.693/Ka can therefore be used to calculate the absorption half-life from Ka.

Apparent Volume of Distribution and Clearance: Vd and ClT can be calculated using the following formulae for a medication with one-compartment kinetics after e.v. administration, where F is the proportion absorbed into the systemic circulation.

$$V_d = \frac{FX_0}{K_E AUC}$$

$$Cl_T = \frac{FX_0}{AUC}$$

Flip-flop phenomenon: When the difference between Ka and KE is considerable (Ka/KE 3), the residual or feathering method for resolving bi-exponential plasma level-time curves works best. The KE acquired following an i.v. bolus is sometimes significantly larger than the Ka (KE/Ka 3), as is the case with isoprenaline. In this case, the results of the terminal and residual slopes are reversed, i.e. the terminal slope estimates Ka and not KE, whereas the slope of the residual line estimates KE and not Ka. Because the slopes of the two lines have swapped meanings, this is known as the flip-flop phenomenon.

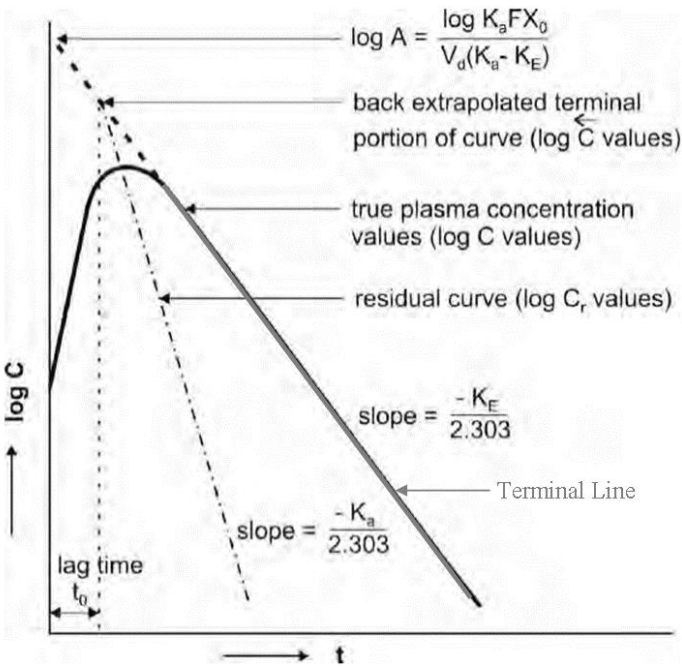

Figure 17.4: Estimation of lag time, K_a, K_E

Lag Time: The extrapolated and residual lines should connect on the y-axis at time t = zero, and there should be no lag in absorption. If such an intersection happens at a time other than zero, temporal lag is present. It is defined as the time interval between when a medicine is administered and when absorption begins.

The elimination rate constant (KE) is a pharmacokinetics term that describes how quickly a substance leaves the body per unit of time. It's made up of urinary excretion (Ke), metabolism (Km), biliary excretion (Kb), pulmonary excretion (Kl), and other processes. Thus, the overall elimination rate constant (KE) is an additive attribute of rate constants for each of these processes.

$K_E = K_e + K_m + K_b + K_l + ...$

Elimination Half-Life = Biological half-life ($t_{1/2}$): It's the time it takes for the amount of drug in the body, as well as plasma concentration, to drop by half or 50% of their initial value. It is measured in minutes or hours.

$$t_{1/2} = \frac{0.693}{K_E}$$

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

It's the period of time it takes for the amount of drug in the body, as well as the plasma concentration, to reduce by half or half of their initial value. The time is expressed in minutes or hours.

Apparent volume of distribution (V_d): It's the estimated amount of bodily fluid into which a medicine is dissolved or dispersed. Because all areas of the body equilibrated with the drug do not have identical concentration, it is called apparent volume.

$$Apparent\ Volume\ of\ Distribution = \frac{Amount\ of\ Drug\ in\ the\ body}{Plasma\ Drug\ Concentration}$$

$$V_d = \frac{X}{C}$$

For drugs administered extravascularly (e.v.),

$$V_{d(area)} = \frac{FX_0}{K_E AUC}$$

where, X_o = dose administered, and F = fraction of drug absorbed into the systemic circulation. F is equal to one i.e. complete availability when the drug is administered intravenously.

Total Body Clearance (Cl_T) is defined as the theoretical volume of drug-containing bodily fluid that can be entirely eliminated in a certain amount of time. It's measured in millilitres per minute or litres per hour.

$$Clearance = \frac{Rate\ of\ Elimination}{Plasma\ Drug\ Concentration}$$

$$Cl_T = \frac{dX/dt}{C}$$

$$Cl_T = \frac{K_E X}{C}$$

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