UNIT

XVIII

MULTICOMPARTMENT MODELS

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INTRODUCTION

One-compartment model assumes the instantaneous distribution of drug in single compartment. However, owing to heterogeneous nature of body tissue, a larger number of drugs does not dispose instantaneously in whole body and follow multi-compartment kinetics or bi- or multi-exponential pharmacokinetics. As a result, multicompartment models are based on the following assumptions:

1. The centre compartment is made up of blood/plasma and strongly perfused tissues.
2. Peripheral compartments are formed by grouping together other tissues with similar distribution characteristics. **(**Such as muscles, skin, adipose, etc.**)**.
3. Drug input occur in the central compartment either by zero order or first order. Similarly irreversible drug elimination takes place only from the central compartment by first-order kinetics.
4. There is reversible distribution between central and peripheral compartments, with distribution equilibrium taking a finite amount of time to achieve.
5. Drug elimination and clearance do not occur in the peripheral compartment, which is normally inaccessible to direct assessment.

TWO-COMPARTMENT OPEN MODEL AFTER INTRAVENOUS BOLUS

Administration

Two-compartment models are the most prevalent. Body tissues are divided into two groups in this model: central and peripheral compartments.

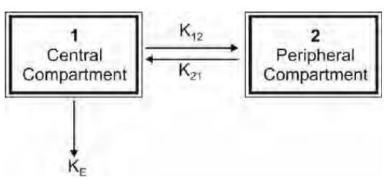

Figure 18.1: Two compartment open model after intravenous bolus drug administration

After the i.v. bolus administration, the plasma drug concentration declines biexponentially as the sum of two first-order processes – **distribution** and **elimination**. Drug plasma concentration shows three phases:

1. Distributive phase- rapid decline in plasma drug concentration due to distribution,
2. Pseudo-distribution equilibrium,
3. Post-distributive or elimination phase: Elimination causes a gradual decrease in plasma drug concentration.

A. We start with virtually no drug in the second compartment, but re-equilibration moves drug in – levels rise
B. A brief equilibrium - no net movement – at the peak of the curve, levels are neither rising nor falling
C. Re-equilibration moves into reverse and drug leaves the second compartment – levels fall

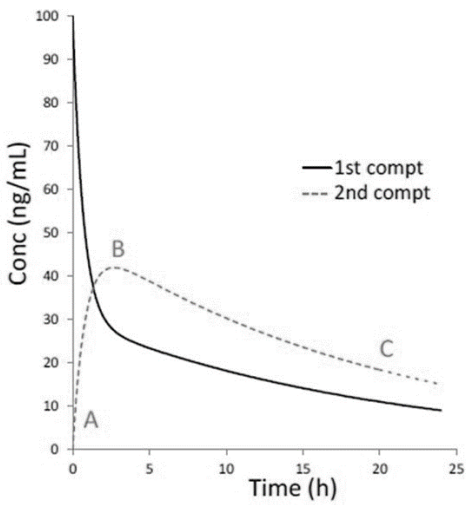

Figure 18.2: Comparison between one compartment and two compartment open model

The rate of change in drug concentration in the central compartment is given by:

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

Extending the relationship $X = V_d \times C$ to the above equation, we have

$$\frac{dC_c}{dt} = K_{21}\frac{X_p}{V_p} - K_{12}\frac{X_c}{V_c} - K_E\frac{X_c}{V_c}$$

Where, X_c and X_p are the amounts of drug in the central & peripheral compartments respectively.

V_c and V_p are the apparent volumes of the central & peripheral compartment respectively.

On integration of above equation-

$$C_C = \frac{X_0}{V_C}\left[\left(\frac{K_{21}-\alpha}{\beta-\alpha}\right)e^{-\alpha t} + \left(\frac{K_{21}-\beta}{\alpha-\beta}\right)e^{-\beta t}\right]$$

Above equation can be simplified as-

$$C_c = Ae^{-\alpha t} + Be^{-\beta t}$$

$$C_c = Distribution\ exponent + elimination\ exponent$$

where X_0 = i.v. bolus dose,

α and β are hybrid first-order constants for the rapid distribution phase and the slow elimination phase respectively,

K_{12} and K_{21} also known as **micro-constants** or **transfer constants.**

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

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

A and B are also hybrid constants with following expression-

$$C_C = \frac{X_0}{V_C}\left[\frac{K_{21}-\alpha}{\beta-\alpha}\right] = C_0\left[\frac{K_{21}-\alpha}{\beta-\alpha}\right]$$

$$C_C = \frac{X_0}{V_C}\left[\frac{K_{21}-\beta}{\alpha-\beta}\right] = C_0\left[\frac{K_{21}-\beta}{\alpha-\beta}\right]$$

ASSESSMENT OF A AND B BY RESIDUAL METHOD

Because the distribution rate constant is more than elimination rate constant, so the expression $e^{-\alpha t}$ approaches zero. As a result, the central compartment concentration equation is:

$$\overleftarrow{C_c} = Be^{-\beta t}$$

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

where $\overleftarrow{C_c}$ = back extrapolated plasma concentration values. A semilog plot of C versus t yields the terminal linear phase of the curve having slope – β/2.303 and intercept log B. **Overall elimination half-life** ($t_{½}$) = 0.693/β.

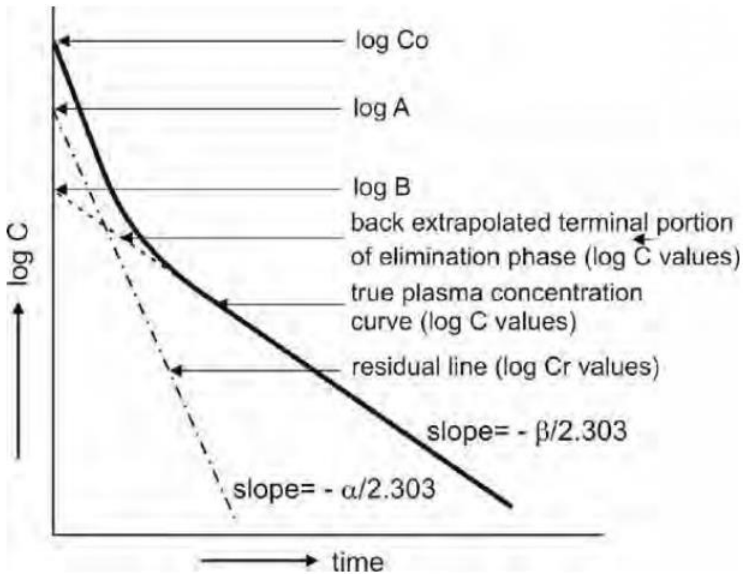

Figure 18.3: Estimation of α and β from semi-log plot.

A series of residual concentration (C_r) can be obtained by subtracting the back extrapolated plasma concentration derived from the true plasma concentration values:

$$C_r = C - \overleftarrow{C_c} = Ae^{-\alpha t}$$

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

A straight line with slope $-/2.303$ and y-intercept log A emerges from a semi log plot of Cr versus t.

ASSESSMENT OF PHARMACOKINETIC PARAMETERS

$$C_0 = A + B$$

$$K_E = \frac{\alpha\beta C_0}{A\beta + B\alpha}$$

$$K_{12} = \frac{AB(\beta - \alpha)^2}{C_0(A\beta + B\alpha)}$$

$$K_{21} = \frac{A\beta + B\alpha}{C_0}$$

Here, K_E is the rate constant for elimination of drug from the central compartment and β is the rate constant for elimination from the entire body.

AREA UNDER THE PLASMA CONCENTRATION-TIME CURVE

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta}$$

Vc is the apparent volume of the central compartment.

$$V_C = \frac{X_0}{C_0} = \frac{X_0}{K_E AUC}$$

The following calculation can be used to calculate the apparent volume of the peripheral compartment*:*

$$V_P = \frac{V_c K_{12}}{K_{21}}$$

At steady-state or equilibrium, the apparent volume of distribution can now be defined as:

$$V_{d,ss} = V_c + V_p$$

Total systemic clearance is given as:

$$Cl_T = \beta V_d$$

KINETICS OF MULTIPLE DOSING

The plasma drug level rises above and then falls below the minimal effective concentration (MEC) after a single-dose medication administration, causing in a loss of therapeutic action. As a result, many medications are given in a multiple-dosage regimen to maintain steady state plasma concentrations and sustained therapeutic efficacy.

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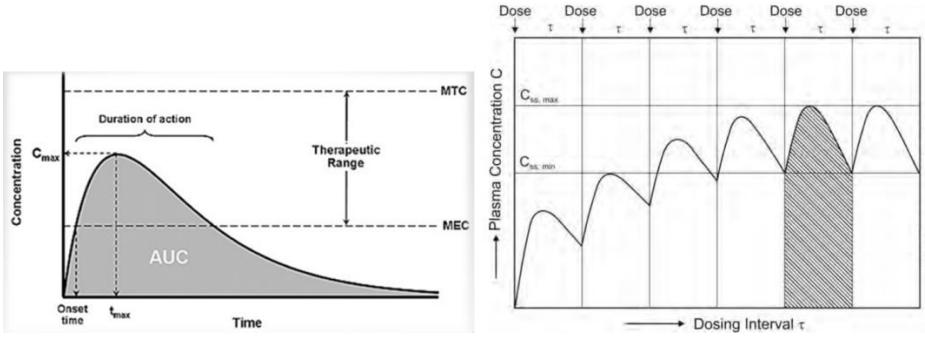

Figure 18.4: Drug-plasma profile after single dose administration and multiple dosing.

A proper balance between both dose size and dosing frequency is often desired to attain steady-state concentration with minimum fluctuations and to ensure therapeutic efficacy and safety.

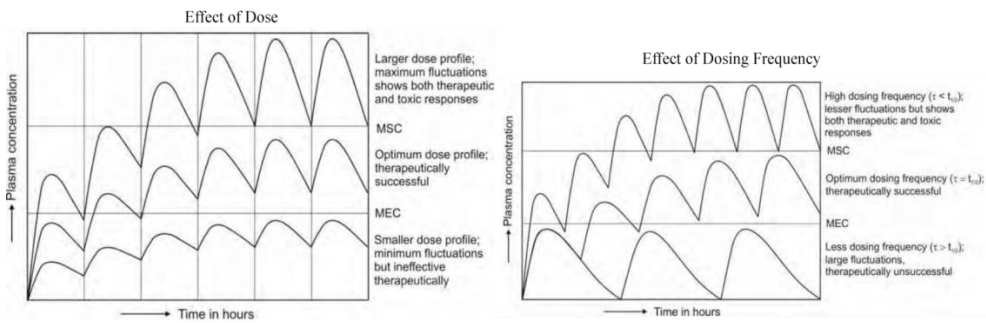

Figure 18.5: Effect of dose and dosing frequency after multiple dosing.

In general, every consecutive dose should be given at a time interval equal to the drug's half-life. As a general rule of thumb,

- For medications having a broad therapeutic index, such as penicillin, higher dosages can be given at longer intervals (greater than the drug's half-life) without causing toxicity.
- For medications having a narrow therapeutic index, such as digoxin, it is preferable to administer tiny doses at frequent intervals (typically shorter than the drug's half-life) to achieve a profile with the fewest variations.

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ACCUMULATION OF DRUGS DURING MULTIPLE DOSES

After i.v. multiple dosage with a dosing interval of one t12, calculate the amount of medication in the body-time profile.

After the first dose has been administered, (X_0), the amount of drug falls to $X_0/2$ at next dosing interval. When the next dose administered, amount rises to $X_0/2 + X_0$. As a result, because the drug from earlier dosages has not been entirely eliminated, buildup occurs. As the amount of drug in the body increases, so does the rate of elimination, until a steady-state or plateau is reached, at which the rate of drug entrance into the body equals the rate of outflow.

The amount of medicine that accumulates in the body during multiple dosage is a function of –

- Dosing interval, and
- Elimination half-life.

The accumulation index R_{ac} indicates how much a drug will accumulate over time with any dose interval:

$$R_{ac} = \frac{1}{1 - e^{-K_E t}}$$

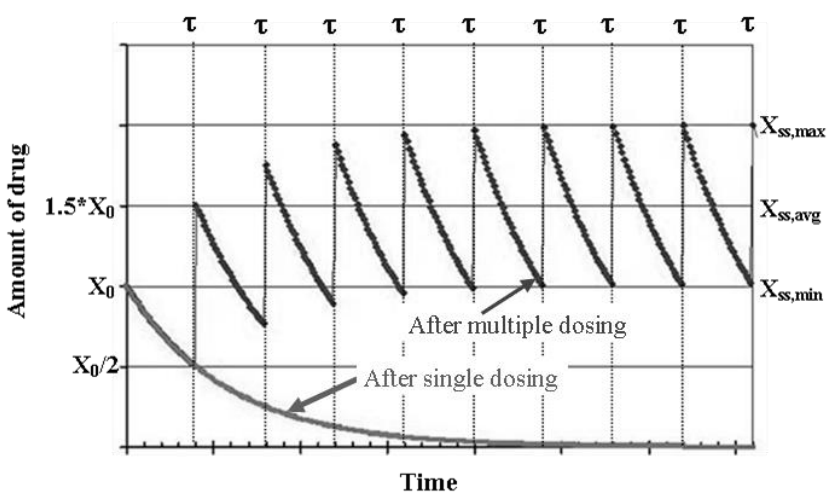

Figure 18.6: Steady-state plasma concentration after single dose and multiple dosing.

To reach steady-state, approximately 5 half-lives are required. provided that $K_a >> K_E$. This is called as *plateau principle*. Only KE determines the time it takes to reach steady-state, and it is unaffected by dose size, dosing interval, or number of doses..

Equations are used to calculate the maximum and minimum drug concentrations in plasma at steady-state.:

$$C_{ss,max} = \frac{C_0}{1 - e^{-K_E \tau}}$$

$$C_{ss,min} = \frac{C_0 e^{-K_E \tau}}{1 - e^{-K_E \tau}} = C_{ss,max}\, e^{-K_E \tau}$$

The ratio C_{max}/C_{min} is used to define fluctuation. The higher the ratio, the more variability. It is determined by the frequency of dosage, the drug's half-life, and the rate of absorption. When the medicine is given as an i.v. bolus, the most variation is seen.

$C_{ss,av}$ is the average drug concentration at steady-state.

$$C_{ss,av} = \frac{FX_0}{Cl_T\, \tau} = \frac{1.44 FX_0 t_{1/2}}{V_d\, \tau} = \frac{AUC\ (single\ dose)}{\tau}$$

where the coefficient 1.44 is the reciprocal of 0.693 (K_E=0.693/$t_{1/2}$). Since X = V_d C, the **body drug content** at steady-state is given as:

$$X_{ss,av} = \frac{1.44 FX_0 t_{1/2}}{\tau}$$

Because the plasma drug concentration drops exponentially, these average values are not the arithmetic mean of Css,max and Css,min.

INFUSION PLUS LOADING DOSE

Until a medicine achieves the desired steady-state, it does not display therapeutic activity. It takes 5 half-lives to get there. Plateau can be attained quickly by giving a dose that produces the desired steady-state soon before starting maintenance doses Xo. A priming dosage or loading dose Xo,L is an initial or first dose intended to be therapeutic. The following is a basic formula for estimating loading dose:

$$X_{0,L} = \frac{C_{ss,av} V_d}{F}$$

For i.v. route:

$$X_{0,L} = C_{ss,av}V_d$$

C_{max} is always lower after e.v. treatment than after i.v. administration, hence the loading dose is proportionally lower. When V_d is unknown, the following equation can be used to compute the loading dose:

$$\frac{X_{0,L}}{X_0} = \frac{1}{(1 - e^{-K_E t})(1 - e^{-K_a t})}$$

The absorption phase is ignored when the medication is delivered intravenously or when absorption is exceptionally rapid, and the above equation reduces to accumulation index:

$$\frac{X_{0,L}}{X_0} = \frac{1}{(1 - e^{-K_E t})} = R_{ac}$$

The dosage ratio is defined as the ratio of the loading dose to the maintenance dose (X0,L/X0). When t12 is equal to 2.0, the dose ratio should be 2.0, but when t12 is larger than 2.0, the dose must be smaller than 2.0.ratio must be smaller than 2.0

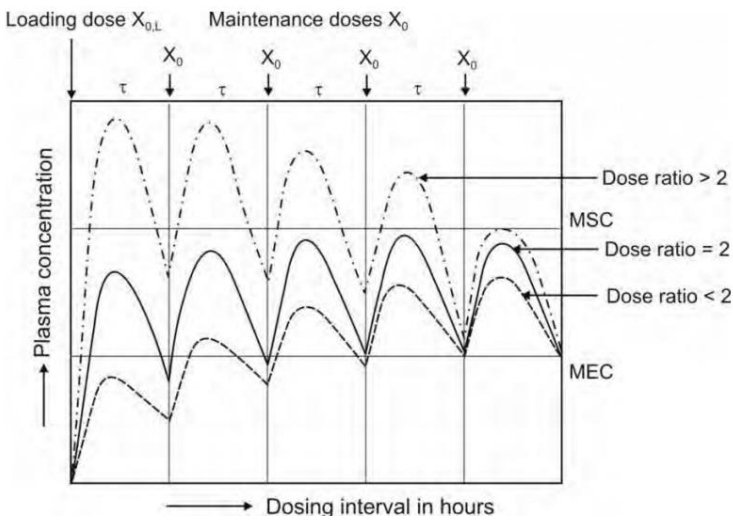

Figure 18.7: Effect of loading dose and maintenance dose

Significance of Loading dose: Loading dosages are a critical component in achieving therapeutic medication concentrations or a quick clinical response.