UNIT

XVI

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

Dr. Gufran Ajmal, Dr. Narender Yadav

Ch.Id:-ASU/NSP/EB/BAP/2022/Ch-16

DOI: https://doi.org/10.52458/9789391842451.nsp2022.eb.asu.ch-16

INTRODUCTION

The simplest model is the one-compartment open model. It is based on the following assumptions due to its simplicity:

1. The human body is viewed as a single, kinetically homogeneous unit with no impediments to drug transport.
2. The drug's equilibrium in plasma and other body fluids (mixing) is achieved instantly and maintained at all times. As a result, this approach only applies to medications that spread quickly throughout the body.
3. Drugs move in (absorption) and out (elimination) of this compartment in a dynamic manner.
4. With a first-order rate constant, elimination is a first-order (mono-exponential) process.
5. Input (absorption) rate > output rate (elimination).
6. Plasma is the anatomical reference compartment, and drug concentrations in plasma are typical of drug concentrations throughout the body.

The term "open" denotes that the drug's input (availability) and output (elimination) are unidirectional and that it can be eliminated from the body.

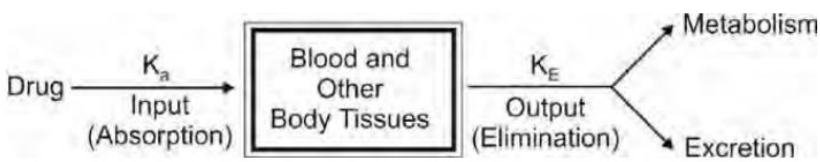

Figure 16.1: Block diagram for a one-compartment open model

Several one-compartment open models can be defined depending on the rate of input:

- One-compartment open model, i.v. bolus administration.
- One-compartment open model, continuous i.v. infusion.

- One-compartment open model, e.v. administration, zero-order absorption.
- One-compartment open model, e.v. administration, first-order absorption.

ONE-COMPARTMENT OPEN MODEL, I.V. BOLUS ADMINISTRATION

Determination of 'Pharmacokinetic Parameters' from Plasma data after Drug administration by Intravenous Bolus

Because it takes around one to three minutes for a drug given as a quick intravenous injection (i.v. bolus) to circulate completely, the rate of absorption is ignored in calculations. The drop in plasma drug concentration is attributed only to drug removal from the body (and not due to distribution). The following is an illustration of the model:

Figure 16.2: Block diagram for one-compartment open model after i.v. bolus drug administration

The rate of change in the amount of drug in the body at any given time is provided by:

$$\frac{dX}{dt} = Rate\ of\ absorption - Rate\ of\ elimination$$

Because the rate of absorption is insignificant and the rate of elimination is governed by first-order kinetics, the equation is as follows:

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

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

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

Integration of equation (1) yields:

$$\ln X = \ln X_0 - K_E t \quad (2)$$

where, Xo = amount of drug at time t = zero i.e. the initial amount of drug injected.

Equation (2) can also be written in the exponential form as:

$$X = X_0 e^{-K_E t} \quad (3)$$

Since ln = 2.303 log, equation (2) can be written as:

$$\log X = \log X_0 - \frac{K_E t}{2.303} \quad (4)$$

Since, a constant relationship exists between drug concentration in plasma i.e. C and X. The equation (4) therefore becomes:

$$\log C = \log C_0 - \frac{K_E t}{2.303} \quad (6)$$

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

A **semilogarithmic plot** of above equation yields a straight line with slope = $-K_E/2.303$ and y-intercept = log Co

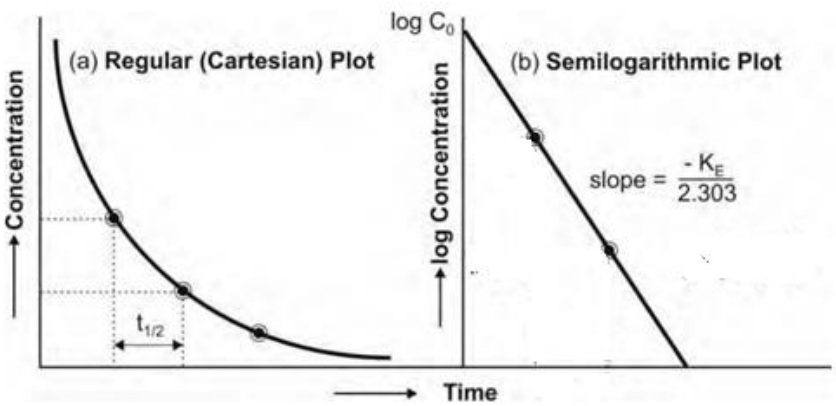

Figure 16.3: Relationship between drug concentration vs time.

- Thus, the intercept and slop of a semi-logarithmic plot can be used to calculate the starting blood concentration (C_0) and elimination rate constant (K_E).
- The following expression can be used to compute the value of the elimination half-life ($t_{1/2}$):

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

- The apparent volume of distribution and clearance are the major characteristics that determine the half-life.
- **Apparent Volume of Distribution (V_d)-** When a drug is administered by i.v. bolus, then V_d is calculated by following equation:

$$V_d = \frac{X_0}{C_0} = \frac{i.v.bolus\ dose}{C_0}$$

- The value of **total body clearance (Cl_T)** is obtained from following expression:

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

ONE-COMPARTMENT OPEN MODEL, INTRAVENOUS INFUSION

Determination of Pharmacokinetic Parameters from Plasma data after Drug administration by Intravenous Infusion

A drug is supplied at a constant pace (zero-order) by i.v. infusion when a quick i.v. injection has the potential to cause toxicity or when maintaining a stable concentration or amount of drug in the body is needed.

The following is a representation of the model:

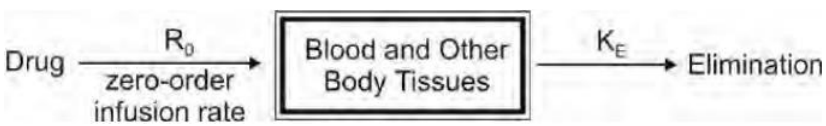

Figure 16.4: Block diagram for one-compartment open model after i.v. infusion drug administration

At any time during infusion, the rate of change in the amount of drug in the body, dX/dt, will be:

$$\frac{dX}{dt} = R_0 - K_E X$$

Integration and rearrangement of above equation yields:

$$X = \frac{R_0}{K_E} = (1 - e^{-K_E t})$$

Since X = V_d C,

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

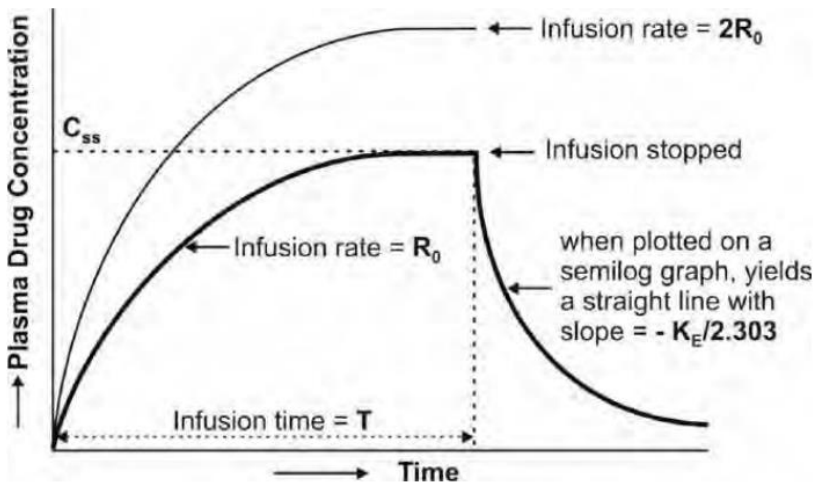

Figure 16.5: Drug plasma profile curve an i.v. infusion dose

At **steady-state**, the **rate of change of amount of drug** in the body is **zero**, hence, equation (1) becomes:

$$Zero = R_0 - K_E X_{ss}$$

$$R_0 = K_E X_{ss}$$

Where, X_{ss} = V_d C_{ss}

$$C_{ss} = \frac{R_0}{K_E V_d} = \frac{R_0}{Cl_T} i.e. \frac{infusion\ rate}{clearance}$$

where, X_{ss} and C_{ss} are amount of drug in the body and concentration of drug in plasma at steady-state respectively.

When the infusion is terminated, the drug plasma concentration in the blood follows the bolus profile injected intravenously. The slope of a straight line created after a semilogarithmic plot (log C against t) of plasma concentration-time data acquired from the time when infusion is stopped can be used to calculate KE. As a result, the rate of elimination can be written as-

$$\frac{dX}{dt} = -K_E X$$

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

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

Integration of above equation yields:

$$\ln X = \ln X_0 - K_E t \qquad (2)$$

where, Xo = amount of drug at time t = zero i.e. the initial amount of drug injected.

Since ln = 2.303 log, equation (2) can be written as:

$$\log X = \log X_0 - \frac{K_E t}{2.303} \qquad (3)$$

Since, a constant relationship exists between drug concentration in plasma i.e. C and X. The equation (3) therefore becomes:

$$\log C = \log C_0 - \frac{K_E t}{2.303} \qquad (4)$$

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

A **semi-logarithmic plot** of above equation yields a straight line with slope = $-K_E/2.303$

- Thus, the **elimination rate constant (K_E)** can be obtained from the slop of semi-logarithmic plot.

- The value of **elimination half-life or biological half-life ($t_{1/2}$)** can be calculated from following expression:

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

- **Apparent volume of distribution** and **total systemic clearance** can be estimated from steady-state concentration and infusion rate

$$C_{ss} = \frac{R_0}{K_E V_d} = \frac{R_0}{Cl_T} i.e. \frac{infusion\ rate}{clearance}$$

- These two parameters (i.e. V_d & Cl_T) can also be computed from the total area under the curve (Fig. 9.3) till the end of infusion:

$$AUC = \frac{R_0 T}{K_E V_d} = \frac{R_0 T}{Cl_T} = C_{ss} T$$

where, T = infusion time

INFUSION PLUS LOADING DOSE IN ONE COMPARTMENT MODEL

It takes a lengthy time for i.v. infusion dose to reach the therapeutic window (e.g. phenobarbital, 5 days). This can be avoided by starting the infusion with an i.v. loading dose big enough to produce the required steady-state soon after injection.

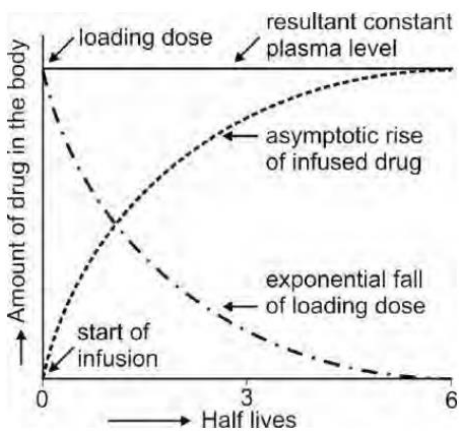

Figure 16.6: Curve showing the drug-plasma concentration after loading dose and infusion dose

The equation for computing the loading dose $X_{0,L}$ can be given:

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

Substitution of $C_{ss} = R_0/K_EV_d$ in above equation yields:

$$X_{0,L} = \frac{R_0}{K_E}$$

The combination of two equations defining each phase describes the plasma concentration-time profile following simultaneous i.v. loading dosage (i.v. bolus) and constant rate i.v. infusion:

$$C = \frac{X_{0,L}}{V_d}e^{-K_Et} + \frac{R_0}{K_EV_d}(1 - e^{-K_Et})$$

Where, $X_{0,L} = C_{ss}\ V_d$ and $R_0 = C_{ss}K_EV_d$

ISBN- 978-93-91842-45-1