One-Compartment Open Model: Intravenous Bolus Administration:

Introduction

The most common and most desirable route of drug administration is orally—by mouth—using tablets, capsules, or oral solutions. In developing pharmacokinetic models to describe and predict drug disposition kinetically, the model must account for both the route of administration and the kinetic behavior of the drug in the body.

The one-compartment open model offers the simplest way to describe the process of drug distribution and elimination in the body. This model assumes that the drug can enter or leave the body (ie, the model is "open"), and the body acts like a single, uniform compartment. The simplest route of drug administration from a modeling perspective is a rapid intravenous injection (IV bolus). The simplest kinetic model that describes drug disposition in the body is to consider that the drug is injected all at once into a box, or compartment, and that the drug distributes instantaneously and homogenously throughout the compartment. Drug elimination also occurs from the compartment immediately after injection.

Of course, this model is a simplistic view of drug disposition in the body, which in reality is infinitely more complex than a single compartment. In the body, when a drug is given in the form of an IV bolus, the entire dose of drug enters the bloodstream immediately, and the drug absorption process is considered to be instantaneous. In most cases, the drug distributes via the circulatory system to potentially all the tissues in the body.

Uptake of drugs by various tissue organs will occur at varying rates, depending on the (blood flow to the tissue, the lipophilicity of the drug, the molecular weight of the drug, and the binding affinity of the drug for the tissue mass).

Most drugs are eliminated from the body either through the kidney and/or by being metabolized in the liver. Because of rapid drug equilibration between the blood and tissue, drug elimination occurs as if the dose is all dissolved in a tank of uniform fluid (a single compartment) from which the drug is eliminated. The volume in which the drug is distributed is termed the apparent volume of distribution, $V_D$. The apparent volume of distribution assumes that the drug is uniformly distributed.
in the body. The $V_D$ is determined from the preinjected amount of the dose in the syringe and the plasma drug concentration resulting immediately after the dose is injected.

The apparent volume of distribution is a parameter of the one-compartment model and governs the plasma concentration of the drug after a given dose. A second pharmacokinetic parameter is the elimination rate constant, $k$, which governs the rate at which the drug concentration in the body declines over time. The one-compartment model that describes the distribution and elimination after an IV bolus dose is given in.

The one-compartment open model does not predict actual drug levels in the tissues. However, the model assumes that changes in the plasma levels of a drug will result in proportional changes in tissue drug levels, since their kinetic profile is consistent with inclusion within the vascular compartment and the various drug concentrations within the compartment are in equilibrium. The drug in the body, $D_B$, cannot be measured directly; however, accessible body fluids (such as blood) can be sampled to determine drug concentrations.

Elimination Rate Constant

The rate of elimination for most drugs from a tissue or from the body is a first-order process, in which the rate of elimination is dependent on the amount or concentration of drug present. The elimination rate constant, $k$, is a first-order elimination rate constant with units of $\text{time}^{-1}$ (eg, $\text{hr}^{-1}$ or 1/hr). Generally, the parent or active drug is measured in the vascular compartment. Total removal or elimination of the parent drug from this compartment is effected by metabolism (biotransformation) and excretion. The elimination rate constant represents the sum of each of these processes:

$$K = K_m + K_e$$

where $k_m =$ first-order rate process of metabolism and $k_e =$ first-order rate process of excretion. There may be several routes of elimination of drug by metabolism or excretion. In such a case, each of these processes has its own first-order rate constant.

A rate expression for is

$$\frac{dD_B}{dt} = -kD_B$$
This expression shows that the rate of elimination of drug in the body is a first-order process, depending on the overall elimination rate constant, \( k \), and the amount of drug in the body, \( D_B \), remaining at any given time, \( t \). Integration of Equation gives the following expression:

\[
\log D_B = \frac{-kt}{2.3} + \log D_B^0
\]

where \( D_B = \) drug in the body at time \( t \) and \( D_B^0 = \) drug in the body at \( t = 0 \). When \( \log D_B \) is plotted against \( t \) for this equation, a straight line is obtained. In practice, instead of transforming values of \( D_B \) to their corresponding logarithms, each value of \( D_B \) is placed at logarithmic intervals on semilog paper.

**Apparent Volume of Distribution**

Each individual tissue in the body may contain a different concentration of drug due to differences in drug affinity for that tissue. Therefore, the amount of drug in a given location can be related to its concentration by a proportionality constant that reflects the volume of fluid the drug is dissolved in. The volume of distribution represents a volume that must be considered in estimating the amount of drug in the body from the concentration of drug found in the sampling compartment. The volume of distribution is also the apparent volume \( (V_D) \) in which the drug is dissolved. Because the value of the volume of distribution does not have a true physiologic meaning in terms of an anatomic space, the term *apparent* volume of distribution is used.

The amount of drug in the body is not determined directly. Instead, a blood sample is removed at periodic intervals and analyzed for its concentration of drug. The \( V_D \)
relates the concentration of drug in plasma ($C_p$) and the amount of drug in the body ($D_B$), as in the following equation:

$$D_B = V_D C_p$$

A similar expression based on drug concentration in plasma is obtained for the first-order decline of drug plasma levels:

$$\log C_p = \frac{-k_t t}{2.3} + \log C_p^0$$

where $C_p = \text{concentration of drug in plasma at time} \ t$ and $C_p^0 = \text{concentration of drug in plasma at} \ t = 0$.

**Calculation of Volume of Distribution**

In a one-compartment model (IV administration), the $V_D$ is calculated with the following equation:

$$V_D = \frac{\text{Dose}}{C_p^0} = \frac{D_B^0}{C_p^0}$$

When $C_p^0$ is determined by extrapolation, it represents the instantaneous drug concentration (concentration of drug at $t = 0$) after drug equilibration in the body. The dose of drug given by IV bolus (rapid IV injection) represents the amount of drug in the body, $D_B^0$, at $t = 0$. Because both $D_B^0$ and $C_p^0$ are known at $t = 0$, then the apparent volume of distribution, $V_D$, may be calculated.
Significance of the Apparent Volume of Distribution

The apparent volume of distribution is not a true physiologic volume. Most drugs have an apparent volume of distribution smaller than, or equal to, the body mass. For some drugs, the volume of distribution may be several times the body mass and for a given dose, a very small $C_p^0$ may occur in the body due to concentration of the drug in peripheral tissues and organs. For this dose, the small $C_p^0$ will result in a large $V_D$.

Drugs with a large apparent $V_D$ are more concentrated in extravascular tissues and less concentrated intravascularly. If a drug is highly bound to plasma proteins or remains in the vascular region, then $C_p^0$ will be higher, resulting in a smaller apparent $V_D$. Consequently, binding of a drug to peripheral tissues or to plasma proteins will significantly affect $V_D$.

The apparent $V_D$ is a volume term that can be expressed as a simple volume or in terms of percent of body weight. In expressing the apparent $V_D$ in terms of percent body weight, a 1-L volume is assumed to be equal to the weight of 1 kg. For example, if the $V_D$ is 3500 mL for a subject weighing 70 kg, the $V_D$ expressed as percent of body weight is

$$\frac{3.5 \, \text{kg}}{70 \, \text{kg}} \times 100 = 5\% \text{ of body weight}$$

If $V_D$ is a very large number—ie, >100% of body weight—then it may be assumed that the drug is concentrated in certain tissue compartments. Thus, the apparent $V_D$ is a useful parameter in considering the relative amounts of drug in the vascular and in the extravascular tissues.

Drug Clearance in the One-Compartment Model

*Clearance* is a measure of drug elimination from the body without identifying the mechanism or process. Drug elimination from the body is an ongoing process due to both metabolism (biotransformation) and drug excretion through the kidney and other routes. The mechanisms of drug elimination are complex, but collectively drug elimination from the body may be quantitated using the concept of drug clearance.

Drug clearance refers to the volume of plasma fluid that is cleared of drug per unit time. Clearance may also be considered as the fraction of drug removed per unit time multiplied by the $V_D$. The rate of drug elimination may be expressed in
several ways, each of which essentially describes the same process, but with different levels of insight and application in pharmacokinetics.

- **Drug Elimination Expressed as Amount Per Time Unit**

The expression of drug elimination from the body in terms of mass per unit time (eg, mg/min, or mg/hr) is simple and absolute. For a zero-order elimination process, expressing the rate of drug elimination as mass per unit time is convenient because the rate is constant. In contrast, the rate of drug elimination for a first-order elimination process is not constant and changes with respect to the drug concentration in the body. For a first-order elimination, drug clearance expressed as volume per unit time (eg, L/hr or mL/min) is convenient because it is a constant.

- **Drug Elimination Expressed as Volume Per Time Unit**

The concept of expressing a rate in terms of volume per unit time is common in pharmacy. For example, a patient may be dosed at the rate of 2 teaspoonsful (10 mL) of a liquid medicine (10 mg/mL) daily, or alternatively, a dose (weight) of 100 mg of the drug daily.

Clearance is a concept that expresses “the rate of drug removal” in terms of volume of drug solution removed per unit time (at whatever drug concentration in the body prevailing at that time). In contrast to a solution in a bottle, the drug concentration in the body will gradually decline by a first-order process such that the mass of drug removed over time is not constant. The plasma volume in the healthy state is relatively constant because water lost through the kidney is rapidly replaced with fluid absorbed from the gastrointestinal tract.

Since a constant volume of plasma (about 120 mL/min in humans) is filtered through the glomeruli of the kidneys, the rate of drug removal is dependent on the plasma drug concentration at all times. This observation is based on a first-order process governing drug elimination. For many drugs, the rate of drug elimination is dependent on the plasma drug concentration, multiplied by a constant factor ($dC/dt = kC$). When the plasma drug concentration is high, the rate of drug removal is high, and vice versa.

Clearance (volume of fluid removed of drug) for a first-order process is constant regardless of the drug concentration because clearance is expressed in volume per unit time rather than drug amount per unit time.
Drug Elimination Expressed as Fraction Eliminated Per Time Unit

Consider a compartment volume, containing $V_D$ liters. If $Cl$ is expressed in liters per minute (L/min), then the fraction of drug cleared per minute in the body is equal to $Cl/V_D$.

Expressing drug elimination as the fraction of total drug eliminated is applicable regardless or whether one is dealing with an amount or a volume. This approach is most flexible and convenient because of its dimensionless nature. Thus, it is valid to express drug elimination as a fraction (eg, one-tenth of the amount of drug in the body is eliminated or one-tenth of the drug volume is eliminated).

Pharmacokineticists have incorporated this concept into the first-order equation (ie, $k$) that describes drug elimination from the one-compartment model. Indeed, the universal nature of many processes forms the basis of the first-order equation of drug elimination (eg, a fraction of the total drug molecules in the body will perfuse the glomeruli, a fraction of the filtered drug molecules will be reabsorbed at the renal tubules, and a fraction of the filtered drug molecules will be excreted from the body giving an overall first-order drug elimination rate constant, $k$).

Example

Consider that 100 mg of drug is dissolved in 10 mL of fluid and 10 mg of drug is removed in the first minute. The drug elimination process could be described as:

a. Number of mg of drug eliminated per minute (mg/min)
b. Number of mL of fluid cleared of drug per minute
c. Fraction of drug eliminated per minute

The relationship of the three drug elimination processes is illustrated in . Note that in , the fraction $Cl/V_D$ is dependent on both the volume of distribution and the rate of drug clearance from the body. This clearance concept forms the basis of classical pharmacokinetics and is later extended to flow models in pharmacokinetic modeling. If the drug concentration is $C_p$, the rate of drug elimination (in terms of rate of change in concentration, $dC_p/dt$) is:

$$\frac{dC_p}{dt} = -(Cl/V_D) \times C_p$$

For a first-order process,

$$\frac{dC_p}{dt} = -kC_p = \text{rate of drug administration}$$

Equating the two expressions yields:
Thus, a first-order rate constant is the fractional constant $\text{Cl}/V_D$.

\[
\kappa C_p = \frac{\text{Cl}}{V_D} \times C_p \\
\kappa = \frac{\text{Cl}}{V_D}
\]