Multicompartment Models: Intravenous Bolus Administration:

Ideally, a model should mimic closely the physiologic processes in the body. In practice, models seldom consider all the rate processes ongoing in the body and are therefore simplified mathematical expressions. The inability to measure all the rate processes in the body, including the lack of access to biological samples from the interior of the body, limits the sophistication of a model. Compartmental models are classical pharmacokinetic models that simulate the kinetic processes of drug absorption, distribution, and elimination with little physiologic detail. In compartmental models, drug tissue concentration is assumed to be uniform within a given hypothetical compartment. However, tissue drug uptake and tissue drug binding from the plasma fluid is kinetically simulated by considering the presence of a tissue compartment. Indeed, most drugs given by IV bolus dose decline rapidly soon after injection, and then decline moderately as some of the drug initially distributes into the tissue moves back into the plasma.

Multicompartment models were developed to explain this observation that, after a rapid IV injection, the plasma level–time curve does not decline linearly as a single, first-order rate process. The plasma level–time curve reflects first-order elimination of the drug from the body only after distribution equilibrium, or plasma drug equilibrium with peripheral tissues occurs. Drug kinetics after distribution is characterized by the first-order rate constant, $b$ ($\beta$ or beta).

Nonlinear plasma level–time curves occur because some drugs distribute at various rates into different tissue groups. Multicompartment models were developed to explain and predict plasma and tissue concentrations for the behavior of these drugs. In contrast, a one-compartment model is used when the drug appears to distribute into tissues instantaneously and uniformly. For both one- and multicompartment models, the drug in the tissues that have the highest blood perfusion equilibrates rapidly with the drug in the plasma. These highly perfused tissues and blood make up the central compartment. While this initial drug distribution is taking place, multicompartment drugs are delivered concurrently to one or more peripheral compartments composed of groups of tissues with lower blood perfusion and different affinity for the drug. A drug will concentrate in a tissue in accordance with the affinity of the drug for that particular tissue. For example, lipid-soluble drugs tend to accumulate in fat tissues. Drugs that bind plasma proteins may be more concentrated in the plasma, because protein-bound drugs do not diffuse easily into the tissues. Drugs may also bind with tissue proteins and other macromolecules, such as DNA and melanin.

Tissue sampling is invasive, and the drug concentration in the tissue sample may not represent the drug concentration in the entire organ. Occasionally, tissue samples may be collected after a drug-overdose episode. For example, the two-compartment model has been used to describe the distribution of colchicine, even though the drug’s toxic tissue levels after fatal overdoses has only been recently described. The drug isotretinoin has a long half-life because of substantial distribution into lipid tissues.

Kinetic analysis of a multicompartment model assumes that all transfer rate processes for the passage of drug into or out of individual compartments are first-order processes. On the basis of
this assumption, the plasma level–time curve for a drug that follows a multicomartment model is best described by the summation of a series of exponential terms, each corresponding to first-order rate processes associated with a given compartment.

The nonlinear profile of plasma drug concentration versus time is the result of many factors interacting together, including (blood flow to the tissues, the permeability of the drug into the tissues, the capacity of the tissues to accumulate drug, and the effect of disease factors on these processes).

Impaired cardiac function may produce a change in blood flow and in the drug distributive phase, whereas impairment of the kidney or the liver may decrease drug elimination as shown by a prolonged elimination half-life and corresponding reduction in the slope of the terminal elimination phase of the curve.

**Two-Compartment Open Model**

Many drugs given in a single intravenous bolus dose demonstrate a plasma level–time curve that does not decline as a single exponential (first-order) process. The plasma level–time curve for a drug that follows a two-compartment model shows that the plasma drug concentration declines biexponentially as the sum of two first-order processes—distribution and elimination.

A drug that follows the pharmacokinetics of a two-compartment model does not equilibrate rapidly throughout the body, as is assumed for a one-compartment model. In this model, the drug distributes into two compartments, the central compartment and the tissue, or peripheral compartment.

- The central compartment represents the blood, extracellular fluid, and highly perfused tissues. The drug distributes rapidly and uniformly in the central compartment.
- A second compartment, known as the tissue or peripheral compartment, contains tissues in which the drug equilibrates more slowly. Drug transfer between the two compartments is assumed to take place by first-order processes.

![Plasma level–time curve for the two-compartment open model (single IV dose) described in (model A).](image)
There are several possible two-compartment models:

- Model A is used most often and describes the plasma level–time curve observed in . By convention, compartment 1 is the central compartment and compartment 2 is the tissue compartment. The rate constants \( k_{12} \) and \( k_{21} \) represent the first-order rate transfer constants for the movement of drug from compartment 1 to compartment 2 (\( k_{12} \)) and from compartment 2 to compartment 1 (\( k_{21} \)). The transfer constants are sometimes termed microconstants, and their values cannot be estimated directly. Most two-compartment models assume that elimination occurs from the central compartment model, as shown in (model A), unless other information about the drug is known. Drug elimination is presumed to occur from the central compartment, because the major sites of drug elimination (renal excretion and hepatic drug metabolism) occur in organs, such as the kidney and liver, which are highly perfused with blood.

The plasma level–time curve for a drug that follows a two-compartment model may be divided into two parts, (a) a distribution phase and (b) an elimination phase.

The two-compartment model assumes that, at \( t = 0 \), no drug is in the tissue compartment. After an IV bolus injection, drug equilibrates rapidly in the central compartment. The distribution phase of the curve represents the initial, more rapid decline of drug from the central compartment into the tissue compartment (line a). Although drug elimination and distribution occur concurrently during the distribution phase, there is a net transfer of drug from the central compartment to the tissue compartment. The fraction of drug in the tissue compartment during the distribution phase increases up to a maximum in a given tissue, whose value may be greater or less than the plasma drug concentration. At maximum tissue concentrations, the rate of drug entry into the tissue equals the rate of drug exit from the tissue. The fraction of drug in the tissue compartment is now in equilibrium (distribution equilibrium) with the fraction of drug in the central compartment, and the drug concentrations in both the central and tissue compartments decline in parallel and more slowly compared to the distribution phase. This decline is a first-order process and is called the elimination phase or the beta phase (line b). Since plasma and tissue concentrations decline in parallel, plasma drug concentrations provide some indication of the concentration of drug in the tissue. At this point, drug kinetics appear to follow a one-
compartment model in which drug elimination is a first-order process described by $b$ (also known as beta).

However, the drug concentration in the tissue compartment represents the average drug concentration in a group of tissues rather than any real anatomic tissue drug concentration. In reality, drug concentrations may vary among different tissues and possibly within an individual tissue. These varying tissue drug concentrations are due to differences in the partitioning of drug into the tissues.

In terms of the pharmacokinetic model, the differences in tissue drug concentration is reflected in the $k_{12}/k_{21}$ ratio. Thus, tissue drug concentration may be higher or lower than the plasma drug concentrations, depending on the properties of the individual tissue. Moreover, the elimination of drug from the tissue compartment may not be the same as the elimination from the central compartment. For example, if $k_{12} \cdot C_p$ is greater than $k_{21} \cdot C_t$ (rate into tissue > rate out of tissue), the tissue drug concentrations will increase and plasma drug concentrations will decrease.

In practice, a blood sample is removed periodically from the central compartment and the plasma is analyzed for the presence of drug. The drug plasma level–time curve represents a phase of initial rapid equilibration with the central compartment (the distribution phase) followed by an elimination phase after the tissue compartment has also been equilibrated with drug. The distribution phase may take minutes or hours and may be missed entirely if the blood is sampled too late or at wide intervals after drug administration.

In the model depicted above, $k_{12}$ and $k_{21}$ are first-order rate constants that govern the rate of drug change in and out of the tissues:

$$\frac{dC_t}{dt} = k_{12}C_p - k_{21}C_t$$

The relationship between the amount of drug in each compartment and the concentration of drug in that compartment:

$$C_{p} = \frac{D_p}{V_p}$$

$$C_{t} = \frac{D_t}{V_t}$$

**Volume of the Central Compartment**

The volume of the central compartment is useful for determining the drug concentration directly after an IV injection into the body. In clinical pharmacy, this volume is also referred to as $V_i$ or the initial volume of distribution as the drug distributes within the plasma and other accessible body fluids. This volume is generally smaller than the terminal volume of distribution after drug distribution to tissue is completed. The volume of the central compartment is generally greater than 3 L, which is the volume of the plasma fluid for an average adult. For many polar drugs, an
initial volume of 7–10 L may be interpreted as rapid drug distribution within the plasma and some extracellular fluids. For example, the $V_p$ of moxalactam ranges from 0.12 to 0.15 L/kg, corresponding to about 8.4 to 10.5 L for a typical 70-kg patient. In contrast, $V_p$ of hydromorphone is about 24 L, possibly because of its rapid exit from the plasma into tissues even during the initial phase.

**Apparent Volume of Distribution at Steady State**

At steady-state conditions, the rate of drug entry into the tissue compartment from the central compartment is equal to the rate of drug exit from the tissue compartment into the central compartment. These rates of drug transfer are described by the following expressions:

\[
D_t k_{21} = D_p k_{12}
\]

\[
D_t = \frac{k_{12} D_p}{k_{21}}
\]

Because the amount of drug in the central compartment, $D_p$, is equal to $V_p C_p$, by substitution in the above equation,

\[
D_t = \frac{k_{12} C_p V_p}{k_{21}}
\]

The total amount of drug in the body at steady state is equal to the sum of the amount of drug in the tissue compartment, $D_t$, and the amount of drug in the central compartment, $D_p$. Therefore, the apparent volume of drug at steady state $(V_D)_{ss}$ may be calculated by dividing the total amount of drug in the body by the concentration of drug in the central compartment at steady state:

\[
(V_D)_{ss} = \frac{D_t + D_p}{C_p}
\]

By substitution, and by expressing $D_p$ as $V_p C_p$, a more useful equation for the calculation of $(V_D)_{ss}$ is obtained:

\[
(V_D)_{ss} = \frac{C_p V_p + k_{12} V_p C_p / k_{21}}{C_p}
\]

which reduces to

\[
(V_D)_{ss} = V_p + \frac{k_{12}}{k_{21}} V_p
\]

The $(V_D)_{ss}$ is a function of the transfer constants, $k_{12}$ and $k_{21}$, which represent the rate constants of drug going into and out of the tissue compartment, respectively. The magnitude of $(V_D)_{ss}$ is
dependent on the hemodynamic factors responsible for drug distribution and on the physical properties of the drug, properties which, in turn, determine the relative amount of intra- and extravascular drug remaining in the body.

**Significance of the Volumes of Distribution**

In a study involving a cardiotonic drug given intravenously to a group of normal and congestive heart failure (CHF) patients, the average AUC for CHF was 40% higher than in the normal subjects. The $b$ elimination constant was 40% less in CHF patients, whereas the average $(V_D)\beta$ remained essentially the same. In spite of the edematous conditions of these patients, the volume of distribution apparently remained constant. Because the dose was the same, the $(V_D)\beta$ would not change unless the increase in AUC is not accompanied by a change in $b$ elimination constant.

The clearance of the drug in CHF patients was reduced by 40% and accompanied by a corresponding decrease in the $b$ elimination constant, possibly due to a reduction in renal blood flow as a result of reduced cardiac output in CHF patients.

In physiologic pharmacokinetics, clearance ($Cl$) and volume of distribution ($V_D$) are assumed to be independent parameters that explain the impact of disease factors on drug disposition. Thus, an increase in AUC of a cardiotonic in a CHF patient was assumed to be due to a reduction in drug clearance, since the volume of distribution was unchanged.

In reality, pharmacokinetic changes in a complex system are dependent on many factors that interact within the system. Clearance is affected by drug uptake, metabolism, binding, and more; all of these factors can also influence the drug distribution volume. Many parameters are assumed to be constant and independent for simplification of the model. Blood flow is an independent parameter that will affect both clearance and distribution. However, blood flow is, in turn, affected and regulated by many physiologic compensatory factors.

**Drug in the Tissue Compartment**

The apparent volume of the tissue compartment ($V_t$) is a conceptual volume only and does not represent true anatomic volumes. The $V_t$ may be calculated from knowledge of the transfer rate constants and $V_p$:

$$V_t = \frac{V_p \cdot k_{12}}{k_{21}}$$

Calculation of the amount of drug in the tissue compartment provides an estimate for drug accumulation in the tissues of the body. This information is vital in estimating chronic toxicity and relating the duration of pharmacologic activity to dose. Tissue compartment drug concentration is an average estimate of the tissue pool and does not mean that all tissues have this concentration. The drug concentration in a tissue biopsy will provide an estimate for drug in that tissue sample. Due to differences in blood flow and drug partitioning into the tissue, and heterogeneity, even a biopsy from the same tissue may have different drug concentrations. Together with $V_p$ and $C_p$, which calculate the amount of drug in the plasma, the compartment model provides mass balance information. Moreover, the pharmacodynamic activity may
correlate better with the tissue drug concentration–time curve. To calculate the amount of drug in the tissue compartment $D_t$, the following expression is used:

$$D_t = \frac{k_{12} D_p^0}{a - b} \left( e^{-bt} - e^{-at} \right)$$

**Drug Clearance**

The definition of clearance of a drug that follows a two-compartment model is similar to that of the one-compartment model. *Clearance* is the volume of plasma that is cleared of drug per unit time. Clearance may be calculated without consideration of the compartment model. Thus, clearance may be viewed as a physiologic concept for drug removal, even though the development of clearance is rooted in classical pharmacokinetics.

**Elimination Rate Constant**

In the two-compartment model (IV administration), the elimination rate constant, $k$, represents the elimination of drug from the central compartment, whereas $b$ represents drug elimination during the beta or elimination phase, when distribution is mostly complete. Because of redistribution of drug out of the tissue compartment, the plasma–drug level curve declines more slowly in the $b$ phase. Hence $b$ is smaller than $k$; thus $k$ is a true elimination constant, whereas $b$ is a hybrid elimination rate constant that is influenced by the rate of transfer of drug in and out of the tissue compartment.

**Three-Compartment Open Model**

The three-compartment model is an extension of the two-compartment model, with an additional deep tissue compartment. A drug that demonstrates the necessity of a three-compartment open model is distributed most rapidly to a highly perfused central compartment, less rapidly to the second or tissue compartment, and very slowly to the third or deep tissue compartment, containing such poorly perfused tissue as bone and fat. The deep tissue compartment may also represent tightly bound drug in the tissues. The three-compartment open model is shown in:

\[
\begin{align*}
\text{Tissue compartment} & \quad k_{21} \quad \text{Central compartment} \quad k_{13} \quad \text{Deep tissue compartment} \\
V_t & \quad k_{12} \quad V_p, C_p, D_p \quad k_{31} \quad V_{ds}, C_{ds}, D_{ds} \\
C(t) & \quad k \\
\end{align*}
\]

solution of the differential equation describing the rates of flow of drug into and out of the central compartment gives the following equation:

$$C_p = Ae^{-at} + Be^{-bt} + Ce^{-ct}$$
where $A$, $B$, and $C$ are the $y$ intercepts of extrapolated lines for the central, tissue, and deep tissue compartments, respectively, and $a$, $b$, and $c$ are first-order rate constants for the central, tissue, and deep tissue compartments, respectively.

Determination of Compartment Models

Models based on compartmental analysis should always use the fewest number of compartments necessary to describe the experimental data adequately.

The observed number of compartments or exponential phases will depend on

1. the route of drug administration,
2. the rate of drug absorption,
3. the total time for blood sampling,
4. the number of samples taken within the collection period, and
5. the assay sensitivity.

If drug distribution is rapid, then, after oral administration, the drug will become distributed during absorption, and the distribution phase will not be observed. For example, theophylline follows the kinetics of a one-compartment model after oral absorption, but after intravenous bolus (given as aminophylline), theophylline follows the kinetics of a two-compartment model. Furthermore, if theophylline is given by a slow intravenous infusion rather than by intravenous bolus, the distribution phase will not be observed. Hydromorphone (Dilaudid), which follows a three-compartment model, also follows a one-compartment model after oral administration, since the first two distribution phases are rapid.
Depending on the sampling intervals, a compartment may be missed because samples may be taken too late after administration of the dose to observe a possible distributive phase. For example, the data plotted in could easily be mistaken for those of a one-compartment model, because the distributive phase has been missed and extrapolation of the data to $C_p^0$ will give a lower value than was actually the case. Slower drug elimination compartments may also be missed if sampling is not performed at later sampling times, when the dose or the assay for the drug cannot measure very low plasma drug concentrations.

The total time for collection of blood samples is usually estimated from the terminal elimination half-life of the drug. However, lower drug concentrations may not be measured if the sensitivity of the assay is not adequate. As the assay for the drug becomes more sensitive in its ability to measure lower drug concentrations, then another compartment with a smaller first-order rate constant may be observed.

In describing compartments, each new compartment requires an additional first-order plot. Compartment models having more than three compartments are rarely of pharmacologic significance. In certain cases, it is possible to "lump" a few compartments together to get a smaller number of compartments, which, together, will describe the data adequately.

An adequate description of several tissue compartments can be difficult. When the addition of a compartment to the model seems necessary, it is important to realize that the drug may be retained or slowly concentrated in a deep tissue compartment.