MULTICOMPARTMENT MODELS: INTRAVENOUS BOLUS ADMINISTRATION:
INTRODUCTION

Compartmental models are classical pharmacokinetic models that simulate the kinetic processes of drug absorption, distribution, and elimination with little physiologic detail. In contrast, the more sophisticated physiologic model. In compartmental models, drug tissue concentration is assumed to be **uniform within a given hypothetical compartment**. **Hence, all muscle mass and connective tissues may be lumped into one hypothetical tissue compartment that equilibrates with drug from the central (or plasma) compartment**. Since no data is collected on the tissue mass, the theoretical tissue concentration is unconstrained and cannot be used to forecast actual tissue drug levels. **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* (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.

Because of these distribution factors, drugs will generally **concentrate unevenly** in the tissues, and different groups of tissues will accumulate the drug at different rates. A summary of the approximate blood flow to major human tissues is presented in table 4.1 . Many different tissues and rate processes are involved in the distribution of any drug. However, limited physiologic significance has been assigned to a few groups of tissues .

TABLE 4.1 Blood Flow to Human Tissues

TISSUE	PERCENT BODY WEIGHT	PERCENT CARDIAC OUTPUT	BLOOD FLOW (mL/100 g tissue per min)
Adrenals	0.02	1	550
Kidneys	0.4	24	450
Thyroid	0.04	2	400
Liver			
Hepatic	2.0	5	20
Portal		20	75
Portal-drained viscera	2.0	20	75
Heart (basal)	0.4	4	70
Brain	2.0	15	55
Skin	7.0	5	5
Muscle (basal)	40.0	15	3
Connective tissue	7.0	1	1
Fat	15.0	2	1

The nonlinear profile of plasma drug concentration versus time is the result of many factors interacting together,
1-including blood flow to the tissues, 2- the permeability of the drug into the tissues, 3- the capacity of the tissues to accumulate drug, 4-and the effect of disease factors on these processes.

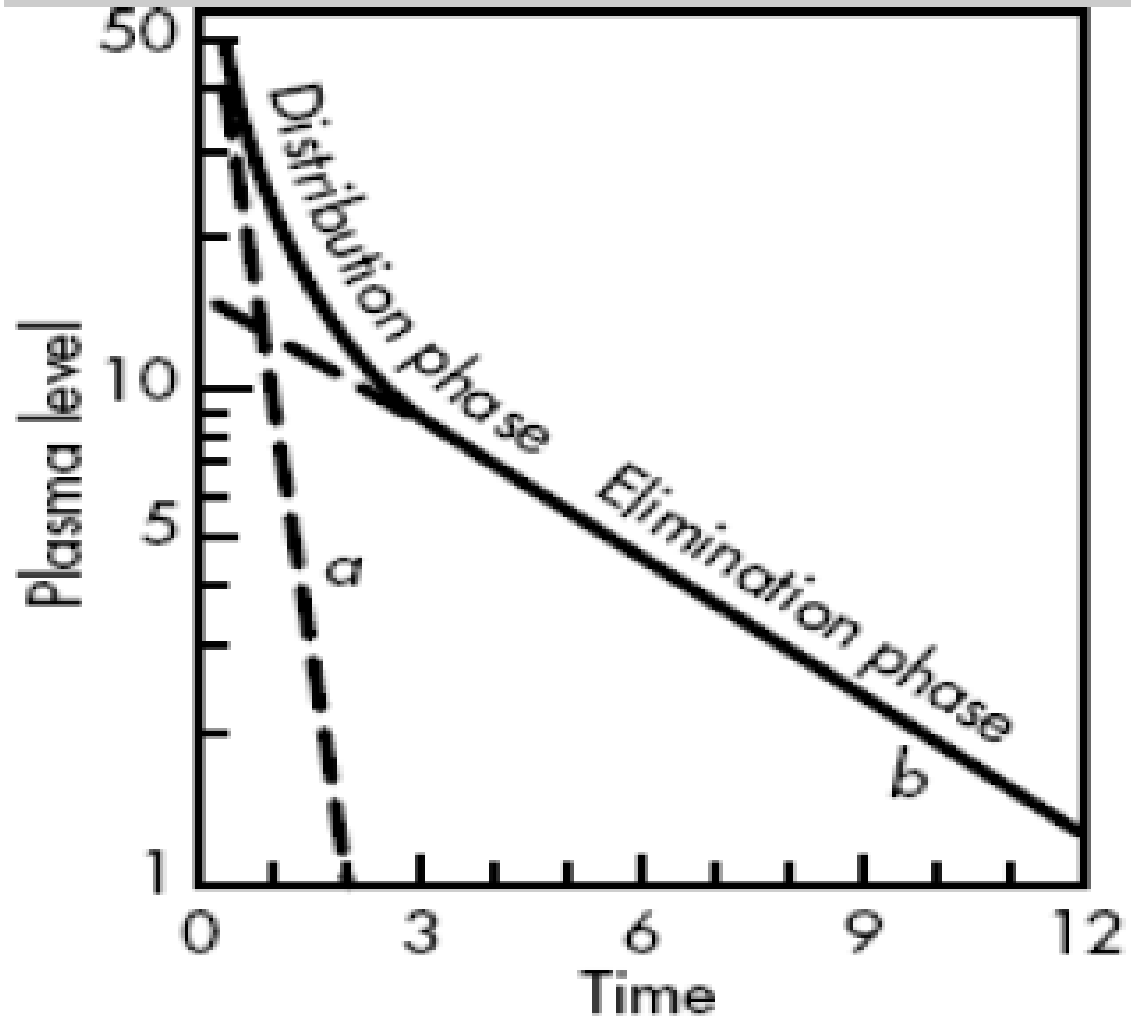
Impaired cardiac function may produce a change in blood flow and in the drug distributive phase, whereas impairment of the kidney or the liver may decrease drug elimination as shown by a prolonged elimination half-life and corresponding reduction in the slope of the terminal elimination phase of the curve. Frequently, multiple factors can complicate the distribution profile in such a way that the profile can only be described clearly with the assistance of a simulation 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.

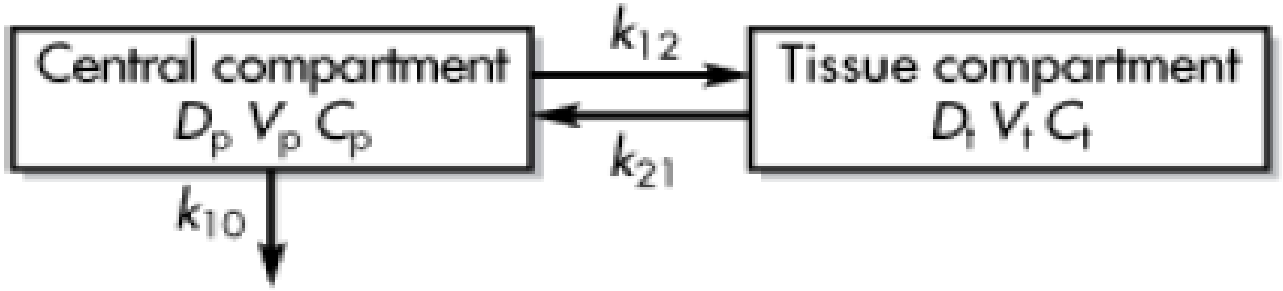

50
10
5
1
Plasma level
Distribution phase
Elimination phase
a
b
0
3
6
9
12
Time

There are several possible two-compartment models. Model A is used most often and describes the plasma level time curve observed . 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).

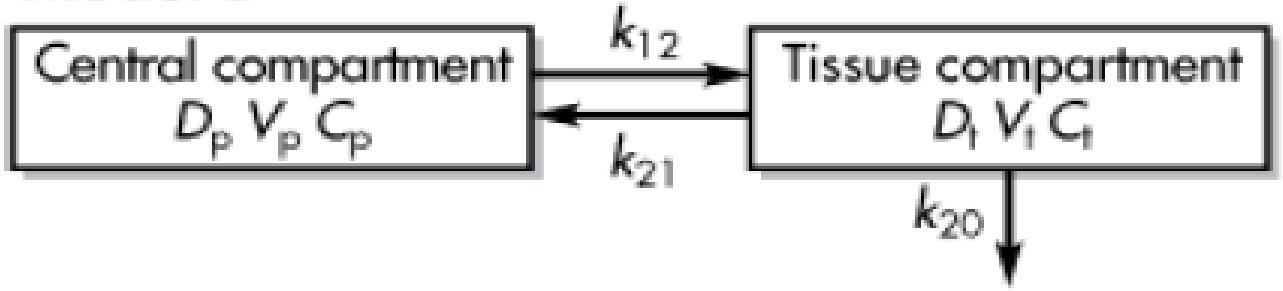
The transfer constants are sometimes termed *microconstants* , and their values cannot be estimated directly.

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.

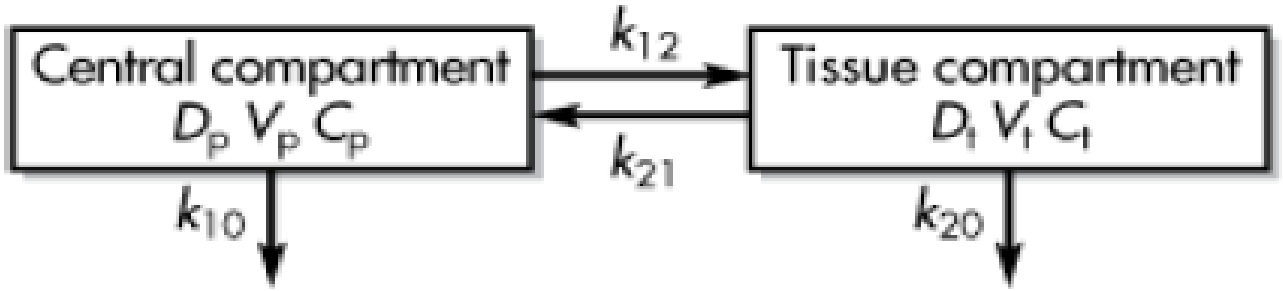
Model A



Model B



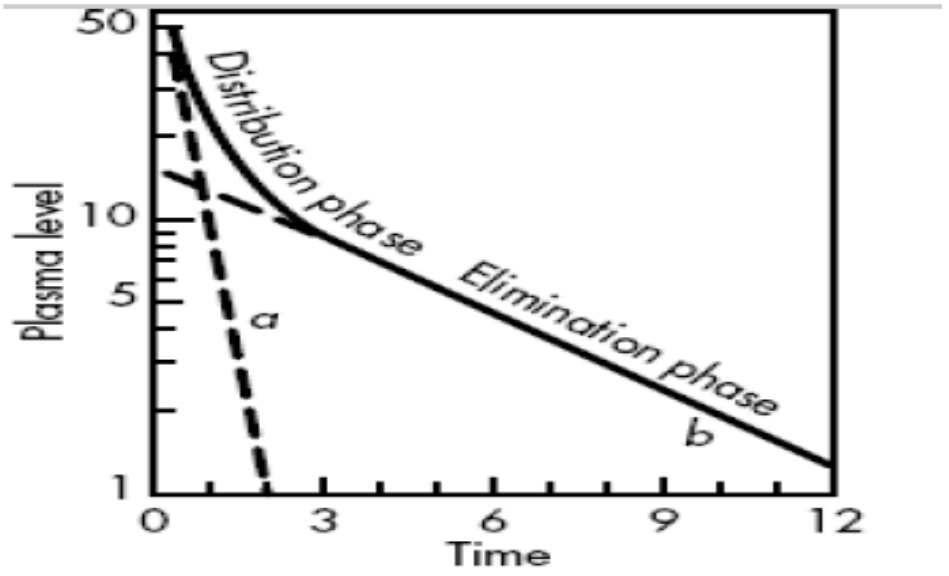
Model C



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.

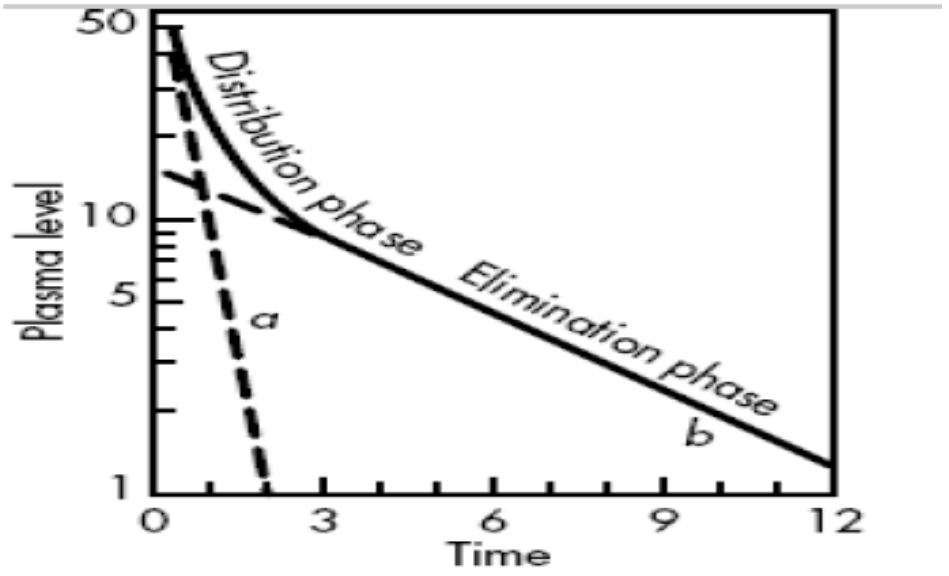
The *distribution phase* of the curve represents the initial, more rapid decline of drug from the central compartment into the tissue compartment (, line *a*). Although drug elimination and distribution occur *concurrently* during the distribution phase, **there is a net transfer of drug from the central 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).



Tissue drug concentrations are theoretical only. The drug level in the theoretical tissue compartment can be calculated once the parameters for the model are determined. **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 *C* p is greater than *k* 21 ·*C* t (rate into tissue > rate out of tissue), the tissue drug concentrations will increase and plasma drug concentrations will decrease.** Real tissue drug concentration can sometimes be calculated by the addition of compartments to the model until a compartment that mimics the experimental tissue concentrations is found.

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:

$$\frac{dC_t}{dt} = k_{12}C_P - k_{21}C_t \qquad (4.1)$$

The relationship between the amount of drug in each compartment and the concentration of drug in that compartment is shown by Equations 4.2 and 4.3:

$$C_P = \frac{D_P}{V_P} \qquad (4.2)$$

$$C_t = \frac{D_t}{V_t} \qquad (4.3)$$

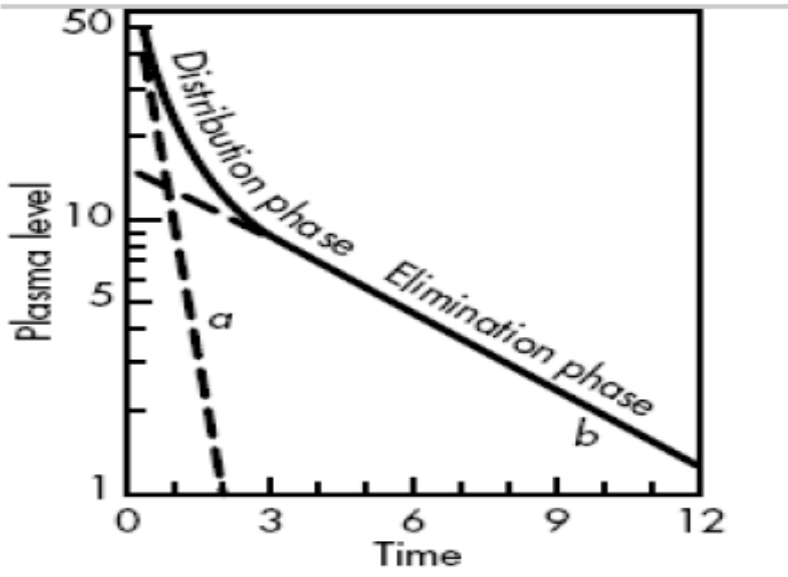
The **constants *a* and *b* are hybrid first-order** rate constants for the distribution phase and elimination phase, respectively. The mathematical relationship of *a* and *b* to the rate constants are given by Equations 4.10 and 4.11, which are derived after integration of Equations 4.4 and 4.5. Equation 4.6 can be transformed into the following expression:

$$C_p = Ae^{-at} + Be^{-bt} \qquad (4.12)$$

The constants *a* and *b* are rate constants for the distribution phase and elimination phase, respectively. The constants *A* and *B* are intercepts on the *y* axis for each exponential segment of the curve in Equation 4.12. These values may be obtained graphically by the method of residuals or by computer**. Intercepts *A* and *B* are actually hybrid constants**, as shown in Equations 4.13 and 4.14, and do not have actual physiologic significance.

$$A = \frac{D_0(a - k_{21})}{V_p(a - b)} \qquad (4.13)$$

$$B = \frac{D_0(k_{21} - b)}{V_p(a - b)} \qquad (4.14)$$

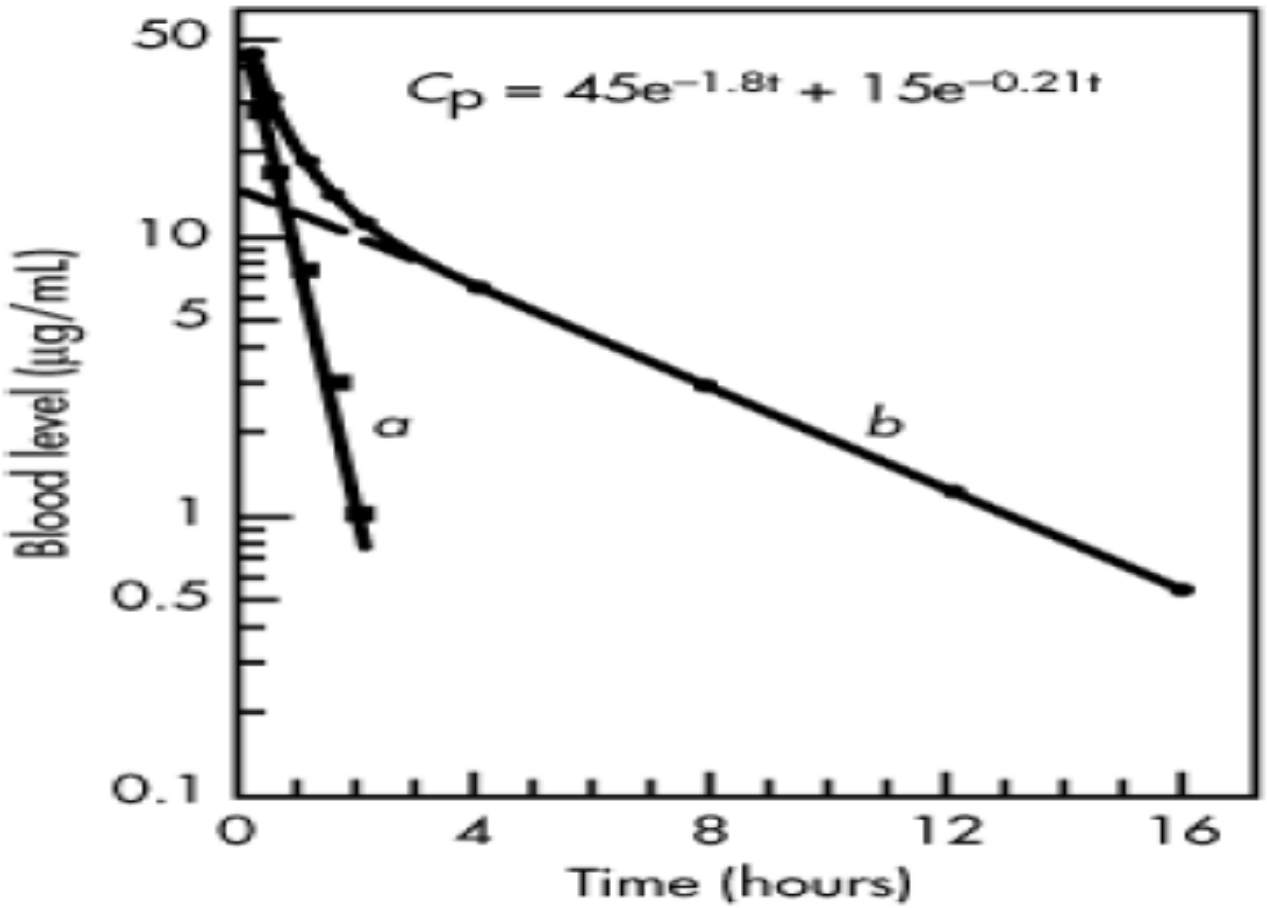


Method of Residuals

The *method of residuals* (also known **as *feathering* or *peeling***) is a useful procedure for fitting a curve to the experimental data of a drug when the drug **does not clearly follow a one-compartment model**. For example, 100 mg of a drug was administered by rapid IV injection to a 70-kg, healthy adult male. Blood samples were taken periodically after the administration of drug, and the plasma fraction of each sample was assayed for drug. The following data were obtained:

Time (hr)	Plasma Concentration (μg/mL)
0.25	43.00
0.5	32.00
1.0	20.00
1.5	14.00
2.0	11.00
4.0	6.50
8.0	2.80
12.0	1.20
16.0	0.52

When these data are plotted on semilogarithmic graph paper, a curved line is observed . **The curved-line relationship between the logarithm of the plasma concentration and time indicates that the drug is distributed in more than one compartment**. From these data a **biexponential** equation, Equation 4.12, may be derived, either by computer or by the method of residuals



Plasma level time curve for a two-compartment open model. The rate constants and intercepts were calculated by the method of residuals

$$C_p = Ae^{-at} + Be^{-bt} \qquad (4.12)$$

As shown in the **biexponential curve** in , the decline in the initial distribution phase is more rapid than the elimination phase. **The rapid distribution phase is confirmed with the constant *a* being larger than the rate constant *b*** . Therefore, at some later time the term Ae^{-at} will approach zero, while Be^{-bt} will still have a value.
At this later time Equation 4.12 will reduce to

$$C_p = Be^{-bt} \qquad (4.15)$$

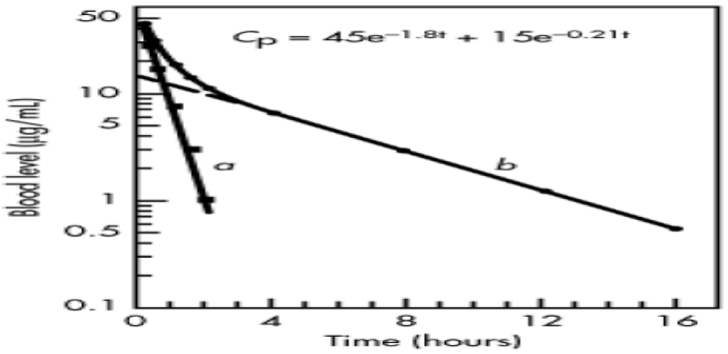
$$C_p = Ae^{-at} + Be^{-bt} \qquad (4.12)$$

which, in common logarithms, is

$$\log C_p = \frac{-bt}{2.3} + \log B \qquad (4.16)$$

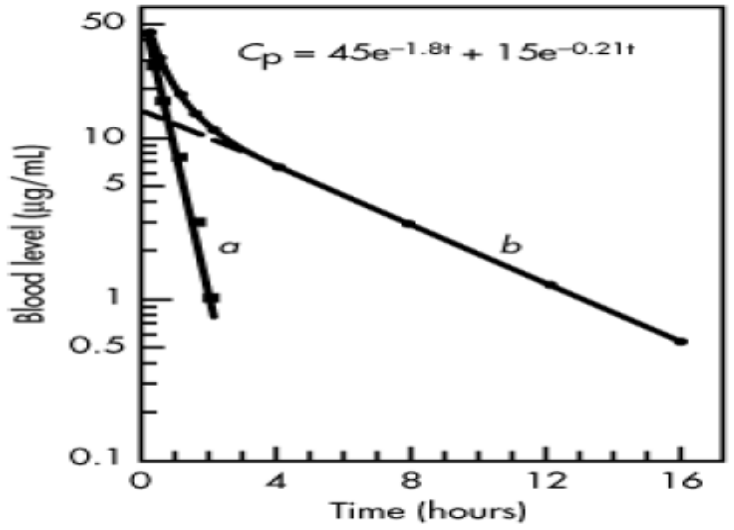
From Equation 4.16, the rate constant can be obtained from the slope (- *b* /2.3) of a straight line representing the terminal exponential phase . The *t* 1/2 for the elimination phase (beta half-life) can be derived from the following relationship:

$$t_{1/2_\beta} = \frac{0.693}{b}$$



In the sample case considered here, *b* was found to be 0.21 hr^{-1} . From this information the regression line for the terminal exponential or *b* phase is extrapolated to the *y* axis; the *y* intercept is equal to *B* , or 15 g/mL.
Values from the extrapolated line are then subtracted from the original experimental data points and a straight line is obtained. This line represents the rapidly distributed *a* phase .

The new line obtained by graphing the logarithm of the residual plasma concentration (*C* p - *C*′ p) against time represents the *a* phase. The value for *a* is 1.8 hr^{-1}, and the *y* intercept is 45 g/mL. The elimination *t* 1/2b is computed from *b* by use of Equation 4.17 and has the value of 3.3 hr.



Apparent Volumes of Distribution

As discussed in , the apparent *V* D is a useful parameter that relates plasma concentration to the amount of drug in the body. For drugs with large extravascular distribution, the apparent volume of distribution is generally large.

Conversely, for **polar drugs** with low lipid solubility, the apparent *V*D is generally small. Drugs with high peripheral tissue binding also contribute to a large apparent *V*D . In **multiple-compartment kinetics**, such as the two compartment model, several volumes of distribution can be calculated.

Volumes of distribution generally reflect the extent of drug distribution in the body on a relative basis, and the calculations depend on the availability of data.

In general, it is important to refer to the same volume parameter when comparing kinetic changes in disease states.

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.

1- As in the case of the one-compartment model, *V* p may be determined from the dose and the instantaneous plasma drug concentration, *C* 0 p .

V p is also useful in the determination of drug clearance if *k* is known.

In the two-compartment model, *V* p may also be considered as **a mass balance** factor governed by the mass balance between **dose and concentration**, ie, **drug concentration multiplied by the volume of the fluid must equal to the dose at time zero**.

2-At time zero, no drug is eliminated, *D* 0 = *V* p *C* p .

The basic model assumption is that Plasma drug concentration is representative of drug concentration within the distribution fluid. If this statement is true, then the volume of distribution will be 3 L; if it is not, then distribution of drug may also occur outside the vascular pool.

$$V_P = \frac{D_0}{C_P^0} \qquad (4.21)$$

At zero time (*t* = 0), all of the drug in the body is in the central compartment. *C* 0p can be shown to be equal to *A*+ *B* by the following equation.

$$C_P = Ae^{-at} + Be^{-bt} \qquad (4.22)$$

At $t = 0$, $e^0 = 1$. Therefore,

$$C_p = Ae^{-at} + Be^{-bt} \qquad (4.22)$$

$$C_p^0 = A + B \qquad (4.23)$$

V p is determined from Equation 4.24 by measuring A and B after feathering the curve, as discussed previously:

$$V_p = \frac{D_0}{A + B} \qquad (4.24)$$

3-Alternatively, the volume of the central compartment may be calculated from the $[AUC]_0^\infty$ in a manner similar to the calculation for the apparent V D in the one-compartment model.

For a one-compartment model,

$$[AUC]_0^\infty = \frac{D_0}{kV_D} \qquad (4.25)$$

Rearrangement of this equation yields

$$V_p = \frac{D_0}{k[AUC]_0^\infty} \qquad (4.27)$$