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MULTICOMPARTMENT MODELS: INTRAVENOUS BOLUS ADMINISTRATION: INTRODUCTION

Pharmacokinetic models may be used to represent drug distribution and elimination in the body. 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 contrast, the more sophisticated physiologic model is discussed in . 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, β).

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 multicompartment 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.

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 . 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 ().

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

Adapted with permission from .

Table 4.2 General Grouping of Tissues According to Blood Supply^a

Blood Supply	Tissue Group	Percent Body Weight
Highly perfused	Heart, brain, hepatic-portal system, kidney, and endocrine glands	9
	Skin and muscle	50
	Adipose (fat) tissue and marrow	19
Slowly perfused	Bone, ligaments, tendons, cartilage, teeth, and hair	22

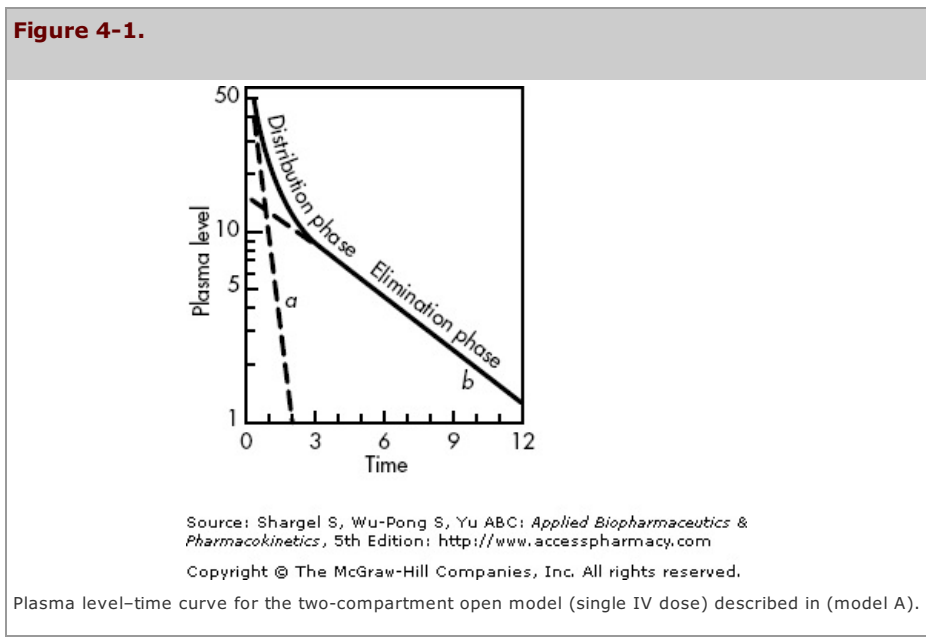
^aTissue uptake will also depend on such factors as fat solubility, degree of ionization, partitioning, and protein binding of the drug.

Adapted from .

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 (see). 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.

TWO-COMPARTMENT OPEN MODEL

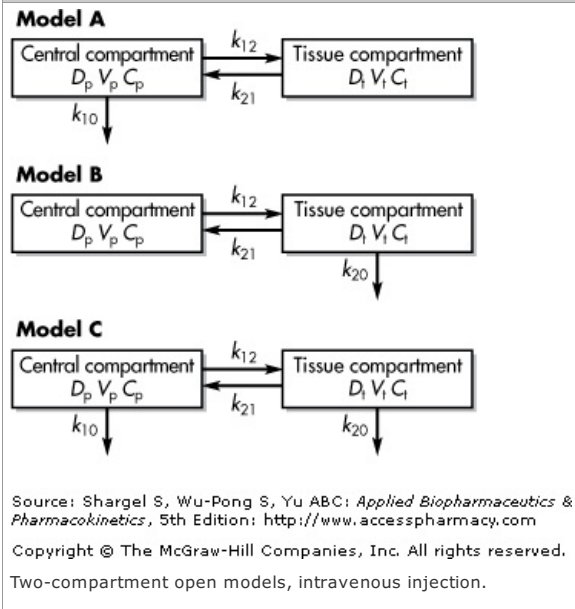
Many drugs given in a single intravenous bolus dose demonstrate a plasma level–time curve that does not decline as a single exponential (first-order) process. The plasma level–time curve for a drug that follows a two-compartment model () shows that the plasma drug concentration declines *biexponentially*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



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

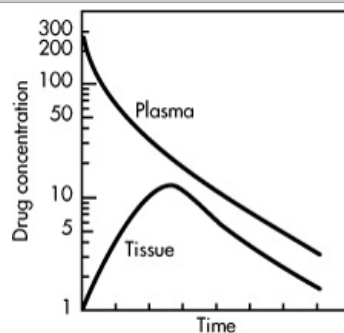
compartment 2 (k_{12}) and from compartment 2 to compartment 1 (k_{21}). The transfer constants are sometimes termed *microconstants*, and their values cannot be estimated directly. Most two-compartment models assume that elimination occurs from the central compartment model, as shown in (model A), unless 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.

Figure 4-2.



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* (β) 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). A typical tissue drug level curve after a single intravenous dose is shown in .

Figure 4-3.



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Relationship between tissue and plasma drug concentrations for a two-compartment open model. The maximum tissue drug concentration may be greater or less than the plasma drug concentration.

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, as discussed in . 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. 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 spite of the hypothetical nature of the tissue compartment, the theoretical tissue level is still valuable information for clinicians. The theoretical tissue concentration, together with the blood concentration, gives an accurate method of calculating the total amount of drug remaining in the body at any time (see digoxin example later,). This information would not be available without pharmacokinetic models.

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:

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

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:

$$C_p = \frac{D_p}{V_p} \quad (4.2)$$

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

where D_p = amount of drug in the central compartment, D_t = amount of drug in the tissue compartment, V_p = volume of drug in the central compartment, and V_t = volume of drug in the tissue compartment.

$$\frac{dC_p}{dt} = k_{21} \frac{D_t}{V_t} - k_{12} \frac{D_p}{V_p} - k \frac{D_p}{V_p} \quad (4.4)$$

$$\frac{dC_t}{dt} = k_{12} \frac{D_p}{V_p} - k_{21} \frac{D_t}{V_t} \quad (4.5)$$

Solving Equations 4.4 and 4.5 will give Equations 4.6 and 4.7, which describe the change in drug concentration in the blood and in the tissue with respect to time:

$$C_p = \frac{D_p^0}{V_p} \left(\frac{k_{21} - a}{b - a} e^{-at} + \frac{k_{21} - b}{a - b} e^{-bt} \right) \quad (4.6)$$

$$C_t = \frac{D_p^0}{V_t} \left(\frac{k_{12}}{b - a} e^{-at} + \frac{k_{12}}{a - b} e^{-bt} \right) \quad (4.7)$$

$$D_p = D_p^0 \left(\frac{k_{21} - a}{b - a} e^{-at} + \frac{k_{21} - b}{a - b} e^{-bt} \right) \quad (4.8)$$

$$D_t = D_p^0 \left(\frac{k_{12}}{b - a} e^{-at} + \frac{k_{12}}{a - b} e^{-bt} \right) \quad (4.9)$$

where D_p^0 = dose given intravenously, t = time after administration of dose, and a and b are constants that depend solely on k_{12} , k_{21} , and k . The amount of drug remaining in the plasma and tissue compartment at any time may be described realistically by Equations 4.8 and 4.9.

The rate constants for the transfer of drug between compartments are referred to as *microconstants* or *transfer constants*, and relate the amount of drug being transferred per unit time from one compartment to the other. The values for these microconstants cannot be determined by direct measurement but can be estimated by a graphic method.

$$a + b = k_{12} + k_{21} + k \quad (4.10)$$

$$ab = k_{21}k \quad (4.11)$$

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:

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

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.

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

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

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 ($\mu\text{g/mL}$)
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

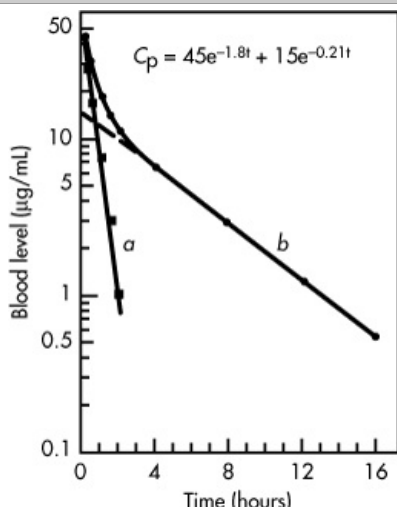
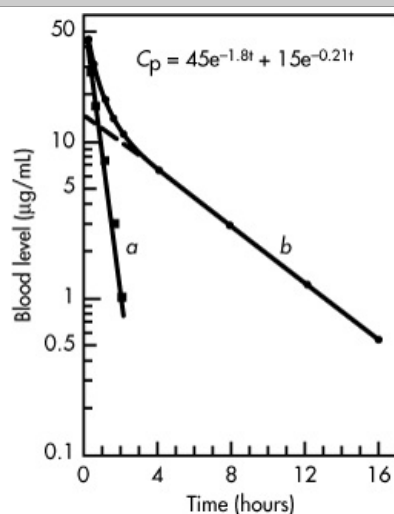
When these data are plotted on semilogarithmic graph paper, a curved line is observed (). The curved-line relationship between the logarithm of the plasma concentration and time indicates that the drug is distributed in more than one compartment. From these data a biexponential equation, Equation 4.12,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

Figure 4-4.



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

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

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

which, in common logarithms, is

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

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:

$$t_{1/2} = \frac{0.693}{b} \quad (4.17)$$

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 $15 \mu\text{g/mL}$. 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 ().

Table 4.3 Application of the Method of Residuals			
TIME (hr)	C_p Observed Plasma Level	C'_p Extrapolated Plasma Concentration	$C_p - C'_p$ Residual Plasma Concentration
0.25	43.0	14.5	28.5
0.5	32.0	13.5	18.5
1.0	20.0	12.3	7.7
1.5	14.0	11.0	3.0
2.0	11.0	10.0	1.0
4.0	6.5		
8.0	2.8		
12.0	1.2		
16.0	0.52		

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 $45 \mu\text{g/mL}$. The elimination $t_{1/2b}$ is computed from b by use of Equation 4.17 and has the value of 3.3 hr.

A number of pharmacokinetic parameters may be derived by proper substitution of rate constants a and b and y intercepts A and B into the following equations:

$$k = \frac{ab(A + B)}{Ab + Ba} \quad (4.18)$$

$$k_{12} = \frac{AB(b - a)^2}{(A + B)(Ab + Ba)} \quad (4.19)$$

$$k_{21} = \frac{Ab + Ba}{A + B} \quad (4.20)$$

Simulation of Plasma and Tissue Level of a Two-Compartment Model Drug—Digoxin in a Normal Patient and in a Renal-Failure Patient

Once the pharmacokinetic parameters are determined for an individual, the amount of drug remaining in the plasma and tissue compartment may be calculated using Equations 4.8 and 4.9. The pharmacokinetic data for digoxin was calculated in a normal and in a renal-impaired, 70-kg subject using the parameters in as reported in the literature. The amount of digoxin remaining in the plasma and tissue compartment are tabulated in and plotted in . It can be seen that digoxin stored in the plasma declines rapidly during the initial distributive phase, while drug amount in the tissue compartment take 3–4 hours ($5t_{1/2} = 5 \times 35 \text{ min}$) to accumulate. It is interesting that clinicians have recommended that digoxin plasma samples be taken at least several hours after IV bolus dosing (), since the equilibrated level is more representative of myocardium digoxin level. In the simulation below, the amount of the drug in the plasma compartment at any time divided by V_p (54.6 L for the normal subject) will yield the plasma digoxin level. At 4 hours after an IV dose of 0.25 mg, $C_p = D_p/V_p = 24.43 \mu\text{g}/54.6 \text{ L} = 0.45 \text{ ng/mL}$, corresponding to $3 \times 0.45 \text{ ng/mL} = 1.35 \text{ ng/mL}$ if a full loading dose of 0.75 mg is given in a single dose. Although the initial plasma drug levels were much

higher than after equilibration, the digoxin plasma concentrations are generally regarded as not toxic, since drug distribution is occurring rapidly. The tissue drug levels were not calculated. The tissue drug concentration represents the hypothetical tissue pool, which may not represent actual drug concentrations in the myocardium. In contrast, the amount of drug remaining in the tissue pool is real, since the amount of drug is calculated using mass balance. The rate of drug entry into the tissue in micrograms per hour at any time is $k_{12}D_p$, while the rate of drug leaving the tissue is $k_{21}D_t$ in the same units. Both of these rates may be calculated from using k_{12} and k_{21} values listed in .

Table 4.4 Two-Compartment Model Pharmacokinetic Parameters of Digoxin

Parameter	Unit	Normal	Renal Impaired
k_{12}	hr ⁻¹	1.02	0.45
k_{21}	hr ⁻¹	0.15	0.11
k	hr ⁻¹	0.18	0.04
V_p	L/kg	0.78	0.73
D	μg/kg	3.6	3.6
a	1/hr	1.331	0.593
b	1/hr	0.019	0.007

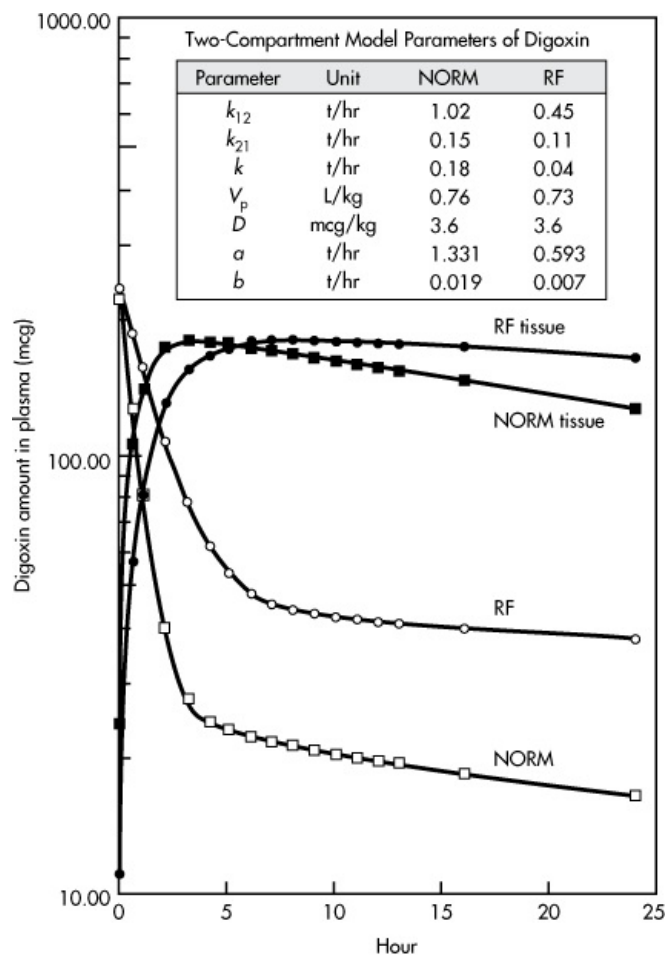
Table 4.5 Amount of Digoxin in Plasma and Tissue Compartment after an IV Dose of 0.252 mg in a Normal and a Renal-Failure Patient Weighing 70 kg^a

Digoxin Amount				
Time (hr)	Normal Renal Function		Renal Failure (RF)	
	D_p (μg)	D_t (μg)	D_p (μg)	D_t (μg)
0.00	252.00	0.00	252.00	0.00
0.10	223.68	24.04	240.01	11.01
0.60	126.94	105.54	189.63	57.12
1.00	84.62	140.46	158.78	85.22
2.00	40.06	174.93	107.12	131.72
3.00	27.95	181.45	78.44	156.83
4.00	24.43	180.62	62.45	170.12
5.00	23.17	177.91	53.48	176.88
6.00	22.53	174.74	48.39	180.04
7.00	22.05	171.50	45.45	181.21
8.00	21.62	168.28	43.69	181.29
9.00	21.21	165.12	42.59	180.77
10.00	20.81	162.01	41.85	179.92
11.00	20.42	158.96	41.32	178.89
12.00	20.03	155.97	40.89	177.77
13.00	19.65	153.04	40.53	176.60
16.00	18.57	144.56	39.62	173.00
24.00	15.95	124.17	37.44	163.59

^a D_p , drug in plasma compartment; D_t , drug in tissue compartment.

Source: Data generated from parameters published by .

Figure 4-5.



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Amount of digoxin (simulated) in plasma and tissue compartment after an IV dose to a normal and a renal-failure (RF) patient.

Although some clinicians assume that tissue and plasma concentrations are equal when at full equilibration, tissue and plasma drug ratios are determined by the partition coefficient (a drug-specific physical ratio that measures the lipid/water affinity of a drug) and the extent of protein binding of the drug. The graph shows that the time for the RF (renal failure or renal impaired) patient to reach stable tissue drug levels is longer than the time for the normal subject due to changes in the elimination and transfer rate constants. As expected, a significantly higher amount of digoxin remains in both the plasma and tissue compartment in the renally impaired subject compared to the normal subject.

PRACTICE PROBLEM

From the graph, how many hours does it take for maximum tissue concentration to be reached in the normal and the renal-impaired patient?

Solution

At maximum tissue concentration, the rate of drug entering the tissue compartment is equal to the rate leaving (ie, at the peak of the tissue curve, where the slope = 0 or not changing). This occurs at about 3–4 hours for the normal patient and at 7–8 hours for the renal-impaired patient. This may be verified by examining at what time $D_p k_{12} = D_t k_{21}$ using the data from the graph. Before maximum C_t is reached, there is a net flux of drug into the tissue, ie, $D_p k_{12} > D_t k_{21}$, and beyond this point, there is a net flux of drug out the tissue compartment, ie, $D_t k_{21} > D_p k_{12}$.

Apparent Volumes of Distribution

As discussed in the text, 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. Unfortunately, values of apparent volumes of distribution of drugs from tables in the clinical literature are often listed without specifying the underlying kinetic processes, model parameter, or method of calculation.

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.

Table 4.6 Pharmacokinetic Parameters (Mean \pm SD) of Moxalactam in Three Groups of Patients

Group	A $\mu\text{g/mL}$	B $\mu\text{g/mL}$	a hr^{-1}	b hr^{-1}	k hr^{-1}
1	138.9 \pm 114.9	157.8 \pm 87.1	6.8 \pm 4.5	0.20 \pm 0.12	0.38 \pm 0.26
2	115.4 \pm 65.9	115.0 \pm 40.8	5.3 \pm 3.5	0.27 \pm 0.08	0.50 \pm 0.17
3	102.9 \pm 39.4	89.0 \pm 36.7	5.6 \pm 3.8	0.37 \pm 0.09	0.71 \pm 0.16
Group	Cl mL/min	V_p L/kg	V_t L/kg	$(V_D)_{ss}$ L/kg	$(V_D)_\beta$ L/kg
1	40.5 \pm 14.5	0.12 \pm 0.05	0.08 \pm 0.04	0.20 \pm 0.09	0.21 \pm 0.09
2	73.7 \pm 13.1	0.14 \pm 0.06	0.09 \pm 0.04	0.23 \pm 0.10	0.24 \pm 0.12
3	125.9 \pm 28.0	0.15 \pm 0.05	0.10 \pm 0.05	0.25 \pm 0.08	0.29 \pm 0.09

As in the case of the one-compartment model, V_p may be determined from the dose and the instantaneous plasma–drug concentration, C_p^0 . V_p is also useful in the determination of drug clearance if k is known, as in .

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. At time zero, no drug is eliminated, $D_0 = V_p C_p^0$. 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.

$$V_p = \frac{D_0}{C_p^0} \quad (4.21)$$

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

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

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

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

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

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

Alternatively, the volume of the central compartment may be calculated from the $[\text{AUC}]_0^\infty$ in a manner similar to the calculation for the apparent V_D in the one-compartment model. For a one-compartment model,

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

In contrast, $[\text{AUC}]_0^\infty$ for the two-compartment model is

$$[\text{AUC}]_0^\infty = \frac{D_0}{kV_p} \quad (4.26)$$

Rearrangement of this equation yields

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

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:

$$D_t k_{21} = D_p k_{12} \quad (4.28)$$

$$D_t = \frac{k_{12} D_p}{k_{21}} \quad (4.29)$$

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

$$D_t = \frac{k_{12} C_p V_p}{k_{21}} \quad (4.30)$$

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:

$$(V_D)_{ss} = \frac{D_p + D_t}{C_p} \quad (4.31)$$

By substitution of Equation 4.30 into Equation 4.31, and by expressing D_p as $V_p C_p$, a more useful equation for the calculation of $(V_D)_{ss}$ is obtained:

$$(V_D)_{ss} = \frac{C_p V_p + k_{12} V_p C_p / k_{21}}{C_p} \quad (4.32)$$

which reduces to

$$(V_D)_{ss} = V_p + \frac{k_{12}}{k_{21}} V_p \quad (4.33)$$

In practice, Equation 4.33 is used to calculate $(V_D)_{ss}$. 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.

EXTRAPOLATED VOLUME OF DISTRIBUTION

The extrapolated volume of distribution $(V_D)_{exp}$ is calculated by the following equation:

$$(V_D)_{exp} = \frac{D_0}{B} \quad (4.34)$$

where B is the y intercept obtained by extrapolation of the b phase of the plasma level curve to the y axis (\cdot). Because the y intercept is a hybrid constant, as shown by Equation 4.14, $(V_D)_{exp}$ may also be calculated by the following expression:

$$(V_D)_{exp} = V_p \left(\frac{a - b}{k_{21} - b} \right) \quad (4.35)$$

This equation shows that a change in the distribution of a drug, which is observed by a change in the value for V_p , will be reflected in a change in $(V_D)_{exp}$.

VOLUME OF DISTRIBUTION BY AREA

The volume of distribution by area $(V_D)_{area}$, also known as $(V_D)_\beta$, is obtained through calculations similar to those used to find V_p , except that the rate constant b is used instead of the overall elimination rate constant k . $(V_D)_\beta$ is often calculated from total body clearance divided by b and is influenced by drug elimination in the beta, or b phase. Reduced drug clearance from the body may increase AUC, such that $(V_D)_\beta$ is either reduced or unchanged depending on the value of b , as shown by Equation 4.35.

$$(V_D)_\beta = (V_D)_{area} = \frac{D_0}{b[\text{AUC}]_0^\infty} \quad (4.36)$$

Generally, reduced drug clearance is accompanied by a decrease in the constant b (ie, an increase in the b elimination half-life).

For example, in patients with renal dysfunction, the elimination half-life of the antibiotic amoxicillin is longer because renal clearance is reduced.

Because total body clearance is equal to $D_0/[AUC]^\infty_0$, $(V_D)\beta$ may be expressed in terms of clearance and the rate constant b :

$$(V_D)\beta = \frac{\text{clearance}}{b} \quad (4.37)$$

By substitution of kV_p for clearance in Equation 4.37, one obtains:

$$(V_D)\beta = \frac{kV_p}{b} \quad (4.38)$$

Theoretically, the value for b may remain unchanged in patients showing various degrees of moderate renal impairment. In this case, a reduction in $(V_D)\beta$ may account for all the decrease in Cl , while b is unchanged in Equation 4.38. Within the body, a redistribution of drug between the plasma and the tissue will mask the expected decline in b . The following example in two patients shows that the b elimination rate constant remains the same, while the distributional rate constants change. Interestingly, V_p is unchanged, while $(V_D)\beta$ would be greatly changed in the simulated example. An example of a drug showing constant b slope while the renal function as measured by Cl_{cr} decreases from 107 to 56, 34, and 6 mL/min () has been observed with the aminoglycoside drug gentamicin in various patients after IV bolus dose (). Gentamicin follows polyexponential decline with a significant distributive phase. The following simulation problem may help to clarify the situation by changing k and clearance while keeping b constant.

PRACTICE PROBLEM

Simulated plasma drug concentration after an IV bolus dose (100 mg) of an antibiotic in two patients, Patient 1 with a normal k , and Patient 2 with a reduced k , is shown in . The data in the two patients were simulated with parameters using the two-compartment model equation. The parameters used are as follows:

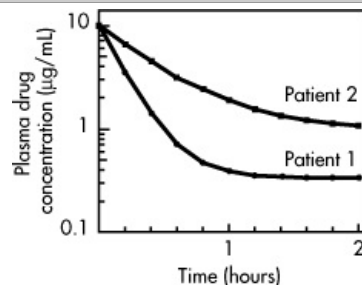
Normal subject, $k = 0.3 \text{ hr}^{-1}$, $V_p = 10 \text{ L}$, $Cl = 3 \text{ L/hr}$

$k_{12} = 5 \text{ hr}^{-1}$, $k_{21} = 0.2 \text{ hr}^{-1}$

Subject with moderate renal impairment, $k = 0.1 \text{ hr}^{-1}$, $V_p = 10 \text{ L}$, $Cl = 1 \text{ L/hr}$

$k_{12} = 2 \text{ hr}^{-1}$, $k_{21} = 0.25 \text{ hr}^{-1}$

Figure 4-6.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: <http://www.accesspharmacy.com>
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Simulation of plasma drug concentration after an IV bolus dose (100 mg) of an antibiotic in two patients, one with a normal k (patient 1) and the other, reduced k (patient 2).

Questions

1. Is a reduction in drug clearance generally accompanied by increase in plasma drug concentration, regardless of which compartment model the drug follows?
2. Is a reduction in drug clearance generally accompanied by an increase in the b elimination half-life of a drug? [Find $(V_D)\beta$ using Eq. 4.37, then b using Eq. 4.38.]
3. Many antibiotics follow multiexponential plasma drug concentration profiles showing drug distribution into tissue compartments. In clinical pharmacokinetics, the terminal half-life is often determined with limited early data. Which patient has a greater terminal half-life based on the simulated data?

Solution

1. A reduction in drug clearance results in less drug being removed from the body per unit time. Drug clearance is model independent. Therefore, the plasma drug concentration should be higher in subjects with decreased drug clearance compared to subjects with normal drug clearance, regardless of which compartment model is used (see).

2. Clearance in the two-compartment model is affected by the elimination rate constant, b , and the volume of distribution in the b phase, which reflects the data. A decrease in the $(V_D)\beta$ with b unchanged is possible, although this is not the common case. When this happens, the terminal data (see) concludes that the beta elimination half-life of patients 1 and 2 are the same due to a similar b . Actually, the real elimination half-life of the drug derived from k is a much better parameter, since k reflects the changes in renal function, but not b , which remains unchanged since it is masked by the changes in $(V_D)\beta$.

3. Both patients have the same b value ($b = 0.011 \text{ hr}^{-1}$); the terminal slopes are identical. Ignoring early points by only taking terminal data would lead to an erroneous conclusion that the renal elimination process is unchanged, while the volume of distribution of the renally impaired patient is smaller. In this case, the renally impaired patient has a clearance of 1 L/hr compared with 3 L/hr for the normal subject, and yet the terminal slopes are the same. The rapid distribution of drug into the tissue in the normal subject causes a longer and steeper distribution phase. Later, redistribution of drug out of tissues masks the effect of rapid drug elimination through the kidney. In the renally impaired patient, distribution to tissue is reduced; as a result, little drug is redistributed out from the tissue in the b phase. Hence, it appears that the beta phases are identical in the two patients.

Significance of the Volumes of Distribution

From Equations 4.31 and 4.32 we can observe that $(V_D)\beta$ is affected by changes in the overall elimination rate (ie, change in k) and by change in total body clearance of the drug. After the drug is distributed, the total amount of drug in the body during the elimination of b phase is calculated by using $(V_D)\beta$.

V_p is sometimes called the initial volume of distribution and is useful in the calculation of drug clearance. The magnitudes of the various apparent volumes of distribution have the following relationships to each other:

$$(V_D)_{\text{exp}} > (V_D)\beta > V_p$$

Calculation of another V_D , $(V_D)_{\text{ss}}$, is possible in multiple dosing or infusion (see and). $(V_D)_{\text{ss}}$ is much larger than V_p ; it approximates $(V_D)\beta$ but differs somewhat in value, depending on the transfer constants.

In a study involving a cardiotoxic 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. No change was found in the V_p or $(V_D)\beta$. In this study, a 40% increase in AUC in the CHF subjects was offset by a 40% smaller b elimination constant estimated by using computer methods. 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.

From Equation 4.31, 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 cardiotoxic in a CHF patient was assumed to be due to a reduction in drug clearance, since the volume of distribution was unchanged. The elimination half-life was reduced due to reduction in drug clearance. 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.

For drugs that follow two-compartment model kinetics, changes in disease states may not result in different pharmacokinetic parameters. Conversely, changes in pharmacokinetic parameters should not be attributed to physiologic changes without careful consideration of method of curve fitting and intersubject differences. Equation 4.38 shows that, unlike a simple one-compartment open model, $(V_D)\beta$ may be estimated from k , b , and V_p . Errors in fitting are easily carried over to the other parameter estimates even if the calculations are performed by computer. The terms k_{12} and k_{21} often fluctuate due to minor fitting and experimental difference and may affect calculation of other parameters.

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 :

$$V_t = \frac{V_p k_{12}}{k_{21}} \quad (4.39)$$

The calculation of the amount of drug in the tissue compartment does not entail the use of V_t . 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:

$$D_t = \frac{k_{12} D_p^0}{a - b} (e^{-kt} - e^{-at}) \quad (4.40)$$

Practical Focus

The therapeutic plasma concentration of digoxin is between 1 and 2 ng/mL; because digoxin has a long elimination half-life, digoxin takes a long time to reach a stable, constant (steady-state) level in the body. A loading dose is usually given with the initiation of digoxin therapy. Consider the implications of the loading dose of 1 mg suggested for a 70-kg subject. The clinical source cited an apparent volume of distribution of 7.3 L/kg for digoxin in determining the loading dose of digoxin. Use the pharmacokinetic parameters for digoxin in .

Solution

The loading dose was calculated by considering the body as a one-compartment during steady state, at which time the drug well penetrates the tissue compartment. The volume of distribution (V_D) β of digoxin is much larger than V_p , or the volume of the plasma compartment.

Using Equation (4.38),

$$\begin{aligned} (V_D)\beta &= \frac{kV_p}{b} \\ &= \frac{0.18/\text{hr} \times 0.78 \text{ L/kg}}{0.19/\text{hr}} = 7.39 \text{ L/kg} \\ D_L &= 7390 \frac{\text{mL}}{\text{kg}} \times 70 \text{ kg} \times 1.5 \frac{\text{ng}}{\text{mL}} \end{aligned}$$

The loading dose is generally divided into two or three doses or is administered as 50% in the first dose and the remaining drug given in two divided doses 6–8 hours apart to minimize potential side effects from overdigitization. If the entire loading dose were administered intravenously, the plasma level would be about 4–5 ng/mL after 1 hour, while the level would drop to about 1.5 ng/mL at about 4 hours. The exact level after a given IV dose may be calculated using Equation 4.6 at any time desired. The pharmacokinetic parameters for digoxin are available in .

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.

Clearance is often calculated by a noncompartmental approach, as in Equation 4.35, in which the bolus IV dose is divided by the area under the plasma–time concentration curve from zero to infinity, $[AUC]_0^\infty$. In evaluating the $[AUC]_0^\infty$, early time points must be collected frequently to observe the rapid decline in drug concentrations (distribution phase) for drugs with multicompartment pharmacokinetics. In the calculation of clearance using the noncompartmental approach, underestimating the area can inflate the calculated value of clearance.

$$Cl = \frac{D_0}{[AUC]_0^\infty} \quad (4.41)$$

Equation 4.41 may be rearranged to Equation 4.42 to show that Cl in the two-compartment model is the product of $(V_D)\beta$ and b .

$$Cl = (V_D)\beta b \quad (4.42)$$

If both parameters are known, then calculation of clearance is simple and more accurate than using the trapezoidal rule to obtain area. Clearance calculations that use the two-compartment model are viewed as model dependent because more assumptions are required, and such calculations cannot be regarded as noncompartmental. However, the assumptions provide additional information and, in some sense, specifically describe the drug concentration–time profile as biphasic.

Clearance is a term that is useful in calculating average drug concentrations. With many drugs, a biphasic profile suggests a rapid tissue distribution phase followed by a slower elimination phase. Multicompartment pharmacokinetics is an important consideration in understanding drug permeation and toxicity. For example, the plasma–time profiles of aminoglycosides, such as gentamicin, are more useful in explaining toxicity than average plasma or drug concentration taken at peak or trough time.

Elimination Rate Constant

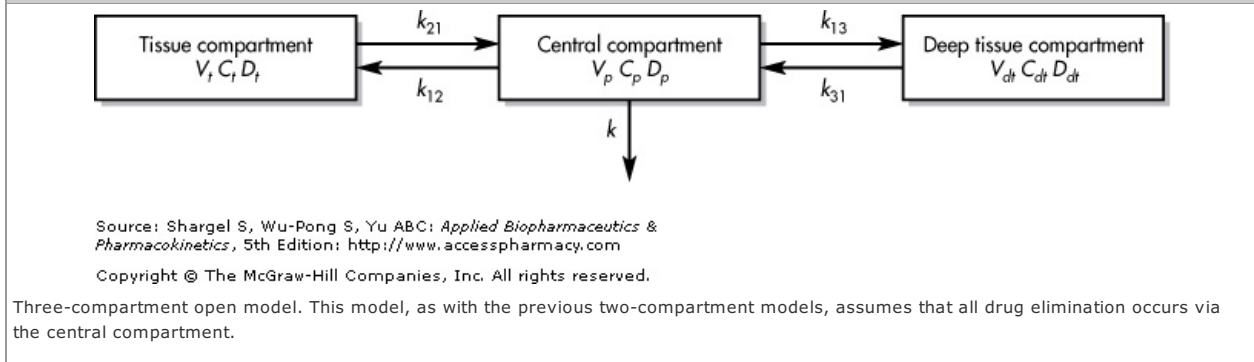
In the two-compartment model (IV administration), the elimination rate constant, k , represents the elimination of drug from the central compartment, whereas b represents drug elimination during the beta or elimination phase, when distribution is mostly complete. Because of redistribution of drug out 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. When it is impractical to determine k , b is

calculated from the b slope. The $t_{1/2\beta}$ is often used to calculate the drug dose.

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 .

Figure 4-7.



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

$$C_p = Ae^{-at} + Be^{-bt} + Ce^{-ct} \quad (4.43)$$

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.

A three-compartment equation may be written by statisticians in the literature as

$$C_p = Ae^{-\lambda_1 t} + Be^{-\lambda_2 t} + Ce^{-\lambda_3 t} \quad (4.43a)$$

instead of a , b , c , etc., λ_1 , λ_2 , λ_3 are substituted to express the triexponential feature of the equation. Similarly, the n -compartment model may be expressed with $\lambda_1, \lambda_2, \dots, \lambda_n$. In classical pharmacokinetics, the symbols a , b , c that we have adopted are actually Greek symbols, α , β , γ . The preexponential terms are sometimes expressed as C_1 , C_2 , and C_3 .

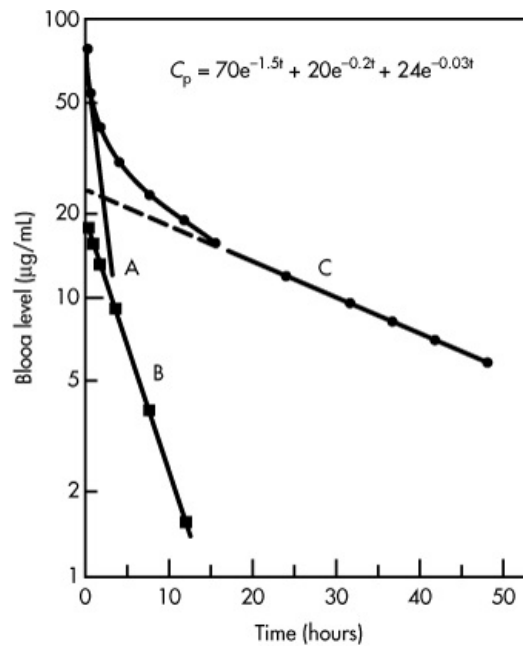
The parameters in Equation 4.43 may be solved graphically by the method of residuals () or by computer. The calculations for the elimination rate constant k , volume of the central compartment, and area are shown in the following equations:

$$k = \frac{(A + B + C)abc}{Abc + Bac + Cab} \quad (4.44)$$

$$V_p = \frac{D_0}{A + B + C} \quad (4.45)$$

$$[\text{AUC}] = \frac{A}{a} + \frac{B}{b} + \frac{C}{c} \quad (4.46)$$

Figure 4-8.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: <http://www.accesspharmacy.com>

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

Practical Focus

Hydromorphone (Dilaudid)

Three independent studies on the pharmacokinetics of hydromorphone after a bolus intravenous injection reported that hydromorphone followed the pharmacokinetics of a one-compartment model (), a two-compartment model () or a three-compartment model (), respectively. A comparison of these studies is listed in .

Table 4.7 Comparison of Hydromorphone Pharmacokinetics

Study	Timing of Blood Samples	Pharmacokinetic Parameters
6 Males, 25–29 yrs; mean weight, 76.8 kg	0, 15, 30, 45 min 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hr	One-compartment model Terminal $t_{1/2} = 2.64 (\pm 0.88)$ hr
Dose, 2-mg IV bolus		
8 Males, 20–30 yrs; weight, 50–86 kg	0, 3, 7, 15, 30, 45 min 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hr	Two-compartment model Terminal $t_{1/2} = 2.36 (\pm 0.58)$ hr
Dose, 2-mg IV bolus		
10 Males, 21–38 yrs; mean weight, 72.7 kg	1, 2, 3, 4, 5, 7, 10, 15, 20, 30, 45 min 1, 1.5, 2, 2.5, 3, 4, 5 hr	Three-compartment model Terminal $t_{1/2} = 3.07 (\pm 0.25)$ hr
Dose, 10, 20, and 40 µg/kg, IV bolus		

Comments

The adequacy of the pharmacokinetic model will depend on the sampling intervals and the drug assay. The first two studies showed a similar elimination half-life. However, both did not observe a three-compartment pharmacokinetic model due to lack of appropriate description of the early distribution phases for hydromorphone. After an IV bolus injection, hydromorphone is very rapidly distributed into the tissues. obtained a triexponential function by closely sampling early time periods after the dose. Average distribution half-lives were 1.27 and 14.7 min, and the average terminal elimination was 184 min ($t_{1/2 \beta}$). The average values for systemic clearance (Cl) was 1.66 L/min; the initial dilution volume was 24.4 L. If distribution is rapid, the drug becomes distributed during absorption. Thus, hydromorphone pharmacokinetics follow a one-compartment model after a single oral dose.

Hydromorphone is administered to relieve acute pain in cancer or postoperative patients. Rapid pain relief is obtained by IV

injection. Although the drug is effective orally, about 50–60% of the drug is cleared by the liver through first-pass effects. The pharmacokinetics of hydromorphone after IV injection suggest a multicompartment model. The site of action is probably within the central nervous system, as part of the tissue compartment. The initial volume or initial dilution volume, V_p , is the volume into which IV injections are injected and diluted. Hydromorphone follows linear kinetics, ie, drug concentration is proportional to dose. Hydromorphone systemic clearance is much larger than the glomerular filtration rate (GFR) of 120 mL/min (see), hence the drug is probably metabolized significantly by the hepatic route. A clearance of 1.66 L/min is faster than the blood flow of 1.2–1.5 L/min to the liver. The drug must be rapidly extracted or, in addition, must have extrahepatic elimination. When the distribution phase is short, the distribution phase may be disregarded, provided that the targeted plasma concentration is sufficiently low and the terminal elimination phase is relatively long. If the drug has a sufficiently high target plasma drug concentration and the elimination half-life is short, the distributive phase must not be ignored. For example, lidocaine target effective concentration often lies close to the distributive phase, since its beta elimination half-life is very short; and ignoring the alpha phase will result in a large error in dosing projection.

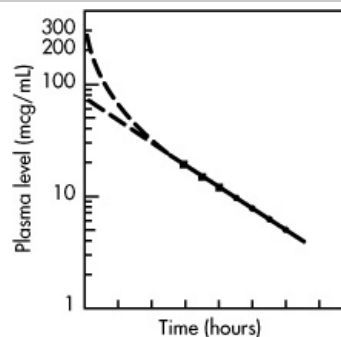
DETERMINATION OF COMPARTMENT MODELS

Models based on compartmental analysis should always use the fewest number of compartments necessary to describe the experimental data adequately. Once an empirical equation is derived from the experimental observations, it becomes necessary to examine how well the theoretical values that are calculated from the derived equation fit the experimental data.

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.

Figure 4-9.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: <http://www.accesspharmacy.com>

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The samples from which data were obtained for this graph were taken too late to show the distributive phase; therefore, the value of C_p^0 obtained by extrapolation (straight broken line) is deceptively low.

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.

Practical Focus

Two-Compartment Model: Relation between Distribution and Apparent (Beta) Half-Life

The distribution half-life of a drug is dependent on the type of tissues the drug penetrates as well as by blood supply to those

tissues. In addition, the capacity of the tissue to store drug is also a factor. Distribution half-life is generally short for many drugs because of the rapid blood supply and drug equilibration in the tissue compartment. However, there is some supporting evidence that a drug with a long elimination half-life is often associated with a longer distribution phase. It is conceivable that a tissue with little blood supply may not attain a sufficiently high drug concentration to exert its impact and influence the overall plasma drug concentration profile in the presence of rapid elimination. In contrast, drugs such as digoxin have a long elimination half-life, and drug concentration declines slowly to allow more time for distribution to tissues. Human follicle-stimulating hormone (hFSH) injected intravenously has a very long elimination half-life, and its distribution half-life is also quite long. Drugs such as lidocaine, theophylline, and milrinone have short elimination half-lives and generally relatively short distributional half-lives.

In order to examine the effect of changing k (from 0.6 to 0.2 hr^{-1}) on the distributional (alpha phase) and elimination (beta phase) half-lives of various drugs, four simulations based on a two-compartment model were generated (). The simulations show that a drug with a smaller k has a longer beta elimination half-life. Keeping all other parameters (k_{12} , k_{21} , V_p) constant, a smaller k will result in a smaller a , or a slower distributional phase. Examples of drugs with various distribution and elimination half-lives are shown in .

Drug	Beta Half-Life	Distributional Half-Life
Lidocaine	1.8 hr	8 min
Cocaine	1 hr	18 min
Theophylline	4.33 hr	7.2 min
Ergometrine	2 hr	11 min
Hydromorphone	3 hr	14.7 min
Milrinone	3.6 hr	4.6 min
Procainamide	2.5–4.7 hr	6 min
Quinidine	6–8 hr	7 min
Lithium	21.39 hr	5 hr
Digoxin	1.6 days	35 min
Human FSH	1 day	60 min
IgG1 kappa MAB	9.6 days (monkey)	6.7 hr
Simulation 1	13.26 hr	36.24 min
Simulation 2	16.60 hr	43.38 min
Simulation 3	26.83 hr	53.70 min
Simulation 4	213.7 hr	1.12 hr

Simulation was performed using V_p of 10 L; dose = 100 mg; $k_{12} = 0.5 \text{ hr}^{-1}$; $k_{21} = 0.1 \text{ hr}^{-1}$; $k = 0.6, 0.4, 0.2$, and 0.02 hr^{-1} for simulations 1–4, respectively (using Eqs. 4.10 and 4.11).

Source: From manufacturer and , with permission.

Clinical Example: Moxalactam, Effect of Changing Renal Function in Patients with Sepsis

The pharmacokinetics of moxalactam (see) was examined in 40 patients with abdominal sepsis (). The patients were grouped according to creatinine clearances into three groups:

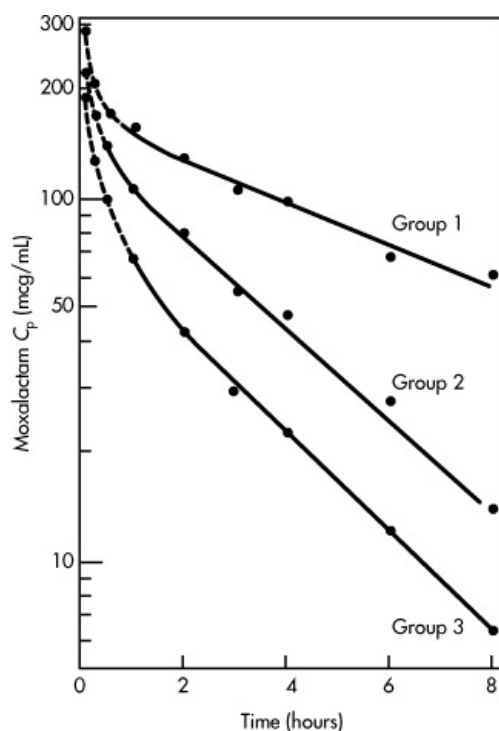
Group 1: Average creatinine clearance = 35.5 mL/min/1.73 m²

Group 2: Average creatinine clearance = 67.1 ± 6.7 mL/min/1.73 m²

Group 3: Average creatinine clearance = 117.2 ± 29.9 mL/min/1.73 m²

After intravenous bolus administration, the serum drug concentrations followed a biexponential decline (). The pharmacokinetics at steady state (2 g every 8 hr) was also examined in these patients. Mean steady-state serum concentrations ranged from 27.0 to 211.0 µg/mL and correlated inversely with creatinine clearance ($r = 0.91$, $p < 0.0001$). The terminal half-life ranged from 1.27 to 8.27 hours and reflected the varying renal function of the patients. Moxalactam total body clearance (Cl) had excellent correlation with creatinine clearance ($r^2 = 0.92$). Cl determined by noncompartmental data analysis was in agreement with Cl determined by nonlinear least-squares regression ($r = 0.99$, $p < 0.0001$). Moxalactam total body clearance was best predicted from creatinine clearance corrected for body surface area.

Figure 4-10.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: <http://www.accesspharmacy.com>
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Moxalactam serum concentration in three groups of patients: group 1, average creatinine concentration = 35.5 mL/min/1.73 m²; group 2, average creatinine concentration = 67.1 ± 6.7 mL/min/1.73 m²; group 3, average creatinine concentration = 117.2 ± 29.9 mL/min/1.73 m².

Questions (Refer to)

1. Calculate the beta half-life of moxalactam in the most renally impaired group.
2. What indicator is used to predict moxalactam clearance in the body?
3. What is the beta volume of distribution of patients in group 3 with normal renal function?
4. What is the initial volume (V_i) of moxalactam?

Solutions

1. Mean beta half-life is $0.693/0.20 = 3.47$ hours in the most renally impaired group.
2. Creatinine is mainly filtered through the kidney, and creatinine clearance is used as an indicator of renal glomerular filtration rate. Group 3 has normal renal function (average creatinine clearance = 117.2 mL/min/1.73 m²) (see).
3. Beta volume of distribution: Moxalactam clearance in group 3 subjects is 125.9 mL/min. From Equation 4.31,

$$\begin{aligned} (V_D)_\beta &= \frac{\text{clearance}}{b} \\ &= \frac{125.9 \text{ mL/min} \times 60 \text{ min/hr}}{0.37 \text{ hr}^{-1}} \\ &= 20,416 \text{ mL} \quad \text{or} \quad 20.4 \text{ L} \end{aligned}$$

4. The volume of the plasma compartment, V_p , is sometimes referred to as the initial volume. V_p ranges from 0.12 to 0.15 L/kg among the three groups and is considerably smaller than the steady-state volume of distribution.

Clinical Example: Azithromycin Pharmacokinetics

Following oral administration, azithromycin is rapidly absorbed and widely distributed throughout the body. Azithromycin is rapidly distributed into tissues, with high drug concentrations within cells, resulting in significantly higher azithromycin concentrations in tissue than in plasma. The high values for plasma clearance (630 mL/min) suggest that the prolonged half-life is due to extensive uptake and subsequent release of drug from tissues.

Plasma concentrations of azithromycin decline in a polyphasic pattern, resulting in an average terminal half-life of 68 hours. With this regimen, C_{\min} and C_{\max} remained essentially unchanged from day 2 through day 5 of therapy. However, without a loading dose, azithromycin C_{\min} levels required 5–7 days to reach desirable plasma levels.

The pharmacokinetic parameters of azithromycin in healthy elderly male subjects (65–85 years) were similar to those in young adults. Although higher peak drug concentrations (increased by 30–50%) were observed in elderly women, no significant accumulation occurred.

Questions

1. Do you agree with the following statements for a drug that is described by a two-compartment pharmacokinetic model? At peak C_t , the drug is well equilibrated between the plasma and the tissue compartment, $C_p = C_t$, and the rates of drug diffusion into and from the plasma compartment are equal.
2. What happens after peak C_t ?
3. Why is a loading dose used?
4. What is V_i ? How is this volume related to V_p ?
5. What population factors could affect the concentration of azithromycin?

Solutions

1. For a drug that follows a multicompartment model, the rates of drug diffusion into the tissues from the plasma and from the tissues into the plasma are equal at peak tissue concentrations. However, the tissue drug concentration is generally not equal to the plasma drug concentration.
2. After peak C_t , the rate out of the tissue exceeds the rate into the tissue, and C_t falls. The decline of C_t parallels that of C_p , and occurs because distribution equilibrium has occurred.
3. When drugs are given in a multiple-dose regimen, a loading dose may be given to achieve desired therapeutic drug concentrations more rapidly (see).
4. The volume of the plasma compartment, V_p , is sometimes referred to as the initial volume.
5. Age and gender may affect the C_{max} level of the drug.

Clinical Example: Etoposide

Etoposide is a drug used for the treatment of lung cancer. Understanding the distribution of etoposide in normal and metastatic tissues is important to avoid drug toxicity. Etoposide follows a two-compartment model. The $(V_D)\beta$ is 0.28 L/kg, and the beta elimination half-life is 12.9 hours. Total body clearance is 0.25 mL/min/kg.

Questions

1. What is the $(V_D)\beta$ in a 70-kg subject?
2. How is the $(V_D)\beta$ different than the volume of the plasma fluid, V_p ?
3. Why is the $(V_D)\beta$ useful if it does not represent a real tissue volume?
4. How is $(V_D)\beta$ calculated from plasma time-concentration profile data for etoposide? Is $(V_D)\beta$ related to total body clearance?

Solutions

1. $(V_D)\beta$ of etoposide in a 70-kg subject is $0.28 \text{ L/kg} \times 70 \text{ kg} = 19.6 \text{ L}$.
2. The plasma fluid volume is about 3 L in a 70-kg subject and is much smaller than $(V_D)\beta$. The apparent volume of distribution, $(V_D)\beta$, is also considerably larger than the volume of the plasma compartment (also referred to as the initial volume by some clinicians), which includes some extracellular fluid.
3. Etoposide is a drug that follows a two-compartment model with a beta elimination phase. Within the first few minutes after an intravenous bolus dose, most of the drug is distributed in the plasma fluid. Subsequently, the drug will diffuse into tissues and drug uptake may occur. Eventually, plasma drug levels will decline due to elimination, and some redistribution as etoposide in tissue diffuses back into the plasma fluid.

The real tissue drug level will differ from the plasma drug concentration, depending on the partitioning of drug in tissues and plasma. This volume of distribution, $(V_D)\beta$, allows the area under the curve to be calculated, an area that has been related to toxicities associated with many cancer chemotherapy agents.

The two-compartment model allows continuous monitoring of the amount of the drug present in and out of the vascular system, including the amount of drug eliminated. This information is important in pharmacotherapy.

4. $(V_D)\beta$ may be determined from the total drug clearance and beta:

$$Cl = b \times (V_D)\beta$$

$(V_D)\beta$ is also calculated from Equation 4.36 where

$$(V_D)\beta = (V_D)_{area} = \frac{D_0}{b[AUC]_0^\infty}$$

This method for $(V_D)\beta$ determination $[AUC]_0^\infty$ is popular because $[AUC]_0^\infty$ is easily calculated using the trapezoidal rule. Many values for apparent volumes of distribution reported in the clinical literature are obtained using the area equation. In general, both volume terms reflect extravascular drug distribution. $(V_D)\beta$ appears to be affected by the dynamics of drug disposition in the beta phase. In clinical practice, many potent drugs are not injected by bolus dose. Instead, these drugs are

infused over a short interval, making it difficult to obtain accurate information on the distributive phase. As a result, many drugs that follow a two-compartment model are approximated using a single compartment. It should be cautioned that there are substantial deviations in some cases. When in doubt, the full equation with all parameters should be applied for comparison. A small bolus (test) dose may be injected to obtain the necessary data if a therapeutic dose injected rapidly causes side effects or discomfort to the subject.

FREQUENTLY ASKED QUESTIONS

1. My preceptors and I both agree that the "hypothetical" or "mathematical" compartment models are just about useless in helping me with dosing in the clinical setting. Does "hypothetical" mean "not real"?
2. What is the apparent volume of distribution, and why are there so many different volumes of distribution?
3. If physiologic models are better than compartment models, why not just use physiologic models?
4. Can I just learn clearance and forget about the other pharmacokinetic parameters, because clearance is the term most often used in clinical pharmacy?
5. What is the error if I assume a one-compartment model instead of a two-compartment or multicompartment model?
6. What kind of improvement in terms of patient care or drug therapy was made using the compartment model?

LEARNING QUESTIONS

1. A drug was administered by rapid IV injection into a 70-kg adult male. Blood samples were withdrawn over a 7-hour period and assayed for intact drug. The results are tabulated below. Using the method of residuals, calculate the values for intercepts A and B and slopes a , b , k , k_{12} , and k_{21} .

Time (hr)	C_p ($\mu\text{g/mL}$)	Time (hr)	C_p ($\mu\text{g/mL}$)
0.00	70.0	2.5	14.3
0.25	53.8	3.0	12.6
0.50	43.3	4.0	10.5
0.75	35.0	5.0	9.0
1.00	29.1	6.0	8.0
1.50	21.2	7.0	7.0
2.00	17.0		

2. A 70-kg male subject was given 150 mg of a drug by IV injection. Blood samples were removed and assayed for intact drug. Calculate the slopes and intercepts of the three phases of the plasma level-time plot from the results tabulated below. Give the equation for the curve.

Time (hr)	C_p ($\mu\text{g/mL}$)	Time (hr)	C_p ($\mu\text{g/mL}$)
0.17	36.2	3.0	13.9
0.33	34.0	4.0	12.0
0.50	27.0	6.0	8.7
0.67	23.0	7.0	7.7
1.00	20.8	18.0	3.2
1.50	17.8	23.0	2.4
2.00	16.5		

3. demonstrated that theophylline followed a two-compartment pharmacokinetic model in human subjects. After administering a single intravenous dose (5.6 mg/kg) in nine normal volunteers, these investigators demonstrated that the equation best describing theophylline kinetics in humans was as follows:

$$C_p = 12e^{-5.8t} + 18e^{-0.16t}$$

What is the plasma level of the drug 3 hours after the IV dose?

4. A drug has a distribution that can be described by a two-compartment open model. If the drug is given by IV bolus, what is the cause of the initial or rapid decline in blood levels (a phase)? What is the cause of the slower decline in blood levels (b phase)?
5. What does it mean when a drug demonstrates a plasma level-time curve that indicates a three-compartment open model? Can this curve be described by a two-compartment model?
6. A drug that follows a multicompartment pharmacokinetic model is given to a patient by rapid intravenous injection. Would the drug concentration in each tissue be the same after the drug equilibrates with the plasma and all the tissues in the body? Explain.
7. studied the pharmacokinetics of amrinone after a single IV bolus injection (75 mg) in 14 healthy adult male volunteers. The

pharmacokinetics of this drug followed a two-compartment open model and fit the following equation:

$$C_p = Ae^{-at} + Be^{-bt}$$

where

$$A = 4.62 \pm 12.0 \mu\text{g/mL}$$

$$B = 0.64 \pm 0.17 \mu\text{g/mL}$$

$$a = 8.94 \pm 13 \text{ hr}^{-1}$$

$$b = 0.19 \pm 0.06 \text{ hr}^{-1}$$

From these data, calculate:

- The volume of the central compartment
 - The volume of the tissue compartment
 - The transfer constants k_{12} and k_{21}
 - The elimination rate constant from the central compartment
 - The elimination half-life of amrinone after the drug has equilibrated with the tissue compartment
8. A drug may be described by a three-compartment model involving a central compartment and two peripheral tissue compartments. If you could sample the tissue compartments (organs), in which organs would you expect to find a drug level corresponding to the two theoretical peripheral tissue compartments?
9. A drug was administered to a patient at 20 mg by IV bolus dose and the time-plasma drug concentration is listed below. Use a suitable compartment model to describe the data and list the fitted equation and parameters. What are the statistical criteria used to describe your fit?

Hour	mg/L
0.20	3.42
0.40	2.25
0.60	1.92
0.80	1.80
1.00	1.73
2.00	1.48
3.00	1.28
4.00	1.10
6.00	0.81
8.00	0.60
10.00	0.45
12.00	0.33
14.00	0.24
18.00	0.13
20.00	0.10

10. The toxicokinetics of colchicine in seven cases of acute human poisoning was studied by . In three further cases, postmortem tissue concentrations of colchicine were measured. Colchicine follows the two-compartment model with wide distribution in various tissues. Depending on the time of patient admission, two disposition processes were observed. The first, in three patients, admitted early, showed a biexponential plasma colchicine decrease, with distribution half-lives of 30, 45, and 90 minutes. The second, in four patients, admitted late, showed a monoexponential decrease. Plasma terminal half-lives ranged from 10.6 to 31.7 hours for both groups.

11. Postmortem tissue analysis of colchicine showed that colchicine accumulated at high concentrations in the bone marrow (more than 600 ng/g), testicle (400 ng/g), spleen (250 ng/g), kidney (200 ng/g), lung (200 ng/g), heart (95 ng/g), and brain (125 ng/g). The pharmacokinetic parameters of colchicine are:

Fraction of unchanged colchicine in urine = 30%

Renal clearance = 13 L/hr

Total body clearance = 39 L/hr

Apparent volume of distribution = 21 L/kg

- Why is colchicine described by a monoexponential profile in some subjects and a biexponential in others?
- What is the range of distribution of half-life of colchicine in the subjects?
- Which parameter is useful in estimating tissue drug level at any time?

- d. Some clinical pharmacists assumed that, at steady state when equilibration is reached between the plasma and the tissue, the tissue drug concentration would be the same as the plasma. Do you agree?
- e. Which tissues may be predicted by the tissue compartment?

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