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PHYSIOLOGIC PHARMACOKINETIC MODELS, MEAN RESIDENCE TIME, AND STATISTICAL MOMENT THEORY: INTRODUCTION

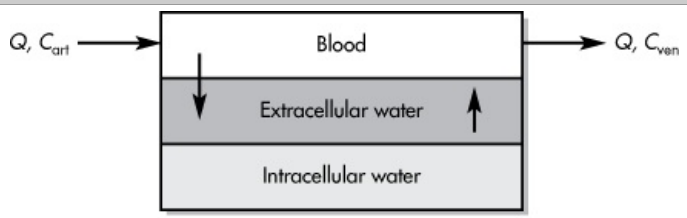
The study of pharmacokinetics describes the absorption, distribution, and elimination of the active drug and metabolites in quantitative terms (). Ideally, a pharmacokinetic model uses the observed time course for drug concentration in the body and, from this data, obtains various pharmacokinetic parameters to predict drug dosing outcomes, pharmacodynamics, and toxicity.

In developing a model, certain underlying assumptions are made by the pharmacokineticist as to the type of pharmacokinetic model, the order of the rate process, the blood flow to a tissue, the method for the estimation of the plasma or tissue volume, and other factors. Even with a more general approach such as model-independent analysis, first-order drug elimination is often assumed in the calculation of AUC_0^∞. In selecting a model for data analysis, the pharmacokineticist may choose more than one method of modeling, depending on the many factors including experimental condition, study design, and completeness of data. The goodness- of-fit to the model and the desired pharmacokinetic parameters are other considerations. Each estimated pharmacokinetic parameter has an inherent variability because of the variability of the biologic system and of the observed data. Moreover, because pharmacokinetic studies are performed on a limited number of subjects, the estimated pharmacokinetic parameters may not be representative of the entire population.

In spite of difficulties in the construction of these pharmacokinetic models, such models have been extremely useful in describing the time course of drug action, improving drug therapy by enhancing drug efficacy, and minimizing adverse reactions through more accurate dose regimens. Pharmacokinetic models are also applied to the development of new drug delivery systems. Three main types of pharmacokinetic models—physiologic, compartment, and statistical moment approach models—are discussed in this chapter.

The human body is composed of organ systems containing living cells bathed in an extracellular aqueous fluid (). Both drugs and endogenous substances, such as hormones, nutrients, and oxygen, are transported to the organs by the same network of blood vessels (arteries). The drug concentration within a target organ depends on plasma drug concentration, the rate of blood flow to an organ and the rate of drug uptake into the tissue. Physiologically, uptake (accumulation) of drug by organ tissues occurs from the extracellular fluid, which equilibrates rapidly with the capillary blood in the organ. Some drugs cross the plasma membrane into the interior fluid (intracellular water) of the cell ().

Figure 22-1.



In describing drug transfer, the physiologic pharmacokinetic model divides a body organ into three parts: capillary vessels, extracellular space, and intracellular space.

In addition to drug accumulation, some organs of the body are involved in drug elimination, either by excretion (eg, kidney) or by metabolism (eg, liver). The elimination of drug by an organ may be described by drug clearance in the organ (and). The liver is an example of an organ with drug metabolism and drug uptake (accumulation). Physiologic pharmacokinetic models consider all processes of drug uptake and elimination.

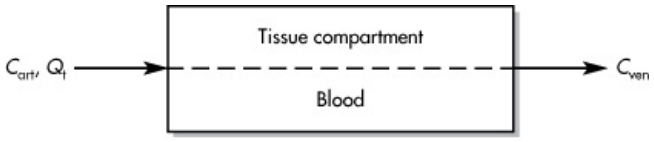
PHYSIOLOGIC PHARMACOKINETIC MODELS

Drugs are carried by blood flow from the administration (input) site to various body organs, where the drug rapidly equilibrates with the interstitial water in the organ. Physiologic pharmacokinetic models are mathematical models describing drug movement and disposition in the body based on organ blood flow and the organ spaces penetrated by the drug. In its simplest form, a physiologic pharmacokinetic model considers the drug to be blood flow limited. Drugs are carried to organs by arterial blood and leave organs by venous blood (). In such a model, transmembrane movement of drug is rapid, and the capillary membrane does not offer any resistance to drug permeation. Uptake of drug into the tissues is rapid, and a constant ratio of drug concentrations between the organ and the venous blood is quickly established. This ratio is the tissue/blood partition coefficient:

$$P_{\text{tissue}} = \frac{C_{\text{tissue}}}{C_{\text{blood}}} \qquad (22.1)$$

where P is the partition coefficient.

Figure 22-2.



Noneliminating tissue organ. The extracellular water is merged with the plasma water in the blood

The magnitude of the partition coefficient can vary depending on the drug and on the type of tissue. Adipose tissue, for example, has a high partition for lipophilic drugs. The rate of drug carried to a tissue organ and tissue drug uptake depend on the rate of blood flow to the organ and the tissue/blood partition coefficient, respectively.

The rate of blood flow to the tissue is expressed as Q_t (mL/min), and the rate of change in the drug concentration with respect to time within a given tissue organ is expressed as

$$\frac{d(V_{\text{tissue}}C_{\text{tissue}})}{dt} = Q_t(C_{\text{in}} - C_{\text{out}}) \qquad (22.2)$$

$$\frac{d(V_{\text{tissue}}C_{\text{tissue}})}{dt} = Q_t(C_{\text{art}} - C_{\text{ven}}) \qquad (22.3)$$

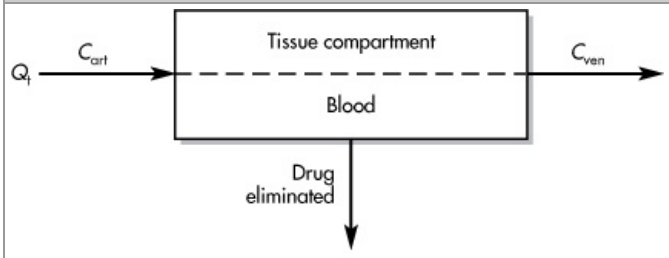
where C_{art} is the arterial blood drug concentration and C_{ven} is the venous blood drug concentration. Q_t is blood flow and represents the volume of blood flowing through a typical tissue organ per unit of time.

If drug uptake occurs in the tissue, the incoming concentration, C_{art}, is higher than the outgoing venous concentration, C_{ven}. The rate of change in the tissue drug concentration is equal to the rate of blood flow multiplied by the difference between the blood drug concentrations entering and leaving the tissue organ. In the *blood flow-limited model,* drug concentration in the blood leaving the tissue and the drug concentration within the tissue are in equilibrium, and C_{ven} may be estimated from the tissue/blood partition coefficient in Equation 22.1. Substituting in Equation 22.3 with $C_{ven} = C_{tissue}/P_{tissue}$ yields

$$\frac{d(V_{\text{tissue}}C_{\text{tissue}})}{dt} = Q_t\left(C_{\text{art}} - \frac{C_{\text{tissue}}}{P_{\text{tissue}}}\right) \qquad (22.4)$$

Equation 22.4 describes drug distribution in a noneliminating organ or tissue group. For example, drug distribution to muscle, adipose tissue, and skin is represented in a similar manner by Equations 22.5, 22.6, and 22.7, respectively, as shown below. For tissue organs in which drug is eliminated (), parmeters representing drug elimination from the liver (k_{LIV}) and kidney (k_{KID}) are added to account for drug removal through metabolism or excretion. Equations 22.8 and 22.9 are derived similarly to those for the noneliminating organs above.

Figure 22-3.



A typical eliminating tissue organ.

Removal of drug from any organ is described by drug clearance (*Cl*) from the organ. The rate of drug elimination is the product of the drug concentration in the organ and the organ clearance.

$$\text{Rate of drug elimination} = \frac{V_{\text{tiss}}\, dC_{\text{tiss}}}{dt} = C_{\text{tiss}} \times Cl_{\text{tiss}}$$

The rate of drug elimination may be described for each organ or tissue ().

$$\textit{Muscle:}\ \frac{d(V_{\text{MUS}}\, C_{\text{MUS}})}{dt} = Q_{\text{MUS}}\left(C_{\text{MUS}} - \frac{C_{\text{MUS}}}{P_{\text{MUS}}}\right) \tag{22.5}$$

$$\textit{Adipose tissue:}\ \frac{d(V_{\text{FAT}}\, C_{\text{FAT}})}{dt} = Q_{\text{FAT}}\left(C_{\text{FAT}} - \frac{C_{\text{FAT}}}{P_{\text{FAT}}}\right) \tag{22.6}$$

$$\textit{Skin:}\ \frac{d(V_{\text{SKIN}}\, C_{\text{SKIN}})}{dt} = Q_{\text{SKIN}}\left(C_{\text{SKIN}} - \frac{C_{\text{SKIN}}}{P_{\text{SKIN}}}\right) \tag{22.7}$$

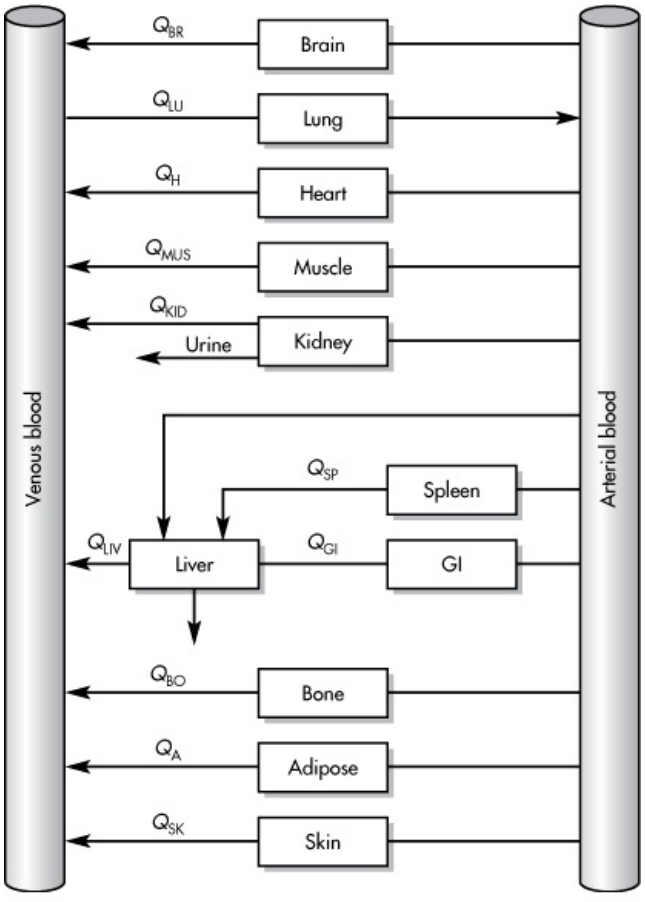
$$\textit{Liver:}\ \frac{d(V_{\text{LIV}}\, C_{\text{LIV}})}{dt} = C_{\text{LIV}}\,(Q_{\text{LIV}} - Q_{\text{GI}} - Q_{\text{SP}}) + Q_{\text{GI}}\left(\frac{C_{\text{GI}}}{P_{\text{GI}}}\right) + Q_{\text{SP}}\left(\frac{C_{\text{SP}}}{P_{\text{SP}}}\right) - Q_{\text{LIV}}\left(\frac{C_{\text{LIV}}}{P_{\text{LIV}}}\right) - C_{\text{LIV}}\left(\frac{Cl_{\text{int}}}{P_{\text{LIV}}}\right) \tag{22.8}$$

$$\textit{Kidney:}\ \frac{d(V_{\text{KID}}\, C_{\text{KID}})}{dt} = Q_{\text{KID}}\left(C_{\text{KID}} - \frac{C_{\text{KID}}}{P_{\text{KID}}}\right) - C_{\text{KID}}\left(\frac{Cl_{\text{KID}}}{P_{\text{KID}}}\right) \tag{22.9}$$

$$\textit{Lung:}\ \frac{d(V_{\text{LU}}\, C_{\text{LU}})}{dt} = Q_{\text{LU}}\left(\frac{C_{\text{LU}}}{P_{\text{LU}}}\right) \tag{22.10}$$

where LIV = liver, SP = spleen, GI = gastrointestinal tract, KID = kidney, LU = lung, FAT = adipose, SKIN = skin, and MUS = muscle.

Figure 22-4.



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

Example of blood flow to organs in a physiologic pharmacokinetic model.

The mass balance for the rate of change in drug concentration in the blood pool is

$$\frac{d(V_b C_b)}{dt} = Q_{MUS}\left(\frac{C_{MUS}}{P_{MUS}}\right) + Q_{LIV}\left(\frac{C_{LIV}}{P_{LIV}}\right) + Q_{KID}\left(\frac{C_{KID}}{P_{KID}}\right) + Q_{SKIN}\left(\frac{C_{SKIN}}{P_{SKIN}}\right) + Q_{FAT}\left(\frac{C_{FAT}}{P_{FAT}}\right) + Q_{LU}\left(\frac{C_{LU}}{P_{LU}}\right) - Q_b C_b \quad (22.11)$$

(muscle) (liver) (kidney) (skin) (adipose) (lung) (blood)

Lung perfusion is unique because the pulmonary artery returns venous blood flow to the lung, where carbon dioxide is exchanged for oxygen and the blood becomes oxygenated. The blood from the lungs flows back to the heart (into the left atrium) through the pulmonary vein, and the quantity of blood that perfuses the pulmonary system ultimately passes through the remainder of the body. In describing drug clearance through the lung, perfusion from the heart (right ventricle) to the lung is considered as venous blood (). Therefore, the terms in Equation 22.11 describing lung perfusion are reversed compared to those for the perfusion of other tissues. With some drugs, the lung is a clearing organ besides serving as a merging pool for venous blood. In those case, a lung clearance term could be included in the general model.

After intravenous drug administration, drug uptake in the lungs may be very significant if the drug has high affinity for lung tissue. If actual drug clearance is at a much higher rate than the drug clearance accounted for by renal and hepatic clearance, then lung clearance of the drug should be suspected, and a lung clearance term should be included in the equation in addition to lung tissue distribution.

The system of differential equations used to describe the blood flow-limited model is usually solved through computer programs. The *Runge–Kutta method* is often used in computer methods for series of differential equations. Because of the large number of parameters involved in the mass balance, more than one set of parameters may fit the experimental data. This is especially true with human data, in which many of the organ tissue data items are not available. The lack of sufficient tissue data sometimes leads to unconstrained models. As additional data become available, new or refined models are adopted. For example, methotrexate was initially described by a flow-limited model, but later work described the model as a *diffusion-limited model.*

Because invasive methods are available for animals, tissue/blood ratios or partition coefficients can be determined accurately by direct measurement. Using experimental pharmacokinetic data from animals, physiologic pharmacokinetic models may yield more reliable predictions.

Physiologic Pharmacokinetic Model with Binding

The physiologic pharmacokinetic model assumes flow-limited drug distribution without drug binding to either plasma or tissues. In reality, many drugs are bound to a variable extent in either plasma or tissues. With most physiologic models, drug binding is assumed to be linear (not saturable or concentration dependent). Moreover, bound and free drug in both tissue and plasma are in equilibrium. Further, the free drug in the plasma and in the tissue equilibrates rapidly. Therefore, the free drug concentration in the tissue and the free drug concentration in the emerging blood are equal:

$$[C_b]_f = [C_t]_f \quad (22.12)$$

$$[C_b]_f = f_b[C_b] \quad (22.13)$$

$$[C_t]_f = f_t[C_t] \quad (22.14)$$

where f_b is the blood free drug fraction, f_t is the tissue free drug fraction, C_t is the total drug concentration in tissue, and C_b is the total drug concentration in blood.

Therefore, the partition ratio, P_t, of the tissue drug concentration to that of the plasma drug concentration is

$$\frac{f_b}{f_t} = \frac{[C_t]}{[C_b]} = P_t \quad (22.15)$$

By assuming linear drug binding and rapid drug equilibration, the free drug fraction in tissue and blood may be incorporated into the partition ratio and the differential equations. These equations are similar to those above except that free drug concentrations are substituted for C_b. Drug clearance in the liver is assumed to occur only with the free drug. The inherent capacity for drug metabolism (and elimination) is described by the term Cl_{int} (). General mass balance of various tissues is described by Equation 22.16:

$$\frac{d(V_{tissue} C_{tissue})}{dt} = Q_t(C_{art} - C_{ven}) \quad (22.16)$$

$$\frac{d(V_{tissue} C_{tissue})}{dt} = Q_t\left(C_{art} - \frac{C_t}{P_t}\right)$$

or

$$\frac{d(V_{tissue} C_{tissue})}{dt} = Q_t\left(C_{art} - \frac{C_t f_t}{f_b}\right)$$

For liver metabolism,

$$\frac{d(V_{LIV}C_{LIV})}{dt} = C_b(Q_{LIV} - Q_{GI} - Q_{SP}) - Q_{LIV}\left(\frac{C_{LIV}}{P_{LIV}}\right)$$

(hepatic drug elimination)

$$+ Q_{GI}\left(\frac{C_{GI}}{P_{GI}}\right) + Q_{SP}\left(\frac{C_{SP}}{P_{SP}}\right) \qquad (22.17)$$

The mass balance for the drug in the blood pool is

$$\frac{d(V_bC_b)}{dt} = \underset{\text{(muscle)}}{Q_{MUS}C_{MUS}} + \underset{\text{(liver)}}{Q_{LIV}\left(\frac{C_{LIV}}{P_{LIV}}\right)} + \underset{\text{(kidney)}}{Q_{KID}\left(\frac{C_{KID}}{P_{KID}}\right)} + \underset{\text{(skin)}}{Q_{SKIN}\left(\frac{C_{SKIN}}{P_{SKIN}}\right)}$$

$$+ \underset{\text{(adipose)}}{Q_{FAT}\left(\frac{C_{FAT}}{P_{FAT}}\right)} + \underset{\text{(lung)}}{Q_{LU}\left(\frac{C_{LU}}{P_{LU}}\right)} - \underset{\text{(blood)}}{Q_bC_b} \qquad (22.18)$$

The influence of binding on drug distribution is an important factor in interspecies differences in pharmacokinetics. In some instances, animal data may predict drug distribution in humans by taking into account the differences in drug binding. For the most part, extrapolations from animals to humans or between species are rough estimates only, and there are many instances in which species differences are not entirely attributable to drug binding and metabolism.

Blood Flow-Limited versus Diffusion-Limited Model

Most physiologic pharmacokinetic models assume rapid drug distribution between tissue and venous blood. Rapid drug equilibrium assumes that drug diffusion is extremely fast and that the cell membrane offers no barrier to drug permeation. If no drug binding is involved, the tissue drug concentration is the same as that of the venous blood leaving the tissue. This assumption greatly simplifies the mathematics involved. lists some of the drugs that have been described by a flow-limited model. This model is also referred to as the *perfusion model.* A more complex type of physiologic pharmacokinetic model is called the *diffusion-limited model* or the *membrane-limited model.* In the diffusion-limited model, the cell membrane acts as a barrier for the drug, which gradually permeates by diffusion. Because blood flow is very rapid and drug permeation is slow, a drug concentration gradient is established between the tissue and the venous blood (). The rate-limiting step of drug diffusion into the tissue depends on the permeation across the cell membrane rather than blood flow. Because of the time lag in equilibration between blood and tissue, the pharmacokinetic equation for the diffusion-limited model is very complicated.

Table 22.1 Drugs Described by Physiologic Pharmacokinetic Model

Drug	Category	Comment	Reference
Thiopental	Anesthetic	Blood, flow limited	
BSP	Diagnostic	Plasma, flow limited	
Nicotine	Stimulant	Blood, flow limited	
Lidocaine	Antiarrhythmic	Blood, flow limited	
Methotrexate	Antineoplastic	Plasma, flow limited	
Biperiden	Anticholinergic	Blood, flow limited	
Cisplatin	Antineoplastic	Plasma, multiple metabolite, binding	

Application and Limitations of Physiologic Pharmacokinetic Models

The physiologic pharmacokinetic model is related to drug concentration and tissue distribution using physiologic and anatomic information. For example, the effect of a change in blood flow on the drug concentration in a given tissue may be estimated once the model is characterized. Similarly, the effect of a change in mass size of different tissue organs on the redistribution of drug may also be evaluated using the system of physiologic model differential equations generated. When several species are involved, the physiologic model may predict the pharmacokinetics of a drug in humans when only animal data are available. Changes in drug–protein binding, tissue organ drug partition ratios, and intrinsic hepatic clearance may be inserted into the physiologic pharmacokinetic model.

Most pharmacokinetic studies are modeled based on blood samples drawn from various venous sites after either IV or oral dosing. Physiologists have long recognized the unique difference between arterial and venous blood. For example, arterial tension (pressure) of oxygen drives the distribution of oxygen to vital organs. and have discussed the pharmacokinetic issues when differences in drug concentrations in arterial and venous are considered (). The implication of venous versus arterial sampling is hard to estimate and may be more drug dependent. Most pharmacokinetic models are based on sampling of venous data. In theory, mixing occurs quickly when venous blood returns to the heart and becomes reoxygenated again in the lung. has estimated that for drugs that are highly extracted, the discrepancies may be substantial between actual concentration and concentration estimated from well-stirred pharmacokinetic models.

Interspecies Scaling

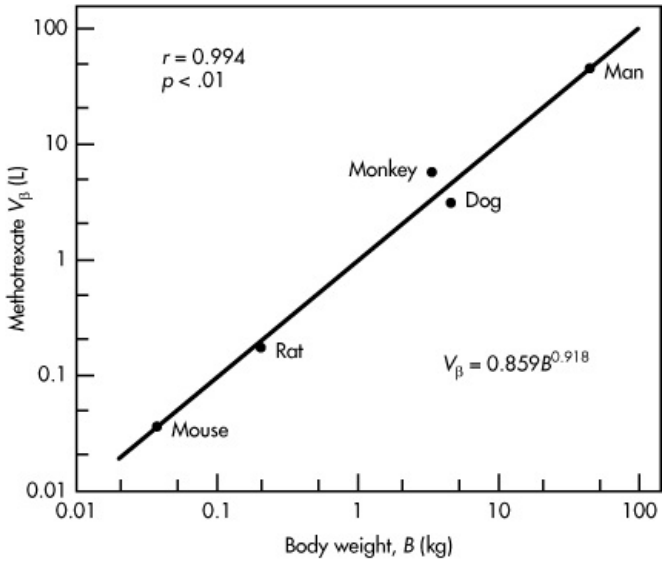
Various approaches have been used to compare the toxicity and pharmacokinetics of a drug among different species. *Interspecies scaling* is a method used in toxicokinetics and the extrapolation of therapeutic drug doses in humans from nonclinical animal drug studies. *Toxicokinetics* is the application of pharmacokinetics to toxicology and pharmacokinetics for interpolation and extrapolation based on anatomic, physiologic, and biochemical similarities (; ; ;).

The basic assumption in interspecies scaling is that physiologic variables, such as clearance, heart rate, organ weight, and biochemical processes, are related to the weight or body surface area of the animal species (including humans). It is commonly assumed that all mammals use the same energy source (oxygen) and energy transport systems across animal species (). Interspecies scaling uses a physiologic variable, *y,* that is graphed against the body weight of the species on log–log axes to transform the data into a linear relationship (). The general allometric equation obtained by this method is

$$y = bW^a \qquad (22.19)$$

where *y* is the pharmacokinetic or physiologic property of interest, *b* is an allometric coefficient, *W* is the weight or surface area of the animal species, and *a* is the allometric exponent. *Allometry* is the study of size.

Figure 22-5.



Interspecies correlation be-tween methotrexate volume of distribution V_β and body weight. Linear regression analysis was performed on logarithmically transformed data.

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Both *a* and *b* vary with the drug. Examples of various pharmacokinetic or physiologic properties that demonstrate allometric relationships are listed in . In the example shown in , methotrexate volume of distribution is related to body weight *B* of five animal species by the equation $V_\beta = 0.859B^{0.918}$.

Table 22.2 Examples of Allometric Relationship for Interspecies Parameters

Physiologic or Pharmacokinetic	Allometric Exponent *a*	Allometric Coefficient *b*
Basal O_2 consumption (mL/hr)	0.734	3.8
Endogenous N output (g/hr)	0.72	0.000042
O_2 consumption by liver slices (mL/hr)	0.77	3.3
Clearance		
Creatinine (mL/hr)	0.69	8.72
Inulin (mL/hr)	0.77	5.36
PAH (mL/hr)	0.80	22.6
Antipyrine (mL/hr)	0.89	8.16
Methotrexate (mL/hr)	0.69	10.9

Phenytoin (mL/hr)	0.92	47.1
Aztreonam (mL/hr)	0.66	4.45
Ara-C and Ara-U (mL/hr)	0.79	3.93
Volume of distribution (V_D)		
Methotrexate (L/kg)	0.92	0.859
Cyclophosphamide (L/kg)	0.99	0.883
Antipyrine (L/kg)	0.96	0.756
Aztreonam (L/kg)	0.91	0.234
Kidney weight (g)	0.85	0.0212
Liver weight (g)	0.87	0.082
Heart weight (g)	0.98	0.0066
Stomach and intestines weight (g)	0.94	0.112
Blood weight (g)	0.99	0.055
Tidal volume (mL)	1.01	0.0062
Elimination half-life:		
Methotrexate (min)	0.23	54.6
Cyclophosphamide (min)	0.24	36.6
Digoxin (min)	0.23	98.3
Hexobarbital (min)	0.35	80.0
Antipyrine (min)	0.07	74.5
Turnover times:		
Serum albumin (1/day)	0.30	5.68
Total body water (1/day)	0.16	6.01
RBC (1/day)	0.10	68.4
Cardiac circulation (min)	0.21	0.44

From , with permission.

The allometric method gives an empirical relationship that allows for approximate interspecies scaling based on the size of the species. Not considered in the method are certain specific interspecies differences such as gender, nutrition, pathophysiology, route of drug administration, and polymorphisms. Some of these more specific cases, such as the pathophysiologic condition of the animal or human, may preclude pharmacokinetic or allometric predictions.

Interspecies scaling has been refined by considering the aging rate and life span of the species. In terms of physiologic time, each species has a characteristic life span, its *maximum life-span potential* (MLP), which is controlled genetically (). Because many energy-consuming biochemical processes, including drug metabolism, vary inversely with the aging rate or life span of the animal, the allometric approach has been used for drugs that are eliminated mainly by hepatic intrinsic clearance.

Through the study of various species in handling several drugs that are metabolized predominantly by the liver, some empirical relationships regarding drug clearance of several drugs have been related mathematically in a single equation. For example, drug hepatic intrinsic clearance of biperiden in rat, rabbit, and dog was extrapolated to humans (). Equation 22.20 describes the relationship between biperiden intrinsic clearance with body weight and MLP:

$$Cl_{\text{int}} \times \text{MLP} = 1.36 \times 10^7 \times B^{0.892} \qquad (22.20)$$

where MLP is the maximum life-span potential of the species, B is the body weight of the species, and Cl_{int} is the hepatic intrinsic clearance of the free drug.

Although further model improvements are needed before accurate prediction of pharmacokinetic parameters can be made from animal data, some interesting results were obtained by on nine acid and six basic drugs. When interspecies differences in protein–drug binding are properly considered, the volume of distribution of many drugs may be predicted with 50% deviation from experimental values ().

Table 22.3 Relationship between Predicted and Observed Values of Various Pharmacokinetic Parameters in Humans for 15 Drugs

	V **(L/kg)**			***Cl*** **$_m$ (mL/min per kg)**			***t*** **$_{1/2,Z}$ (min)**		
Drug	**Observed**	**Predicted**	**Percent[a]**	**Observed**	**Predicted**	**Percent[a]**	**Observed**	**Predicted**	**Percent[a]**
Phenytoin	0.640	0.573	10.5	0.574	0.483	15.9	792	822	3.79

Quinidine	3.20	3.69	22.2	2.91	3.25	11.7	470	785	67.0
Hexobarbital	1.27	0.735	42.1	3.57	4.25	19.0	261	120	54.0
Pentobarbital	0.999	1.57	57.2	0.524	0.964	84.0	1340	1126	16.0
Phenylbutazone	0.122[b]	0.0839[c]	31.2	0.0205	0.0162	21.0	4110	3590	12.7
Warfarin	0.108	0.109	0.926	0.0367	0.0165	55.0	2040	4560	124
Tolbutamide	0.112	0.116	3.57	0.180	0.0589	67.3	434	1360	214
Chlorpromazine	11.2[b]	9.05[c]	19.2	4.29	4.63	7.93	1810	1350	25.2
Propranolol	3.62	3.77	4.14	11.2	15.56	38.9	167	135	19.2
Pentazocine	5.56	7.19	29.3	18.3	11.6	36.6	203	408	101
Valproate	0.151	0.482	219	0.110	0.159	44.5	954	2110	121
Diazepam	0.950	1.44	51.6	0.350	2.13	509	1970	469	76.2
Antipyrine	0.869	0.878	1.04	0.662	0.664	3.02	654	917	40.2
Phenobarbital	0.649	0.817	25.9	0.0530	0.0825	55.7	6600	5870	11.0
Amobarbital	1.04	1.21	16.3	0.556	1.01	81.7	1360	827	39.2

[a]Absolute percent of error.

[b]The value of V_{SS}.

[c]Predicted from the value of V_{SS} in the rat.

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The application of MLP to pharmacokinetics has been described by . Initially, hepatic intrinsic clearance was considered to be related to volume or body weight. Indeed, a plot of the log drug clearance versus body weight for various animal species resulted in an approximately linear correlation (ie, a straight line). However, after correcting intrinsic clearance by MLP, an improved log–linear relationship was achieved between free drug Cl_{int} and body weight for many drugs. A possible explanation for this relationship is that the biochemical processes, including Cl_{int}, in each animal species are related to the animal's normal life expectancy (estimated by MLP) through the evolutionary process. Animals with a shorter MLP have higher basal metabolic rates and tend to have higher intrinsic hepatic clearance and thus metabolize drugs faster. () postulated a constant "life stuff" in each species, such that the faster the life stuff is consumed, the more quickly the life stuff is used up. In the fourth-dimension scale (after correcting for MLP), all species share the same intrinsic clearance for the free drug.

$$\frac{(\mathrm{MLP})(Cl_{\mathrm{int}})}{B} = \text{constant} \qquad (22.21)$$

$$Cl_{\mathrm{int}} = aB^{\times} \qquad (22.22)$$

Extensive work with caffeine in five species (mouse, rat, rabbit, monkey, and humans) by verified this approach. Caffeine is a drug that is metabolized predominantly by the liver. For caffeine,

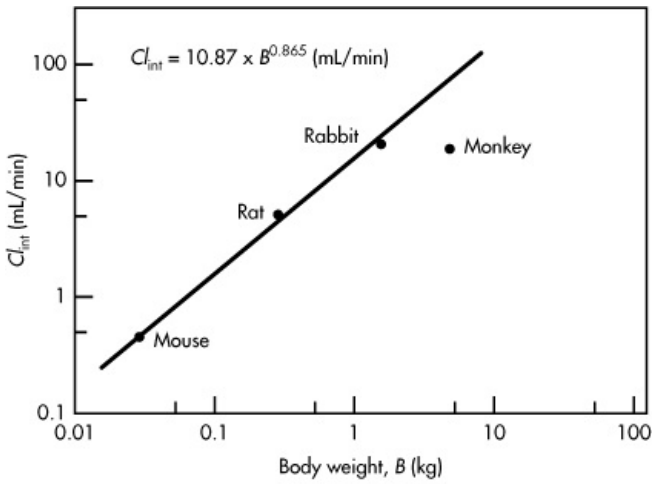
$$Q = 0.0554 \times B^{0.894}$$

$$L = 0.0370 \times B^{0.849}$$

where B is body weight, L is liver weight, and Q is blood flow.

Hepatic clearance for the unbound drug did not show a direct correlation among the five species (). After intrinsic clearance was corrected for MLP (calculation based on brain weight), an excellent relationship was obtained among the five species ().

Figure 22-6.



Caffeine Cl_{int} (free drug) in mammalian species as a function of body weight. Line does not utilize man and monkey points.

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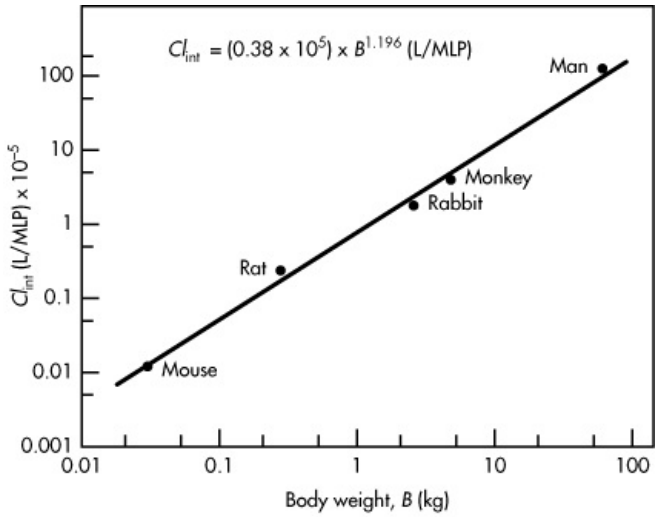
Figure 22-7.



Caffeine (free drug) Cl_{int} per maximum life-span potential (MLP) in mammalian species as a function of body weight. MLP values were calculated for monkeys, rabbits, rats, and mice employing the following numeric values: MLP = 10.389 x (brain weight)$^{0.636}$ x (body weight)$^{0.225}$.

()

More recently, the subject of interspecies scaling was investigated using *Cl* values for 91 substances for several species by . These investigators used $Y = a\ (BW)^b$ in their analysis, similar to Equation 22.19 above but with different symbols: Y = biological variable dependent on the body weight of the species, a = allometric coefficient, b = allometric exponent, BW = body weight of the species. One issue discussed by Hu and Hayton is the uncertainty in the allometric exponent (b) of xenobiotic clearance (CL). Published literature has focused on whether the basal metabolic rate scale is a 2/3 or 3/4 power of the body mass (BW). When the uncertainty in the determination of a b value is relatively large, a fixed-exponent approach might be feasible according to Hu and Hayton. In this regard, 0.75 might be used for substances that are eliminated mainly by metabolism or by metabolism and excretion combined, whereas 0.67 might apply for drugs that are eliminated mainly by renal excretion. The researchers pointed out that genetic (intersubject) difference may be a limitation for using a single universal constant.

Physiologic versus Compartment Approach

Compartmental models represent a simplified kinetic approach to describe drug absorption, distribution, and elimination (and). The major advantage of compartment models is that the time course of drug in the body may be monitored quantitatively with a

limited amount of data. Generally, only plasma drug concentrations and limited urinary drug excretion data are available. Compartmental models have been applied successfully to prediction of the pharmacokinetics of the drug and the development of dosage regimens. Moreover, compartmental models are very useful in relating plasma drug levels to pharmacodynamic and toxic effects in the body.

The simplicity and flexibility of the compartment model is the principal reason for its wide application. For many applications, the compartmental model may be used to extract some information about the underlying physiologic mechanism through model testing of the data. Thus, compartment analysis may lead to a more accurate description of the underlying physiologic processes and the kinetics involved. In this regard, compartmental models are sometimes misunderstood, overstretched, and even abused. For example, the tissue drug levels predicted by a compartment model represent only a composite pool for drug equilibration between all tissue and the circulatory system (plasma compartment). However, extrapolation to a specific tissue drug concentration is inaccurate and analogous to making predictions without experimental data. Although specific tissue drug concentration data are missing, many investigators may make general predictions about average tissue drug levels.

Compartment models account accurately for the mass balance of the drug in the body and the amount of drug eliminated. Mass balance includes the drug in the plasma, the drug in the tissue pool, and the amount of drug eliminated after dosage administration. The compartment model is particularly useful for comparing the pharmacokinetics of related therapeutic agents. In the clinical pharmacokinetic literature, drug data comparisons are based on compartment models. Though alternative pharmacokinetic models have been available for approximately 20 years, the simplicity of the compartment model allows easy tabulation of parameters such as V_{DSS}, alpha $t_{1/2}$, and beta $t_{1/2}$. The alternative pharmacokinetic models, including the physiologic and statistical moment (mean residence time) approaches, are used much less frequently, even though a substantial body of data has been generated using both of these models.

In spite of these advantages, the compartmental model is generally regarded as somewhat empirical and lacking physiologic relevance. Many disease-related changes in pharmacokinetics are the result of physiologic changes, such as impairment of blood flow or a change in organ mass. These pathophysiologic changes are better evaluated using a physiologic-based pharmacokinetic model.

Because of its simplicity, the compartment model often serves as a "first model" that requires further refinement in order to describe the physiologic and drug distribution processes in the body accurately. The physiologic pharmacokinetic model—which accounts for processes of drug distribution, drug binding, metabolism, and drug flow to the body organs—is much more realistic. Disease-related changes in physiologic processes are more readily related to changes in the pharmacokinetics of the drug. Furthermore, organ mass, volumes, and blood perfusion rates are often scalable, based on size, among different individuals and even among different species. This allows a perturbation in one parameter and the prediction of changing physiology on drug distribution and elimination.

The physiologic pharmacokinetic model may also be modified to include a specific feature of a drug. For example, for an antitumor agent that penetrates into the cell, both the drug level in the interstitial water and the intracellular water may be considered in the model. Blood flow and tumor size may even be included in the model to study any change in the drug uptake at that site.

The physiologic pharmacokinetic model can calculate the amount of drug in the blood and in any tissues for any time period if the initial amount of drug in the blood is known and the dose is given by IV bolus. In contrast, the tissue compartment in the compartmental model is not related to any actual anatomic tissue groups. The tissue compartment is needed when the plasma drug concentration data are fitted to a multicompartment model. In theory, when tissue drug concentration data are available, the multiple-compartment models may be used to fit both tissue and plasma drug data together, including the drug concentration in a specific tissue. In such a case, the compartment model would mimic the system of equations used in the physiologic model, except that in place of blood flows, transfer constants would be used to describe the mass transfer in the model. The latter approach would probably, at best, yield less useful information than that obtained from the physiologic model.

MEAN RESIDENCE TIME

After an intravenous bolus drug dose (D_0), the drug molecules distribute throughout the body. These molecules stay (reside) in the body for various time periods. Some drug molecules leave the body almost immediately after entering, whereas other drug molecules leave the body at later time periods. The term *mean residence time* (MRT) describes the average time for all the drug molecules to reside in the body. MRT may be considered also as the mean transit time or mean sojourn time. The residence time for the drug molecules in the dose may be sorted into groups i (i = 1, 2, 3, . . . , m) according to their residing time. The total residence time is the summation of the number of molecules in each group i multiplied by the residence time, t_i, for each group. The summation of n_i (number of molecules in each group) is the total number of molecules, N. Thus, MRT is the total residence time for all molecules in the body divided by the total number of molecules in the body, as shown in Equation 22.23:

$$\text{MRT} = \frac{\text{total residence time for all drug molecules in body}}{\text{total number of drug molecules}}$$

$$\text{MRT} = \frac{\sum_{i=1}^{m} n_i t_i}{N} \qquad (22.23)$$

where n_i is the number of molecules and t_i is the residence time of the ith group of molecules.

The drug dose (mg) may be converted to the number of molecules by dividing the dose (mg) by 1000 and the molecular weight of the drug to obtain the number of moles of drug, and then multiplying the number of moles of drug by 6.023×10^{23} (Avogadro's

number) to obtain the number of drug molecules. For convenience, Equation 22.23 may be written in terms of milligrams (instead of molecules) by substitution of n_i with $De_i \times f$, where De_i is the number of drug molecules (as mg) leaving the body with residence time t_i ($i = 1, 2, 3, \ldots, m$). The f is a conversion factor. The number of molecules or milligrams of drug cancels out in Equation 22.24, showing that MRT is independent of mass:

$$\text{MRT} = \frac{\sum_{i=1}^{m} De_i f t_i}{\sum_{i=1}^{m} De_i f} = \frac{\sum_{i=1}^{m} De_i t_i}{\sum_{i=1}^{m} De_i} \qquad (22.24)$$

where De_i ($i = 1, 2, 3, \ldots, m$) is the amount of drug (mg) in the ith group with residence time t_i.

Drug molecules may have a residence time ranging from values near zero (eg, 0.1, 0.2) to very large values (100, 1000, 10,000). The number of i groups may be large and the summation approach to calculate MRT will be only an approximation. Also, for the summation process to be accurate, data must be collected continuously in order not to miss any groups. Integration is an accurate method that replaces summation when the data or function needs to be continuously summed over time.

Mean Residence Time—IV Bolus Dose

The drug concentration in the body after an IV bolus injection for a drug that follows the pharmacokinetics of a one-compartment model is given by

$$C_p = \left(\frac{D_0}{V_D}\right) e^{-kt} \qquad (22.25)$$

$$D_p = D_0 e^{-kt} \qquad (22.26)$$

where V_D is the apparent volume of distribution, k is the first-order elimination rate constant, and t is the time after the injection of the drug. The drug exit rate was generated in with a numerical example until most drug was eliminated.

Table 22.4 Simulated Plasma Data after an IV Bolus Dose, Illustrating Calculation of MRT[a]

	Rate Eliminated	**Rate Eliminated**	
Time (hr)	***d*De/*dt* (mg/hr)**	**Time (*t*) x *dt* (mg/hr)**	**C_p (mg/L)**
0	231.000	0	100
1	183.354	183.354	79.374
2	145.535	291.070	63.002
3	115.517	346.551	50.007
4	91.690	366.762	39.693
5	72.778	363.891	31.506
6	57.767	346.602	25.007
7	45.852	320.964	19.849
8	36.395	291.156	15.755
9	28.888	259.990	12.506
10	22.929	229.293	9.926
42	0.014	0.593	0.006
43	0.011	0.482	0.005
44	0.009	0.392	0.004
45	0.007	0.318	0.003
46	0.006	0.258	0.002
47	0.004	0.209	0.002
48	0.004	0.170	0.002
49	0.003	0.137	0.001
Total drug exited = 1004.43[b]		Total drug residence time = 4310[c]	

[a]Drug exiting (first-order rate) tank or body compartment after IV bolus injection. Data generated with Equation 22.25. Dose = 1000 mg, volume = 10 L, $k = 0.231\ hr^{-1}$.

[b]Total drug exited = average rate x dt and sum total.

[c]Total drug residence time (expressed as mg hr) = rate x t x dt and sum total.

The rate of change in the amount of drug in the body with respect to time (dD_p/dt) reflects the rate at which the drug molecules leave the body at any time t. Although all drug molecules enter the body at the same time, the exit time, or the residing time, for each molecule is different. Equation 22.27 is obtained by taking the derivative of Equation 22.26, with all the drug molecules exiting the body from $t = 0$ to ∞ ():

$$\frac{dD_p}{dt} = -kD_0e^{-kt} \qquad (22.27)$$

Alternatively, the rate of drug molecules exiting at any time t is given by

$$\frac{d\mathrm{De}}{dt} = \frac{-dD_p}{dt} = kD_0e^{-kt} \qquad (22.28)$$

Rearranging yields

$$d\mathrm{De} = kD_0e^{-kt}dt \qquad (22.29)$$

At any time t, dDe molecules exit. Therefore, multiplying Equation 22.29 by t on both sides yields the residence for each molecule exiting with a residence time t. Summation of the residence time for each drug molecule, and division by the total number of molecules, estimates the mean residence time (Eq. 22.30):

$$\frac{\int_0^\infty dD_0e^{-kt}t}{D_0} = \frac{\int_0^\infty kD_0e^{-kt}t\,dt}{D_0} \qquad (22.30)$$

$$\mathrm{MRT} = \int_0^\infty ke^{-kt}t\,dt \qquad (22.31)$$

As shown in Equation 22.30, the MRT is related to the product of the elimination rate constant k and the function describing drug elimination in the body. MRT is the integrated normalized form of the differential function representing drug amount (or concentration) in the body. The term *differential probability* is used to reflect that the function is a *probability density function* (PDF), which represents the residence time probability of a molecule in the population. The mean residence time is the normalized (divided by D_0) differential of the function governing drug elimination in the body. When a function is normalized, it becomes dimensionless, without units.

Equation 22.30 was derived in terms of amount of drug. Because $D_0 = C^0_pV_D$, substituting for D_0 with $C^0_pV_D$ into the right side of Equation 22.30 yields

$$\frac{\int_0^\infty dD_et}{D_0} = \frac{\int_0^\infty kC_P^0t\,dt}{C_P^0} \qquad (22.32)$$

Equation 22.32 may be used to determine MRT directly or may be rearranged to Equation 22.33 by dividing the numerator and denominator by k to yield a moment equation.

$$\mathrm{MRT} = \frac{\int_0^\infty d\mathrm{D_e}\,t}{D_0} = \frac{\int_0^\infty C_P^0e^{-kt}t\,dt}{C_P^0/k} \qquad (22.33)$$

The plasma concentration equation [function $f(t)$] multiplied by time and integrated from 0 = ∞ gives a term called the *first moment* of the plasma drug curve. The denominator is the area under the curve, AUC^∞_0. The AUC^∞_0 is equal to $\int^\infty_0 C_p dt$ or D_0/V_Dk. Because $C^0_p = D_0/V_D$, the denominator of Equation 22.33 is the AUC^∞_0 of the time–concentration curve ($AUC^\infty_0 = D_0/kV_D$); see . Equation 22.33 is used in pharmacokinetics to determine MRT; the equation is abbreviated in the literature as shown in Equation 22.34:

$$\mathrm{MRT} = \frac{\mathrm{AUMC}}{\mathrm{AUC}} \qquad (22.34)$$

where AUMC is the area under the (first) moment-versus-time curve from $t = 0$ to infinity. AUC is the area under plasma time-versus-concentration curve from $t = 0$ to infinity. AUC is also known as the *zero moment curve.* shows how summation may be used to calculate MRT from generated data when the function is known.

Table 22.5 Equations and Parameters Used in Generating Data for Figure 22.8. Summation Method Was Used to Mimic Actual Calculation of MRT by the Moment Method[a]

Parameters	
$i = 0, \ldots, 50$	Number of groups summed

$t_i = 1 \times i$	Residence time t_i
$k = 0.231$	
Dose = 1000 mg Volume = 10 L	
$Db_i = 1000 \times \exp(-kt_i)$	Equation showing drug in body at t_i
$De_i = 1000k \times \exp(-kt_i)$	Equation showing drug exiting at t_i
$rt_i = De_i \times t_i$	
$\Sigma_i rt_i = 4.31 \times 10^3$	Total residence time found by summation, $MRT = \frac{4310}{1004.43} = 4.29$ hr
$\frac{1}{0.231} = 4.329$	MRT by calculation from $1/k$

[a]MATHCAD was used for calculation. Complete data generated are listed in .

Example

A drug that follows the kinetics of a one-compartment model is given by IV bolus injection at a dose of 1000 mg. The drug has an elimination rate constant of 0.231 hr^{-1} and a volume of distribution of 10 L. The body is considered as a single compartment with no drug permanently bound in the body. (Use for this problem; 50 data points were generated with Equation 22.25 for C_p and Equation 22.28 for dDe/dt.)

1. Calculate the MRT of the drug molecules in the body using the moment method. Assume AUC is 432.9 (mg/L) hr and AUMC is 1865.465 (mg/L)hr^2.

2. Calculate MRT using the total residence times of all molecules exited and divide by the total dose. Compare the answer to part 1.

Solution

1. Using the equation MRT = AUMC/AUC,

$$\text{MRT} = \frac{1865.465\ (\text{mg/L})\ \text{hr}^2}{432.9\ (\text{mg/L})\ \text{hr}} = 4.309\ \text{hr}$$

2. The residence time for most of the drug molecules exiting from the body (t = 0 to ∞) is approximated by the first 50 points (only few drug molecules remained in the body after 50 hours). Total residence time is the sum of the number of molecules at each exit time point multiplied by the time. The mean residence time is the sum of all the residence times for all drug molecules divided by the total number of molecules (Eq. 22.23). Multiplying columns 1 and 2 yields column 3:

$$\text{Total drug molecule residence time} = 4310\ \text{mg hr}$$
$$\text{Sum of drug exited} = 1004.43\ \text{mg}$$

(The sum of drug exited was obtained by averaging the rate of drug exited for each time point and multiplied by the time interval, 1 hour in this case; then sum up to obtain the total drug excreted. See .)

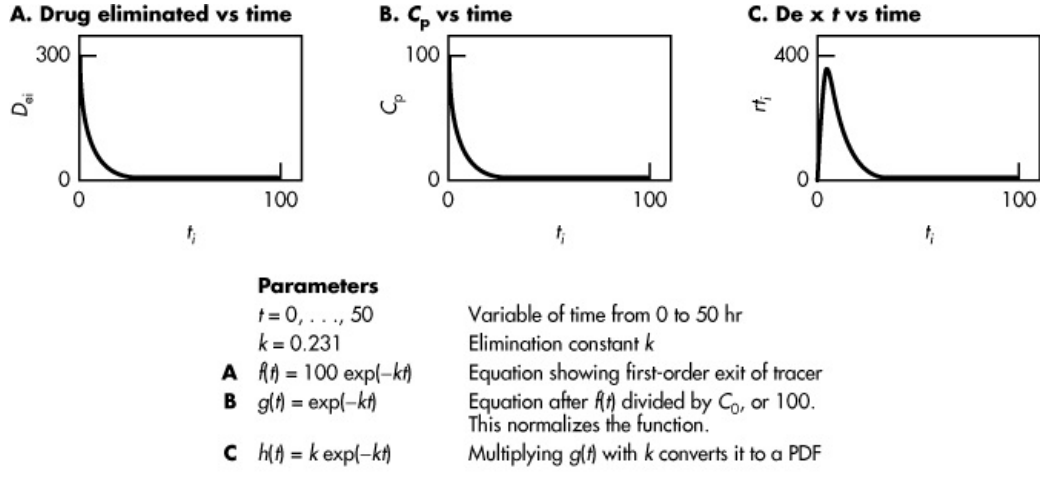
$$\text{MRT} = \frac{4310}{1004.43\ \text{hr}} = 4.29\ \text{hr}$$

The example is basically a verification of Equation 22.30. The approximation shows that when the function is not known, MRT may be estimated from the rate of drug excreted or from the plasma drug concentration–time curve. In practice, unless the entire dose is known, there is no assurance that all drug molecules are excreted through the plasma compartment if multiple compartments are involved.

MRT may also be calculated using the compartmental approach by considering the MRT for a drug after IV bolus injection as the reciprocal of the elimination rate constant, k. In this case, MRT is inversely related to the elimination constant, and MRT = 1/k. Therefore, MRT = 1/0.231 hr^{-1} = 4.329 hr. MRT was estimated earlier as 4.309 hr using the moment method. The slightly smaller value for the MRT here is due to approximation in the summation of the moment area and AUC.

Using the method of MRT = AUMC/AUC, MRT may be estimated using the AUC calculated from the C_p–t curve (). Alternatively, the MRT can be estimated accurately using integration when the function that describes plasma drug concentrations is known (). A plot of De and C_p versus time, and the moment curve De × t versus t, are shown in . For drugs that follow the kinetics of a one-compartment model with drug elimination only from the plasma, MRT may be calculated by either the area method or from the first moment curve. In data analysis, the function that governs drug disposition is generally not known, and the MRT is generally calculated from the plasma drug concentration–time curve.

Figure 22-8.

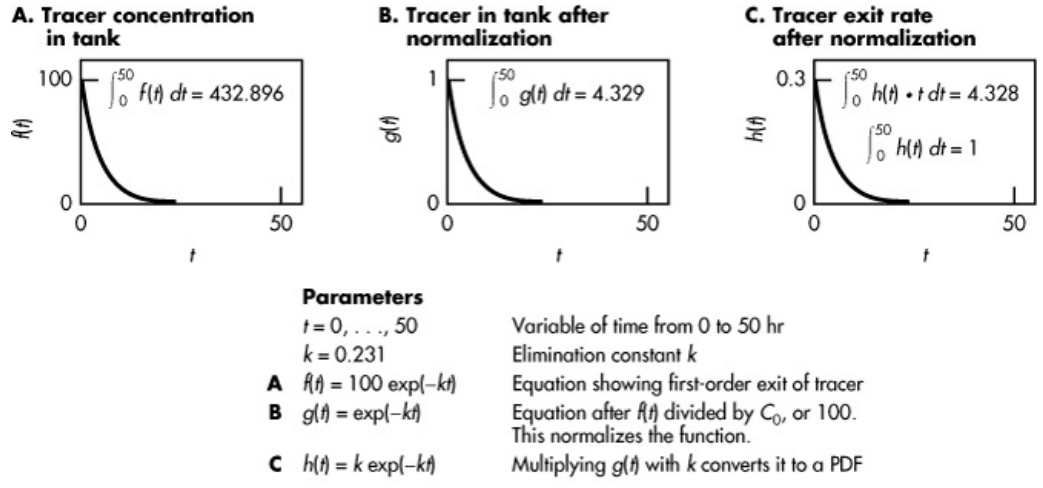


Plot of **(A)** drug eliminated versus time; **(B)** C_p versus time; and **(C)** De versus time. The data generated for these plots are tabulated in . The actual equations and parameters used are listed in .

STATISTICAL MOMENT THEORY

Statistical moment theory provides a unique way to study time-related changes in *macroscopic events.* A macroscopic event is considered as the overall event brought about by the constitutive elements involved. For example, in chemical processing, a dose of tracer molecules may be injected into a reactor tank to track the transit time (residence time) of materials that stay in the tank. The constitutive elements in this example are the tracer molecules, and the macroscopic events are the residence times shared by groups of tracer molecules. Each tracer molecule is well mixed and distributes noninteractively and randomly in the tank. In the case of all the molecules ($\int^{D_0}_0 dDe = D_0$) that exit from the tank, the rate of exit of tracer molecules ($-dDe/dt$) divided by D_0 yields the probability of a molecule having a given residence time t (). A mathematical formula describing the probability of a tracer molecule exited at any time is a probability density function. MRT is merely the expected value or mean of the distribution.

Figure 22-9.



Simulated tracer concentration in a tank over time. The three plots were generated by MATHCAD. The AUC under each curve is evaluated by integration. In **C,** the tracer concentration exit rate plot is a PDF and the AUC is 1. The mean of this function is simply the first moment and equal to the mean residence time of 4.328.

MRT provides a fundamentally different approach than classical pharmacokinetic models, which involve the concept of dose, half-life, volume, and concentration. The classical approach is macroscopic and does not account for the observation that molecules in a cluster move individually through space and are more appropriately tracked as statistical distribution based on residence-time

considerations. Consistent with the concept of mass and the dynamic movement of molecules within a region or "space," MRT is an alternative concept to describe how drug molecules move in and out of a system. The concept is well established in chemical kinetics, where the relationships between MRT and rate constants for different systems are known.

In the last two decades, MRT has been well characterized for various pharmacokinetic models, although MRT application is less developed in pharmacodynamics. In the future, the residence-time concept will probably be applied further in pharmacodynamics if a useful model can be developed relating MRT to the intensity and duration of drug action that yields more insight than a conventional pharmacokinetic model. Empirically, it has been observed that changing from a slow rate of IV injection of a fast-acting drug may result in quite different response in a subject compared to rapid injection of the same drug solution. This observation has been attributed to a transient change in concentration at the site. Alternatively, the response may be explained by modeling the MRT change of the drug at the site.

Example

Assume the tracer molecules are eliminated according to a kinetic function, $f(t) = C_0 e^{-kt}$. The tank volume V_D and k are similar to the previous one-compartment-model example (k = 0.231 hr^{-1}, D_0 = 1000 mg, V_D = 10). What is the MRT? What is the probability density function?

Because $f(t)$ describes drug elimination in terms of concentration units, $f(t)$ is divided by C_0 for normalization (). The function is then differentiated to obtain $h(t)$. Next, $h(t) = ke^{-kt}$ is plotted in . This is the PDF (probability density function), also obtained by $k \times C$. Integration of $h(t)\,tdt$ yields MRT (4.329 hours) directly. Integration of $f(t)$ yields the AUC of 432.896 (mg/L) hr. All integration in were computed using MATHCAD software.

In the one-compartment model, AUC divided by C_0 also yields MRT (432.896/100 = 4.33 hr). This example is another way to calculate MRT, as will be demonstrated later. MRT may also be computed by integrating $f(t)/C_0$ (). However, if $f(t)$ represents a two- or multicompartment function, the computed MRT using this method is only for the central compartment, whereas using the AUMC/AUC approach leads to an MRT for the body (a larger value). The latter method treats the molecules as a single population within the body, tracking them only as they exit and without supposing any knowledge of molecular exchanges between the plasma and tissue compartments.

In the previous discussion, Equation 22.34 was derived to estimate MRT without applying the concept of probability density functions. However, the equation may be rearranged in the form of a PDF, as in Equation 22.31. This result is plotted in for comparison. The moment theory facilitates calculation of MRT and related parameters from the kinetic function, as discussed below.

A probability density function $f(t)$ multiplied by t^m and integrated over time yields the moment curve (Eq. 22.35). The moment curve shows the characteristics of the distribution.

$$\mu_m \text{ or } m\text{th moment} = \int_0^\infty t^m f(t)\ dt \qquad (22.35)$$

where $f(t)$ is the probability density function, t is time, and m is the mth moment.

For example, when m = 0, substituting for m = 0 yields Equation 22.36, called the *zero moment,* μ_0:

$$\mu_0 = \int_0^\infty f(t)\ dt \qquad (22.36)$$

If the distribution is a true probability function, the area under the zero moment curve is 1.

Substituting into Equation 22.35 with m = 1, Equation 22.37 gives the first moment μ_1

$$\mu_1 = \int_0^\infty t^1 f(t)\ dt \qquad (22.37)$$

The area under the curve $f(t)$ times t is called the AUMC, or the *area under the first moment curve.* The *first moment,* μ_1, defines the *mean* of the distribution.

Similarly, when m = 2, Equation 22.35 becomes the *second moment,* μ_2:

$$\mu_2 = \int_0^\infty t^2 f(t)\ dt \qquad (22.38)$$

where μ_2 defines the variance of the distribution. Higher moments, such as μ_3 or μ_4, represent skewness and kurtosis of the distribution. Equation 22.35 is therefore useful in characterizing family of moment curves of a distribution.

The principal use of the moment curve is the calculation of the MRT of a drug in the body. The elements of the distribution curve describe the distribution of drug molecules after administration and the residence time of the drug molecules in the body.

In Equation 22.31, the plasma equation, $f(t) = C_{0\,p} e^{-kt}$, was converted to a PDF [ie, $f(t) = ke^{-kt}$]. It can be shown that μ_0 for this function = 1 (total probability adds up to 1 by summing zero moment), and the mean of the function is the area under the

first moment curve (the mean is the MRT).

By comparison, Equation 22.25 is not a true PDF, because its mean is not given by the AUMC, and its AUC is not 1. Nonetheless, Equation 22.34 may be used to calculate MRT independent of the PDF concept, although some confusion over its application appears in the literature.

Example

An antibiotic was given to two subjects by an IV bolus dose of 1000 mg. The drug has a volume of distribution of 10 L and follows a one-compartment model with an elimination constant of (1) 0.1 hr^{-1} and (2) 0.2 hr^{-1} in the two subjects. Determine the MRT from each C_p–time curve () and compare your values with the MRT determined by taking the reciprocal of *k*.

Table 22.6 Simulated Data for a Drug Administered by IV Bolus[a]

				Subjects 1 and 2	
	C_p1	C_p2	*t*	AUMC1	AUMC2
0	100.000	100.000	0	0.000	0.000
1	90.484	81.873	1	90.484	81.873
2	81.873	67.032	2	163.746	134.064
3	74.082	54.881	3	222.245	164.643
4	67.032	44.933	4	268.128	179.732
5	60.653	36.788	5	303.265	183.940
6	54.881	30.119	6	329.287	180.717
7	49.659	24.660	7	347.610	172.618
8	44.933	20.190	8	359.463	161.517
9	40.657	16.530	9	365.913	148.769
10	36.788	13.534	10	367.879	135.335
11	33.287	11.080	11	366.158	121.883
12	30.119	9.072	12	361.433	108.862
13	27.253	7.427	13	354.291	96.556
14	24.660	6.081	14	345.236	85.134
15	22.313	4.979	15	334.695	74.681
16	20.190	4.076	16	323.034	65.220
17	18.268	3.337	17	310.562	56.735
18	16.530	2.732	18	297.538	49.183
19	14.957	2.237	19	284.180	42.504
20	13.534	1.832	20	270.671	36.631
21	12.246	1.500	21	257.158	31.491
22	11.080	1.228	22	243.767	27.010
23	10.026	1.005	23	230.595	23.119
24	9.072	0.823	24	217.723	19.751
25	8.208	0.674	25	205.212	16.845
26	7.427	0.552	26	193.111	14.343
27	6.721	0.452	27	181.455	12.195
28	6.081	0.370	28	170.268	10.354
29	5.502	0.303	29	159.567	8.780
30	4.979	0.248	30	149.361	7.436
91	0.011167	0.00000125	91	1.0162	0.0001135
92	0.010104	0.00000102	92	0.9296	0.0000939
93	0.009142	0.00000084	93	0.8502	0.0000777
94	0.008272	0.00000068	94	0.7776	0.0000643
95	0.007485	0.00000056	95	0.7111	0.0000532
96	0.006773	0.00000046	96	0.6502	0.0000440
97	0.006128	0.00000038	97	0.5944	0.0000364
98	0.005545	0.00000031	98	0.5434	0.0000301

99	0.005017	0.00000025	99	0.4967	0.0000249
100	0.004540	0.00000021	100	0.4540	0.0000206

[a](1) k = 0.1 hr^{-1}, (2) k = 0.2 hr^{-1}.

Note the corresponding AUMC for the two subjects in the last two columns.

Solution

***Noncompartmental Approach* (MRT = AUMC/AUC)**

1. From , multiply each time point with the corresponding plasma C_p to obtain points for the moment curve. Use the trapezoid rule and sum the area to obtain area under the moment curve ($AUMC_1$) for subject 1. Also, determine the area under the plasma curve using the trapezoid rule.

2. The steps are as follows.

a. Multiply each C_p by t as in column 5 of .

b. Sum all $C_p \times t$ values, and find the area under the moment curve (AUMC)—that is, 9986.45 (μg/mL) hr^2.

c. Estimate tail area of the moment curve (beyond the last data point) using the equation

$$\text{AUMC} = \frac{C_P t}{k} + \frac{C_P}{k^2} \qquad (22.39)$$

Substituting the last data point, C_p = 0.00454 μg/mL, the last time point, 100 hours, and the last moment curve point, 0.454 (μg/mL) hr^2:

$$\text{Tail AUMC} = \frac{0.454}{0.1} + \frac{0.00454}{0.1^2} = 4.99\ (\mu\text{g/mL})\ \text{hr}^2$$

$$\text{Total AUMC} = 9986.46 + 4.99 = 9991.45\ (\mu\text{g/mL})\ \text{hr}^2$$

(Note that k is determined from the slope to be 0.1 hr^{-1}.)

d. Estimate AUC using the trapezoid rule from columns 1 and 2 (AUC = 1000.79 μg/mL/hr).

$$\text{e. MRT} = \frac{\text{AUMC}}{\text{AUC}} = \frac{9991.45\ (\mu\text{g/mL})\ \text{hr}^2}{1000.79\ (\mu\text{g/mL})\ \text{hr}} = 9.98\ \text{hr}$$

When data are available for a long period, 6 to 7 half-lives and beyond, the last C_p will be very small and no extrapolation will be needed. If a model-independent approach is needed, no extrapolation beyond the data should be used (in this example, extrapolation was used only for illustration). Instead, additional data should be collected, or the assay sensitivity improved so that more data at later time periods may be obtained. All data extrapolation, linear or log-linear, will be subject to error, because the real rate process is determined from the experimental data and is not assumed.

Note that without the extrapolation to infinity, MRT = 9986.45/1000.79 = 9.978 hours, because extensive plasma drug concentration data are available. This value is fairly close to the value of 9.98 hours when the plasma drug concentration data are extrapolated to infinity.

2. From the tabulated results, summing up column 6, $AUMC_2$ = 2491.68 (μg/mL) hr^2. AUC for patient 2 = 500 (μg/mL) hr (calculated from the trapezoid rule using the time–plasma concentration data for subject 2).

(*Note:* In this case, the AUMC tail area was not extrapolated because the drug concentration was already very low at the last data point.)

$$\text{MRT} = \frac{2491.68\ (\mu\text{g/mL})\ \text{hr}^2}{500\ (\mu\text{g/mL})\ \text{hr}} = 4.98\ \text{hr}$$

Compartment Approach

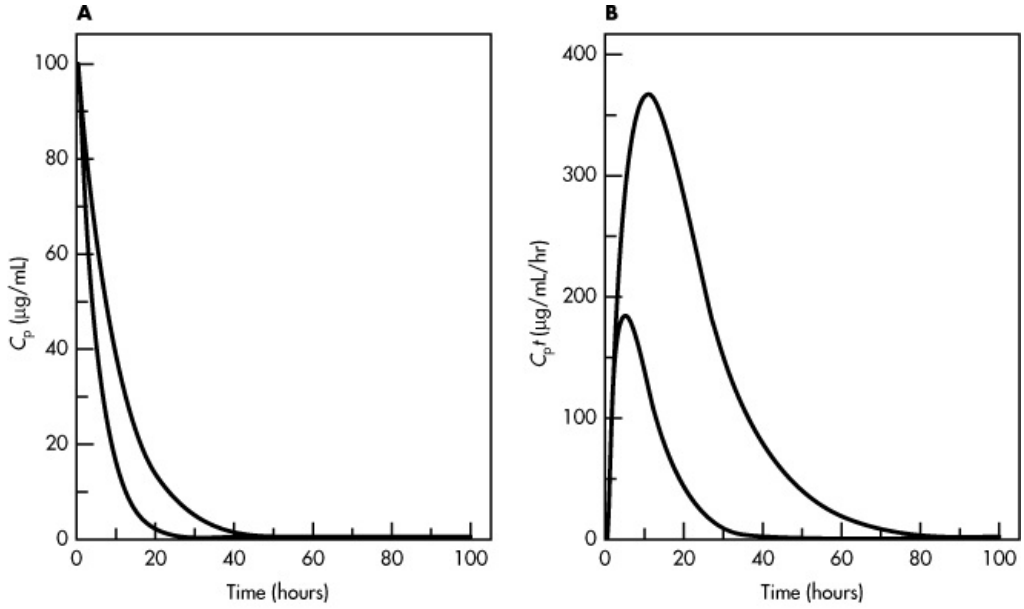
1. If a one-compartment model is assumed and k is determined from the slope, MRT is simply $1/k$ = 1/0.1 = 10 hours.

2. As determined from the slope of a C_p–t curve, k = 0.2 hr^{-1}, and MRT = 1/0.2 = 5 hours.

In a one-compartment model IV bolus, MRT is inversely proportional to the elimination constant and directly proportional to the half-life of the drug in the patient. The elimination half-lives of the drug in the two patients are 6.93 and 3.47 hours, respectively.

The plasma drug concentration–time curves for the two cases above were plotted with the moment curves. The use of moment ($C_p \times t$) changes the typical monoexponential plasma–time curve into a profile very similar to that of a nonsymmetric bell-shaped curve () similar to a statistical distribution (see). Furthermore, in the one-compartment IV bolus case, the mean of the distribution may be seen as 10 and 5 hours, respectively, from the curve. A smaller k widens the distribution and increases the total residence times of all the drug molecules in the body. The shape of the moment curve depends on the function describing the plasma drug concentration, and may be skewed.

Figure 22-10.



Simulated plasma drug concentration curves (left) and the corresponding AUMC curves (right). Dose = 1000 mg, V_D = 10 L, k = 0.1, and 0.2 hr^{-1}, by IV bolus administration.

MRT for Multicompartment Model with Elimination from the Central Compartment

The moment theory provides a means for calculating MRT for the body from plasma drug concentration data obtained for drugs that follow one-compartment models. In this section, the MRT is determined for a drug that has a plasma (central) compartment and one or more tissue or peripheral compartments. The assumptions are (1) that the drug is eliminated only from the central compartment and (2) that all drug is eliminated by a linear process (constant clearance). The MRT for a multicompartment model drug is the summation of the residence time of the drug in each compartment,

$$\mathrm{MRT_{body}} = \mathrm{MRT_c} + \mathrm{MRT_{p1}} + \mathrm{MRT_{p2}} + \cdots + \mathrm{MRT_{pn}} \qquad (22.40)$$

where MRT_{pi} represents MRT in the ith peripheral or tissue compartments and $\mathrm{MRT_c}$ = MRT for the central compartment.

MRT for the body may be calculated from the plasma concentration curve using AUMC/AUC as discussed earlier, because the body (including all compartments) may be treated as a single compartment.

$\mathrm{MRT_c}$ is known as the mean residence time or mean transit time for the central compartment. This is calculated by AUC/C^0_p, where AUC is the area under the plasma drug concentration curve and C^0_p is the initial plasma drug concentration curve.

DERIVATION OF $\mathrm{MRT_C}$

Let

De = amount of drug eliminated at time t

D_0 = does or drug at time zero

D_P = amount of drug in the plasma compartment from which drug is eliminated at time t

C_P = drug concentration in the plasma compartment (volume, V_D)

At time t, $d\mathrm{De}$ units of drug are eliminated, the residence time is $t d\mathrm{De}$, and integrating from D^{∞}_e yields the total residence time (see the numerator of Eq. 22.41). Integrating De will yield the total units of drug eliminated (see the denominator of Eq. 22.41), and MRT is obtained by dividing the total residence time by the total unit of drugs. If elimination occurs only from the central compartment, then at any instant dt, $d\mathrm{De} = -d\mathrm{D_p}$.

$$\mathrm{MRT_c} = \frac{\int_0^{\mathrm{De}^0} t\, d\mathrm{De}}{\int_0^{\mathrm{De}^0} d\mathrm{De}} = \frac{\int_0^{\mathrm{D_o}} t\, d\mathrm{D_p}}{\int_0^{\mathrm{D_o}} d\mathrm{D_p}} \qquad (22.41)$$

$$\mathrm{MRT_C} = \frac{\int_0^{C_\mathrm{P}^0} tV_\mathrm{D}\, dC_\mathrm{P}}{\int_0^{C_\mathrm{P}^0} V_\mathrm{D}\, dC_\mathrm{P}} = \frac{\int_0^{C_\mathrm{P}^0} t\, dC_\mathrm{P}}{\int_0^{C_\mathrm{P}^0} dC_\mathrm{P}} \qquad (22.42)$$

Since

$$t\, dC_\mathrm{P} = -C_\mathrm{P}\, dt \qquad \text{and} \qquad \int_0^0 dC_\mathrm{P} = C_\mathrm{P}^0$$

$$\mathrm{MRT_c} = \frac{\int_0^\infty C_\mathrm{P}\, dt}{C_\mathrm{P}^0} = \frac{\mathrm{AUC}_0^\infty}{C_\mathrm{P}^0} \qquad (22.43)$$

When a drug is distributed between a central and one or more peripheral compartments, the peripheral compartment is not available for sampling. Therefore, both the drug and tissue MRT have to be determined from the plasma data. If a two-compartment model is involved, the peripheral MRT is given by

$$\mathrm{MRT_P} = \frac{\mathrm{AUMC}}{\mathrm{AUC}} - \frac{\mathrm{AUC}}{C_\mathrm{P}^0} \qquad (22.44)$$

EXAMPLE

The plasma drug concentrations of a drug that follows a two-compartment model after IV bolus were simulated with the following parameters () and the plasma concentration equation for the two-compartment model. Determine MRT for the plasma and tissue compartments and verify Equation 22.43. Use these parameters: a = 2.2346, b = 0.4654, k = 0.946 (overall elimination constant from the central compartment), k_{12} = 0.655, k_{21} = 1.1 (all rate constants in hr^{-1}). Also, V_p = 10 L, D_0 = 1000 mg, C_0 = 100 µg/mL.

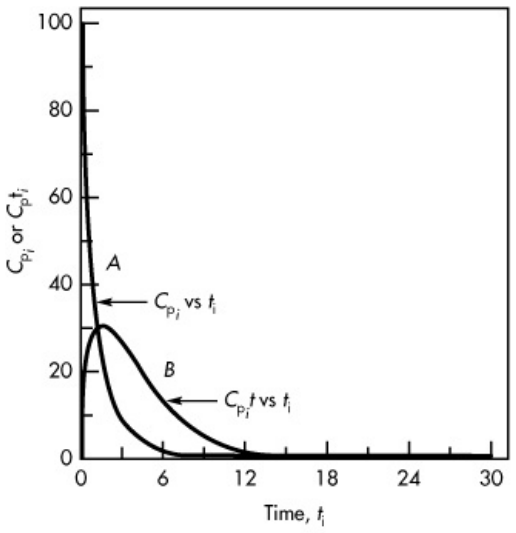
Using the above parameters, the plasma drug concentrations, C_p, at any point is given by Equation 22.45 () and is plotted in .

Table 22.7 Simulated Data Showing How to Calculate MRT from AUMC/AUC; 50 Points Were Generated Using Two-Compartment Equation after IV Bolus

t	C_p	AUC	$C_\mathrm{p}t$	AUMC
0	100	21.076	0	2.144
0.25	68.611	14.752	17.153	5.232
0.5	49.404	10.838	24.702	6.585
0.75	37.302	8.336	27.976	7.170
1	29.386	6.670	29.386	7.419
1.25	23.974	5.508	29.968	7.513
1.5	20.092	4.658	30.138	7.523
1.75	17.170	4.006	30.048	7.475
2	14.876	3.485	29.752	7.377
10	0.342	0.081	3.416	0.817
10.25	0.304	0.072	3.117	0.745
10.5	0.271	0.064	2.842	0.679
10.75	0.241	0.057	2.590	0.619
11	0.214	0.051	2.359	0.563
11.25	0.191	0.045	2.148	0.513
11.5	0.17	0.040	1.954	0.467
11.75	0.151	0.036	1.778	0.424
12	0.135	0.032	1.616	0.386
12.25	0.12	0.028	1.469	0.35

Total sum of column		106.6		177.915

Figure 22-11.



Plot of (*A*) C_p and (*B*) C_p versus time $C_p dt$ after a bolus dose IV.

$$C_p = 100\left[\left(\frac{k_{21} - a}{b - a}\right)e^{-at} - \left(\frac{k_{21} - b}{a - b}\right)e^{-bt}\right] \qquad (22.45)$$

The AUMC is found by determining the $C_p \times t$ at each point and summing up for the entire curve (). The AUMC = 177.915 and the AUC = 106.6. The MRT of the drug in the body is 1.67 hours. MRT of the drug in the plasma is AUC/C_0 = 106.6/100 = 1.066 hours. The MRT for the tissue compartment is 1.67 – 1.066 = 0.604 hour.

From statistical moment theory, MRT is the mean of the statistical distribution, $k \times C_p \times dt$, where k is the elimination constant and each C_p has been normalized by dividing by C_0 (to give a PDF). MRT for the body is then simply the first moment of the distribution:

$$\text{MRT} = \int_0^\infty \frac{100}{C_0}\left[\left(\frac{k_{21} - a}{b - a}\right)e^{-at} - \left(\frac{k_{21} - b}{a - b}\right)e^{-bt}\right]k\,dt \qquad (22.46)$$

$$\text{MRT} = 1.687 \text{ hr}$$

The answer should agree with that given above, by AUMC/AUC. The second method illustrates the relationship of the plasma concentration data and the PDF. Because k (the elimination constant from the central compartment) is not known from plasma data, the second approach is not applied directly. The PDF approach may also be used to determine MRT_c, or mean residence time from the central compartment. Taking the derivative of the two-compartment equation for plasma drug concentration yields a PDF; this function may be calculated directly using software such as MATHCAD. Integration of the result yields MRT = 1.066 hours (the mean of the PDF), the same as that calculated using AUC/C^0_p. AUMC/AUC of the differential function also yields an MRT of 1.066 hours.

In contrast, when AUMC/AUC is applied to the plasma drug concentration equation directly, AUC/C^0_p yields 1.066 hours, while AUMC/AUC yields 1.687 hours. The latter approach has caused some controversy in the literature because two different definitions were independently derived that apply independently during calculation. When the PDF approach is applied, this confusion is avoided. When the PDF is applied to the equation describing the drug in the body, an MRT of 1.687 hours is obtained, which is the sum of MRT in the tissue and the plasma compartment. In each case, MRT is simply the mean of the distribution that has a definite variance. The MRT may still be calculated without any knowledge of the distribution function, in which case the MRT is the ratio of two area-under-the-curve terms used in calculating V_{SS} or *Cl*. The two approaches are contrasted below.

Analysis Based on *f*(t), the Function Describing Plasma Drug Concentration

$$f(t) = \frac{(k_{21} - a)e^{-at}}{b - a} + \frac{(k_{21} - b)e^{-bt}}{a - b}$$

$$\int_0^{50} f(t)\,t\,dt = \mathrm{AUC}_0^{\infty} = 1.058$$

$$\int_0^{50} f(t)\,t\,dt = \mathrm{AUMC}_0^{\infty} = 1.784$$

$$\frac{\mathrm{AUMC}}{\mathrm{AUC}} = \frac{1.784}{1.058} = 1.688$$

$$\mathrm{MRT} = \frac{\mathrm{AUC}}{C_{\mathrm{P}}^0} = \frac{1.058}{1} = 1.058$$

Analysis Based on Differential Function, *f'(t)*, the Derivative of *f(t)*

$$g(t) = \frac{(k_{21} - a)\,e^{-at}}{b - a}(a) + \frac{(k_{21} - b)\,e^{-bt}}{a - b}(b)$$

$$\int_0^{50} g(t)\,t\,dt = \mathrm{AUMC}_0^{\infty} = 1.058 \qquad (\text{MRT from PDF})$$

$$\int_0^{50} g(t)\,dt = \mathrm{AUC}_0^{\infty} = 1$$

$$\frac{\mathrm{AUMC}}{\mathrm{AUC}} = \frac{1.058}{1} = 1.058 \qquad (\text{MRT using AUMC/AUC})$$

The first approach depends on $C^0{}_{\mathrm{p}}$ evaluation. The second approach allows two ways to evaluate MRT. The two approaches agree with each other.

The Model-Independent and Model-Dependent Nature of MRT

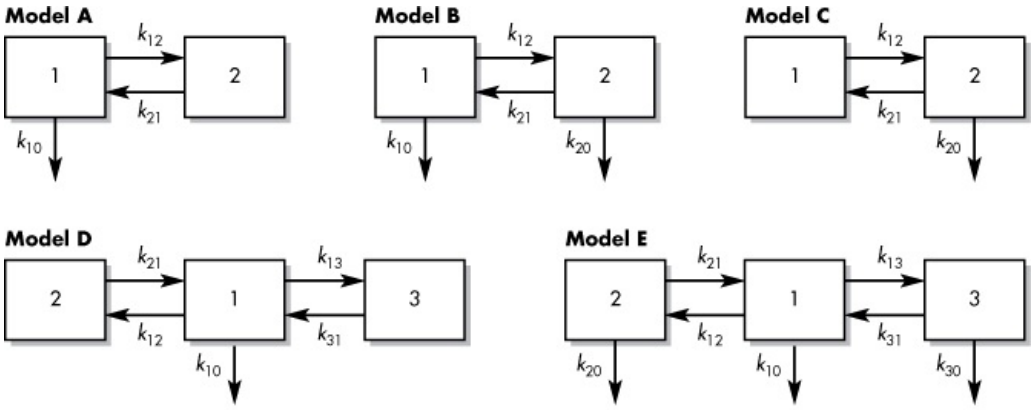
MRT evaluated from AUMC/AUC assumes that most drugs are excreted through the central compartment or that they are metabolized in highly vascular tissues that kinetically are considered part of the central compartment. For drugs eliminated through tissues that are not part of the central compartment, the MRT calculated by AUMC/AUC is smaller than that calculated by considering both peripheral and central compartment elimination.

Compare models A and B generated by in and . Both models A and B have identical rate constants except that model B has an elimination rate constant, k_{20}, from the peripheral compartment. MRT calculated using the new approach, referred to as MRT (new), is 1.687 hours for model A and 2.212 hours for model B. The new equation for MRT (new) of model B is

$$\mathrm{MRT\ (new)} = \frac{\mathrm{AUMC}}{\mathrm{AUC}} + \frac{k_{20}\,V_2}{E_2\,Cl} \qquad (22.47)$$

where k_{20} = elimination rate for drug eliminated in compartment 2; V_2 = the distribution volume of compartment 2; E_2 = the sum of rate constants exiting from compartment 2 (in model B, $E_2 = k_{20} + k_{21}$); *Cl* = total body clearance; $\mathrm{MRT_c}$ = MRT from the central compartment; $\mathrm{MRT_p}$ = MRT from the peripheral or tissue compartment, also referred to as $\mathrm{MRT_t}$; MRT = AUMC/AUC; and MRT (new) = MRT as calculated with correction for peripheral elimination.

Figure 22-12.



The three possible linear two-compartment open models and two possible three-compartment models. In each case, the concentration in compartment 1 (the central compartment) represents the measurable concentration of drug.

()

Table 22.8 Parameter Values for Models Depicted in Figure 22-12 Consistent with the Following Equations: $C_p = 64.131e^{-2.2346t} + 35.869e^{-0.4654t}$ for Models A, B, and C; and $C_p = 53.55e^{-0.1212t} + 18.4e^{-0.0361t} + 28.013e^{-0.01049t}$ for Models D and E

	Two-Compartment Models			Three-Compartment Models	
Parameter	**Model A**	**Model B**	**Model C**	**Model D**	**Model E**
Dose (D_0)	1000	1000	1000	1000	1000
V_1	10	10	10	10	10
V_{SS}	15.95	20.91	24.55	20.73	25.83
V_{area}	20.32	28.91	35.21	26.31	34.80
Cl	9.455	9.455	9.455	0.276	0.276
k_{12}	0.655	1.2	1.6	0.0323	0.0379
k_{21}	1.1	0.6	0.45	0.0693	0.0593
k_{10}	0.946	0.4	0	0.0276	0.0118
k_{20}	0	0.5	0.65	0	0.01
k_{13}	—	—	—	0.0146	0.0249
k_{31}	—	—	—	0.024	0.0141
k_{30}	—	—	—	0	0.01
f_1	1.0	0.423	0	1.0	0.4265
f_2	0	0.577	1	0	0.1983
f_3	—	—	—	0	0.3752
MRTC	1.058	1.058	1.058	36.23	36.23
$MRTP_2$	0.629	1.154	1.538	16.89	19.83

$MRTP_3$	—	—	—	22.07	37.52
MRT from Eq. 22.48	1.687	2.212	2.596	75.19	93.57
AUMC	178.4	178.4	178.4	272335	272335
AUC	105.8	105.8	105.8	3622	3622
AUMC/AUC	1.687	1.687	1.687	75.19	75.19
MRT from urine	1.687	1.687	ND[a]	75.19	75.19

[a]Intact drug will not be measured in urine.

From , with permission.

The equation also applies for other multicompartment models. For a three-compartment model, (model E), a third term is added to Equation 22.47 to reflect drug exiting in compartment 3, as in Equation 22.48.

$$\text{MRT (new)} = \frac{\text{AUMC}}{\text{AUC}} + \frac{k_{20}V_2}{E_2Cl} + \frac{k_{30}V_3}{E_3Cl} \qquad (22.48)$$

From , MRT (new) calculated using Equations 22.47 and 22.48 is model dependent. The original MRT calculated using AUMC/AUC yields the same MRT value of 1.687 hours for models A, B, and C. The original method, frequently quoted as a model-independent method for calculating MRT from plasma data, in effect, treats the body as a single unit from which drugs are eliminated from the plasma pool regardless of the true nature of the model. Unfortunately, it is not possible to know, from plasma data alone, whether drug elimination occurs in the peripheral compartment. Therefore, it is not possible to interpret unambiguously the calculated MRT parameters without making some assumptions. and showed that MRT is related to V_{SS} and clearance (Eq. 22.49), as illustrated in . The clearances among models A, B, and C are identical, showing that clearance is site independent and may be calculated through MRT. However, the three-compartment model clearances were clearly different.

$$\text{MRT} = \frac{Cl}{V_{SS}} \qquad (22.49)$$

MRT is useful in calculating the steady-state volume of distribution and additional parameters in compartmental and other models. In the compartmental models, MRT may give some idea of how long the drug molecules stay in the peripheral compartment. For example, for the drug digoxin, MRT for the body is 49.5 hours; for the central and peripheral compartments, MRT is 3.68 hours and 45.8 hours as calculated (). The peripheral MRT is the mean total time the drug molecules spend in the peripheral tissue, considering the first entry as well as possibly subsequent entries into the peripheral tissue from the central, general systemic circulation. An overview of MRT values for various pharmacokinetic models is given in .

Table 22.9 Mean Residence Time for Different Pharmacokinetic Models

Model	MRT
One-compartment bolus IV	$1/k$
One-compartment oral bolus	$1/k_a + 1/k$
Two-compartment bolus IV	$(k_{12} + k_{21})/kk_{21}$ [a]
Two-compartment oral bolus	$1/k_a + (k_{12} + k_{21})/kk_{21}$
One-compartment infusion (for period τ)	$1/k + \tau/2$
Two-compartment IV bolus	$\text{AUMC} = A_1/a^2 + A_2/b^2$

[a]Alternatively, this may be calculated as $1/a + 1/b - 1/k_{21}$.

Compiled from and .

Mean Absorption Time (MAT) and Mean Dissolution Time (MDT)

After IV bolus injecton, the rate of systemic drug absorption is zero, because the drug is placed directly into the bloodstream. The MRT calculated for a drug after IV bolus injection basically reflects the elimination rate processes in the body. After oral drug administration, the MRT is the result of both drug absorption and elimination. The relationship between the *mean absorption time,* MAT, and MRT is given by

$$\mathrm{MRT}_{\mathrm{oral}} = \mathrm{MAT} + \mathrm{MRT}_{\mathrm{IV}} \qquad (22.50)$$

$$\mathrm{MAT} = \mathrm{MRT}_{\mathrm{oral}} - \mathrm{MRT}_{\mathrm{IV}} \qquad (22.51)$$

For a one-compartment model, $\mathrm{MRT}_{\mathrm{IV}} = 1/k$:

$$\mathrm{MAT} = \mathrm{MRT}_{\mathrm{oral}} - \frac{1}{k}$$

In some cases, IV data are not available and an MRT for a solution may be calculated. The *mean dissolution time* (MDT), or *in-vivo* mean dissolution time, for a solid drug product is

$$\mathrm{MDT}_{\mathrm{solid}} = \mathrm{MRT}_{\mathrm{solid}} - \mathrm{MRT}_{\mathrm{solution}} \qquad (22.52)$$

MDT reflects the time for the drug to dissolve *in vivo*. Equation 22.52 calculates the *in-vivo* dissolution time for a solid drug product (tablet, capsule) given orally. MDT has been evaluated for a number of drug products. MDT is most readily estimated for the drugs that follow the kinetics of a one-compartment model. MDT is considered model independent because MRT is model independent. MDT has been used to compare the *in-vitro* dissolution versus *in-vivo* bioavailability for immediate-release and extended-release drug products (and). Even with complete experimental data, the parameters obtained are quite dependent on the method of computation method employed.

EXAMPLE

Data for ibuprofen () are shown in . Serum concentrations for ibuprofen after a capsule and a solution are tabulated as a function of time in and .

Table 22.10 Serum Concentrations for Capsule Ibuprofen

Time (hr)	C_p	$C_p t$	$tC_p \Delta t$
0	0	0	
0.167	0.06	0.01002	0.000836
0.333	3.59	1.195	0.1000
0.50	7.79	3.895	0.425
1	13.3	13.300	4.298
1.5	14.5	21.750	8.762
2	16.9	33.80	63.887
3	16.6	49.80	41.80
4	11.9	47.60	48.70
6	6.31	37.86	85.46
8	3.54	28.32	66.18
10	1.36	13.60	41.92
12	0.63	7.56	21.16
			Total AUMC = 382.695

$k = 0.347\ \mathrm{hr}^{-1}$, $\mathrm{AUC}^{\infty}_{0} = 91.5$

$$\text{AUMC of tail piece} = \frac{C_p' t}{k} + \frac{C_p}{k^2} = \frac{(0.63)(12)}{0.347} + \frac{0.63}{0.347^2}$$

$$(\text{extrapolation to } \infty) \qquad = 21.79 + 5.23 = 27.02$$

$$\mathrm{AUMC}^{\infty}_{0} = 382.695 + 27.02 = 409.72$$

$$\mathrm{MRT}_{\mathrm{product}} = \frac{409.72}{91.5} = 4.48\ \mathrm{hr}$$

Data adapted from , with permission.

Table 22.11 Serum Concentrations for Solution Ibuprofen

Time (hr)	C_p	$C_p t$	$tC_p \Delta t$
0	0	0	
0.167	17.8	2.973	0.248
0.333	29.0	9.657	1.048
0.5	29.7	14.85	2.046
1	25.7	25.7	10.14

1.5	19.7	29.55	13.81
2	17.0	34.0	15.88
3	11.0	33.0	33.50
4	7.1	28.4	30.70
6	3.82	22.92	51.33
8	1.44	11.52	34.45
10	0.57	5.70	17.22
12	0.38	4.56	10.26
			Total AUMC = 220.64

k = 0.455 hr^{-1}, AUC^{∞}_{0} = 88.5

$$\text{AUMC (tailpiece, extrapolation to } \infty) = \frac{C_p t}{k} = \frac{C_p}{k^2} = \frac{(0.38)(12)}{0.455} + \frac{0.38}{0.455^2}$$
$$= 10.02 + 1.84 = 11.86$$

$AUMC^{\infty}_{0}$ = 220.64 + 11.86 = 232.50 (μg/mL) hr^2

$$MRT_{solution} = \frac{232.50}{88.5} = 2.63 \text{ hr}$$

Data adapted from , with permission.

The MRT was determined using the trapezoid method and Equation 22.43. The MRT for the solution was 2.63 hours and for the product was 4.48 hours. Therefore, MDT for the product is 4.48 – 2.63 = 1.85 hours.

$$MAT_{solution} = MRT_{solution} - \frac{1}{k} = 2.63 - \frac{1}{0.455} = 2.2 \text{ hr}$$

$$MAT_{product} = MRT_{product} - \frac{1}{k} = 4.48 - \frac{1}{0.347} = 4.48 - 2.88 = 1.6 \text{ hr}$$

Applying Equation 22.52 directly (),

$$MDT = 4.48 - 2.63 = 1.85 \text{ hr}$$

Alternatively,

$$MDT = MAT_{product} - MAT_{solution} = 2.69 - 2.2 = 0.49 \text{ hr}$$

The MDT obtained for the product differs according to the method of calculation. Therefore, the errors in calculating the elimination constant, k, may greatly affect the values for MAT and MDT. Equation 22.52 is recommended because it is less affected by k. When the above data are fitted to an oral one-compartment model and the AUMC and AUC are calculated using Equation 22.34, the results in are obtained.

Table 22.12 Parameters for Capsule and Solution Ibuprofen

Parameter	Units	Capsule	Solution
AUC	(μg/mL) hr	92.55	85.50
AUMC	(μg/mL) hr^2	396.1	210.5
k_a	hr^{-1}	0.46	4.90
k	hr^{-1}	0.47	0.437
MRT	hr	4.28	2.49

Parameters were calculated from data of .

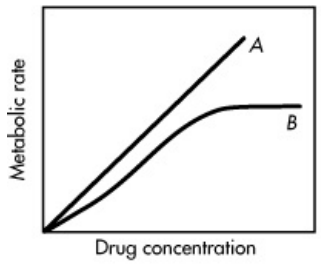
SELECTION OF PHARMACOKINETIC MODELS

Several objectives should be considered when using mathematical models to study rate processes (eg, pharmacokinetics of a drug). The primary objective in developing a model is to conceptualize the kinetic process in a quantitative manner that can be tested experimentally (). A model that cannot be tested is weak and will not improve or yield new knowledge about the process. In contrast, a wrong model that can be tested may be useful if the proposed hypotheses and its subsequent rejection leads to the correct model. To be statistically vigorous, a hypothesis or model is tested with the *null hypothesis* (H_0) (). Only after rejection of the null hypothesis (tested beyond chance probability) is the hypothesis accepted. When the null hypothesis is rejected, the probability (eg, $p < 0.05$) means that the chance of error is less than 5% and the hypothesis or model is accepted.

In fitting data using linear regression, the correlation of coefficient, r^2, is calculated, where r^2 is an indication of how well the data are predicted by the model. For example, $r = 0.9$ or $r^2 = 0.81$ indicates that 81% of the data agree with the model. The r^2 is not always a very good criterion. The sum of the squared differences (between the observed and predicted data) is a better criterion.

Adequate experimental design and the availability of valid data are important considerations in model selection and testing. For example, the experimental design should determine whether a drug is being eliminated by saturable (dose-dependent) or simple linear kinetics. A plot of metabolic rate versus drug concentration can be used to determine dose dependence, as in . Metabolic rate can be measured at various drug concentrations using an *in-vitro* system (). In , curve *B,* saturation occurs at higher drug concentration.

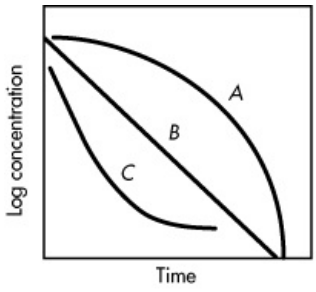
Figure 22-13.



Metabolic rate versus drug concentration. Drug *A* follows first-order pharmacokinetics, whereas drug *B* follows nonlinear pharmacokinetics and saturation occurs at higher drug concentrations.

For illustration, consider the drug concentration–time profile for a drug given by IV bolus. The combined metabolic and distribution processes may result in profiles like those in . Curve *A* represents a slow initial decline due to saturation and a faster terminal decline as drug concentration decreases. Curve *C* represents a dominating distributive phase masking the effect of nonlinear metabolism. Finally, a combination of *A* and *C* may approximate a rough overall linear decline (curve *B*). Notice that the drug concentration–time profile is shared by many different processes and that the goodness-of-fit is not an adequate criterion for adopting a model. For example, concluding linear metabolism based only on curve *B* would be incorrect. Contrary to common belief, complex models tend to mask opposing variables that must be isolated and tested through better experimental designs. In this case, a constant infusion until steady-state experiment would yield information on saturation without the influence of initial drug distribution.

Figure 22-14.



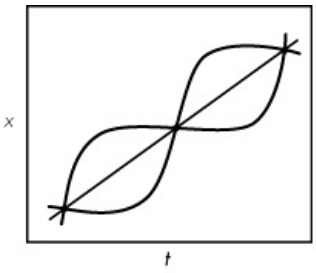
Plasma drug concentration profiles due to distribution and metabolic process. (See text for description of *A,B,* and *C*.)

The use of pharmacokinetic models has been critically reviewed by and by . These authors emphasize the difference between model building and simulation. A model is a secondary system designed to test the primary system (real and unknown). The assumptions in a model must be realistic and consistent with physical observations. On the other hand, a simulation may emulate the phenomenon without resembling the true physical process. A simulation without identifiable support of the physical system does little to aid understanding of the basic mechanism. The computation has only hypothetical meaning.

For example, the data in may be described by three different equations: a straight line, a hyperbola, and an equation with trigonometric functions. Without physical support, the model gives little understanding of the mechanisms involved. Regression or data fitting (computation of parameters of a given equation so that divergence of the data from the equation is minimized) is considered to be modulation. All forms of modulation represent data manipulation and, as such, decrease information.

Information comes from observations and observations only. If more points were available in this example, we could distinguish different processes if the data represent a straight line. Simulations within the realm of data allow for the determination of a quantitative relationship that is useful but does not actually increase understanding of the underlying physiologic processes governing the sojourn of the drug in the body.

Figure 22-15.



Data described by a straight line, a hyperbola, and an equation with trigonometric functions.

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Data dredging, such as manipulating the data to influence a stated study objective or model, is considered statistically undesirable because it may lead to a biased or a nonobjective analysis of the study. Ideally, statisticians prefer that details such as inclusion and exclusion criteria, the number of subjects per group, and the method of analysis or modeling be designed with sufficient power written into the protocols in advance. Pharmacokineticists are interested in understanding underlying kinetic processes that yield the results (data); statisticians are more interested in knowing that the conclusions drawn are real and not the result of random distribution.

It is perhaps refreshing to reexamine the basic paradigm of pharmacokinetics, or kinetics, which may be described as "observing how a given process changes over time." For example, by monitoring a change in the drug concentration in a patient over time, drug absorption and elimination from the patient may be modeled. If a statistician wishes to extrapolate the conclusion to a larger population, he or she may choose to enroll a sufficient number of subjects, and consider inclusion or exclusion criteria such as age, sex, other diseases, and genetics.

Basic pharmacokinetic concepts should be simple with few assumptions are made. The clinician may choose to weigh the risk of extrapolating the data and conclusions from a study with a few patients to a larger patient population. With recent advances in genetics, there are thousands of known genomic and environmental factors that may potentially influence disease and pharmacotherapy. The combination of genetic and environmental factors is very large and may make it very difficult to apply average information to an individual subject (see). However, the concept of adjusting dosing based on individual pharmacokinetic/pharmacodynamic information is still the most reliable approach to optimize dosing and drug efficacy and avoid toxicity. Ultimately, individual pharmacokinetic information will be combined with pharmacogenetic information obtained from the patient to allow the development of even better models to improve drug therapy.

FREQUENTLY ASKED QUESTIONS

1. Why are differential equations used to describe physiologic models?

2. Why do we assume that drug concentrations in venous and arterial blood are the same in pharmacokinetics?

3. Why is statistical moment used in pharmacokinetics?

4. Why is MRT used in pharmacokinetics?

LEARNING QUESTIONS

1. After an intravenous dose (500 mg) of an antibiotic, plasma–time concentration data were collected and the area under the curve was computed to be 20 mg/L hr. The $AUMC^{\infty}_{0}$ area was found to be 100 mg/L hr^2.

a. What is the mean residence time of this drug?

b. What is the clearance of this drug?

c. What is the steady-state volume of distribution of this drug?

2. Why is MRT calculated from moment and AUC curves (ie $[AUMC]^{\infty}_{0}/[AUC]^{\infty}_{0}$) rather than $[AUC]^{\infty}_{0}/C_0$ directly, as the term was defined in Equation 22.43?

3. If the data in Question 1 above are fit to a one-compartment model with an elimination *k* that is found to be 0.25 hour, MRT may be calculated simply as 1/*k*. What different assumptions are used in here versus Question 1?

4. What are the principal considerations in interspecies scaling?

5. What are the key considerations in fitting plasma drug data to a pharmacokinetic model?

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