# Lecture-2

## Significance of Measuring Plasma Drug Concentrations

- The intensity of the pharmacologic or toxic effect of a drug is often related to the concentration of the drug at the receptor site, usually located in the tissue cells.
- Because most of the tissue cells are richly perfused with tissue fluids or plasma, measuring the plasma drug level is a responsive method of monitoring the course of therapy.

- Pharmacokinetic models allow more accurate interpretation of the relationship between plasma drug levels and pharmacologic response.
- In the absence of pharmacokinetic information, plasma drug levels are relatively useless for dosage adjustment.

- For example, suppose a single blood sample from a patient was assayed and found to contain 10 mg/mL. According to the literature, the maximum safe concentration of this drug is 15 mg/mL.
- In order to apply this information properly, it is important to know when the blood sample was drawn, what dose of the drug was given, and the route of administration. If the proper information is available, the use of pharmacokinetic equations and models may describe the blood level-time curve accurately.

- In many cases, the pharmacodynamic response to the drug may be more important to measure than just the plasma drug concentration.
- For example, the electrophysiology of the heart, including an electrocardiogram (ECG), is important to assess in patients medicated with cardiotonic drugs such as digoxin.
- For an anticoagulant drug, such as dicumarol, prothrombin clotting time may indicate whether proper dosage was achieved.
- Most diabetic patients taking insulin will monitor their own blood or urine glucose levels.

# Definitions and notes

- A **model** is a hypothesis using mathematical terms to describe quantitative relationships concisely.

- The predictive capability of a model lies in the proper selection and development of mathematical function(s) that parameterize the essential factors governing the kinetic process.

- The key parameters in a process are commonly estimated by fitting the model to the experimental data, known as **variables**.

- A **pharmacokinetic parameter** is a constant for the drug that is estimated from the experimental data. For example, estimated pharmacokinetic parameters such as k depend on the method of tissue sampling, the timing of the sample, drug analysis, and the predictive model selected.

- A pharmacokinetic function relates an **independent variable** to a **dependent variable**, often through the use of parameters.
- For example, a pharmacokinetic model may predict the drug concentration in the liver 1 hour after an oral administration of a 20-mg dose.
- The independent variable is time and the dependent variable is the drug concentration in the liver.
- Based on a set of time-versus-drug concentration data, a model equation is derived to predict the liver drug concentration with respect to time.
- In this case, the drug concentration depends on the time after the administration of the dose, where the time: concentration relationship is defined by a pharmacokinetic parameter, **k** , the elimination rate constant.

- Such mathematical models can be devised to simulate the rate processes of drug absorption, distribution, and elimination to describe and predict drug concentrations in the body as a function of time.
- **Pharmacokinetic models are used to**:

1. Predict plasma, tissue, and urine drug levels with any dosage regimen
2. Calculate the optimum dosage regimen for each patient individually
3. Estimate the possible accumulation of drugs and/or metabolites
4. Correlate drug concentrations with pharmacologic or toxicologic activity
5. Evaluate differences in the rate or extent of availability between formulations (bioequivalence)
6. Describe how changes in physiology or disease affect the absorption, distribution, or elimination of the drug
7. Explain drug interactions.

- A very simple and useful tool in pharmacokinetics is compartmentally based models.
- For example, assume a drug is given by intravenous injection and that the drug dissolves (distributes) rapidly in the body fluids.
- One pharmacokinetic model that can describe this situation is a tank containing a volume of fluid that is rapidly equilibrated with the drug. The concentration of the drug in the tank after a given dose is governed by **two parameters**:

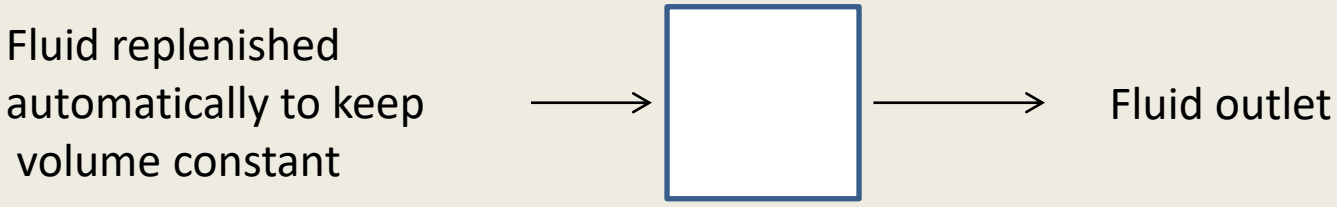
  (1) the fluid volume of the tank that will dilute the drug, and

  (2) the elimination rate of drug per unit of time.

Though this model is perhaps an overly simplistic view of drug disposition in the human body, a drug's pharmacokinetic properties can frequently be described using a fluid-filled tank model called **the one compartment open model.**

- In both the tank and the one-compartment body model, a fraction of the drug would be continually eliminated as a function of time.
- In pharmacokinetics, these parameters are assumed to be constant for a given drug. If drug concentrations in the tank are determined at various time intervals following administration of a known dose, then the volume of fluid in the tank or compartment ($V_D$ , volume of distribution) and the rate of drug elimination can be estimated.

Tank with a constant volume of fluid equilibrated with drug. The volume of the fluid is 1.0 L. The fluid outlet is 10 mL/min. The fraction of drug removed per unit of time is 10/1000, or 0.01.



# Compartment models

- A compartment is not a real physiologic or anatomic region but is considered as a tissue or group of tissues that have similar blood flow and drug affinity.
- Within each compartment, the drug is considered to be uniformly distributed.
- Mixing of the drug within a compartment is rapid and homogeneous and is considered to be "well stirred," so that the drug concentration represents an average concentration, and each drug molecule has an equal probability of leaving the compartment.
- Rate constants are used to represent the overall rate processes of drug entry into and exit from the compartment.

- The model is an open system because drug can be eliminated from the system.
- Compartment models are based on linear assumptions using linear differential equations.

# Mammillary Model

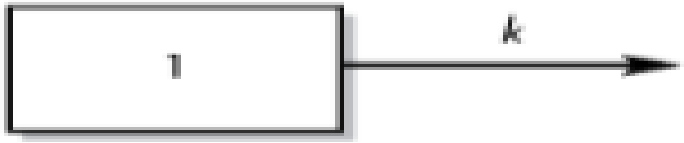
- A compartmental model provides a simple way of grouping all the tissues into one or more compartments where drugs move to and from the central or plasma compartment.
- The mammillary model is the most common compartment model used in pharmacokinetics.
- The mammillary model is a strongly connected system, because one can estimate the amount of drug in any compartment of the system after drug is introduced into a given compartment.

- In the one-compartment model, drug is both added to and eliminated from a central compartment.
- The central compartment is assigned to represent plasma and highly perfused tissues that rapidly equilibrate with drug.
- When an intravenous dose of drug is given, the drug enters directly into the central compartment.
- Elimination of drug occurs from the central compartment because the organs involved in drug elimination, primarily kidney and liver, are well-perfused tissues.

- In a two-compartment model, drug can move between the central or plasma compartment to and from the tissue compartment.
- Although the tissue compartment does not represent a specific tissue, the mass balance accounts for the drug present in all the tissues.
- In this model, the total amount of drug in the body is simply the sum of drug present in the central compartment plus the drug present in the tissue compartment.

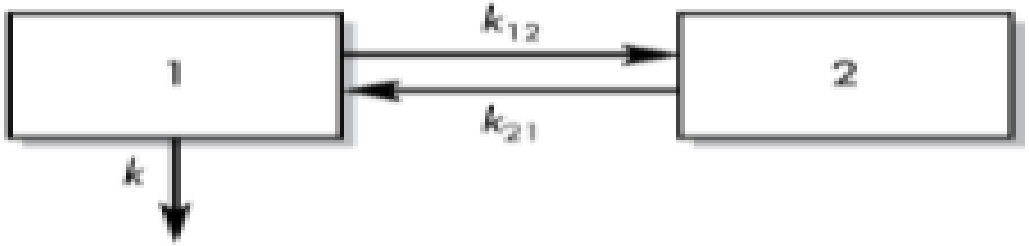
- Knowing the parameters of either the one- or two-compartment model, one can estimate the amount of drug left in the body and the amount of drug eliminated from the body at any time.
- The compartmental models are particularly useful when little information is known about the tissues.
- Several types of compartment models are described in figure 1-5.

MODEL 1. One-compartment open model, IV injection.

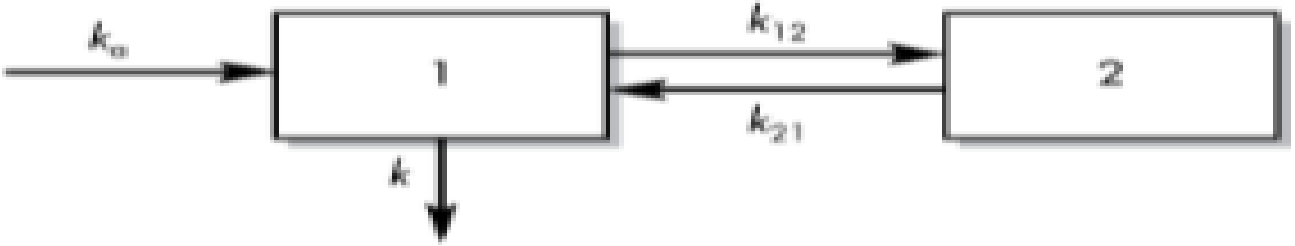



MODEL 2. One-compartment open model with first-order absorption.


MODEL 3. Two-compartment open model, IV injection.




MODEL 4. Two-compartment open model with first-order absorption.




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

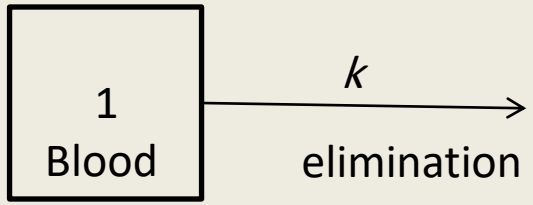


Various compartment models.

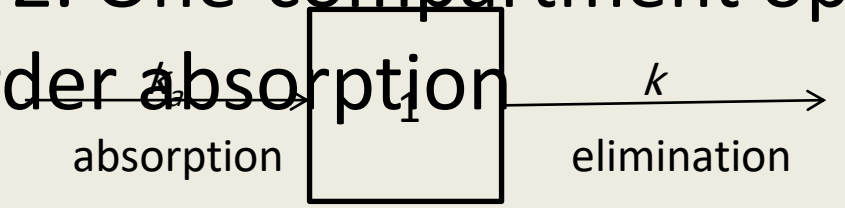
- The pharmacokinetic rate constants are represented by the letter k .
- Compartment 1 represents the plasma or central compartment, and compartment 2 represents the tissue compartment.
- The drawing of models has three functions. The model

1. enables the pharmacokineticist to write differential equations to describe drug concentration changes in each compartment,
2. gives a visual representation of the rate processes, and
3. shows how many pharmacokinetic constants are necessary to describe the process adequately.

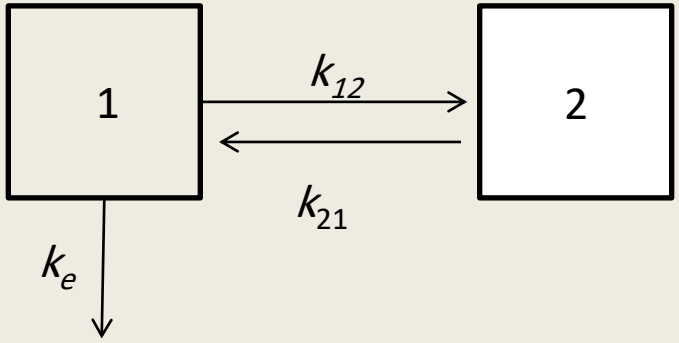
- Model 1. One-compartment open model, IV injection



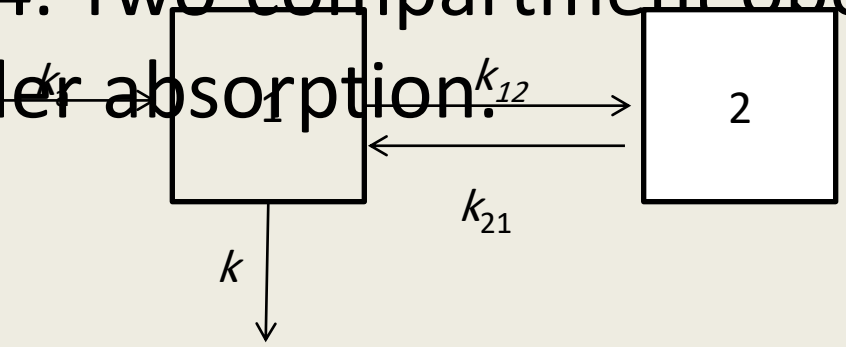

- Model 2. One-compartment open model with first-order absorption



- Model 3. Two-compartment open model, IV injection.




- model 4. Two-compartment open model with first-order absorption.



# Example

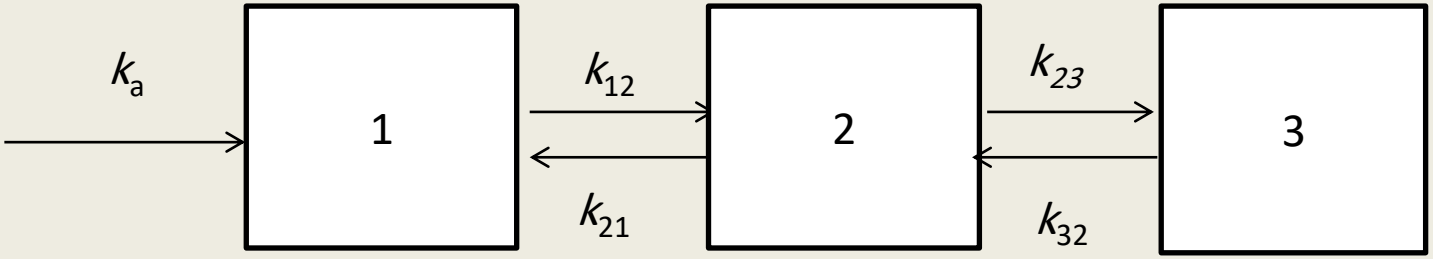
- Two parameters are needed to describe model 1: the volume of the compartment and the elimination rate constant, *k*.
- In the case of model 4, the pharmacokinetic parameters consist of the volumes of compartments 1and 2 and the rate constants *k*a, *k*, $k_{12}$, *and* $k_{21}$ for a total of six parameters.
- In studying these models, it is important to know whether drug concentration data may be sampled directly from each compartment.

- For model 3 and 4, data concerning compartment 2 can not be obtained easily because tissues are not easily sampled and may not contain homogenous concentrations of drug.
- If the amount of drug absorbed and eliminated per unit time is obtained by sampling compartment 1, then the amount of drug contained in the tissue compartment 2 can be estimated mathematically.

# Catenary Model

- In pharmacokinetics, the mammillary model must be distinguish from another type of compartmental model called the catenary model.
- The catenary model consists of compartments joined to one another like the compartments of train.
- In contrast, the mammillary model consists of one or more compartments around central compartment like satellites.
- Because the catenary model does not apply to the way most functional organs in the body are directly connected to the plasma, it is not used often as the mammillary model.

# Example of caternary model



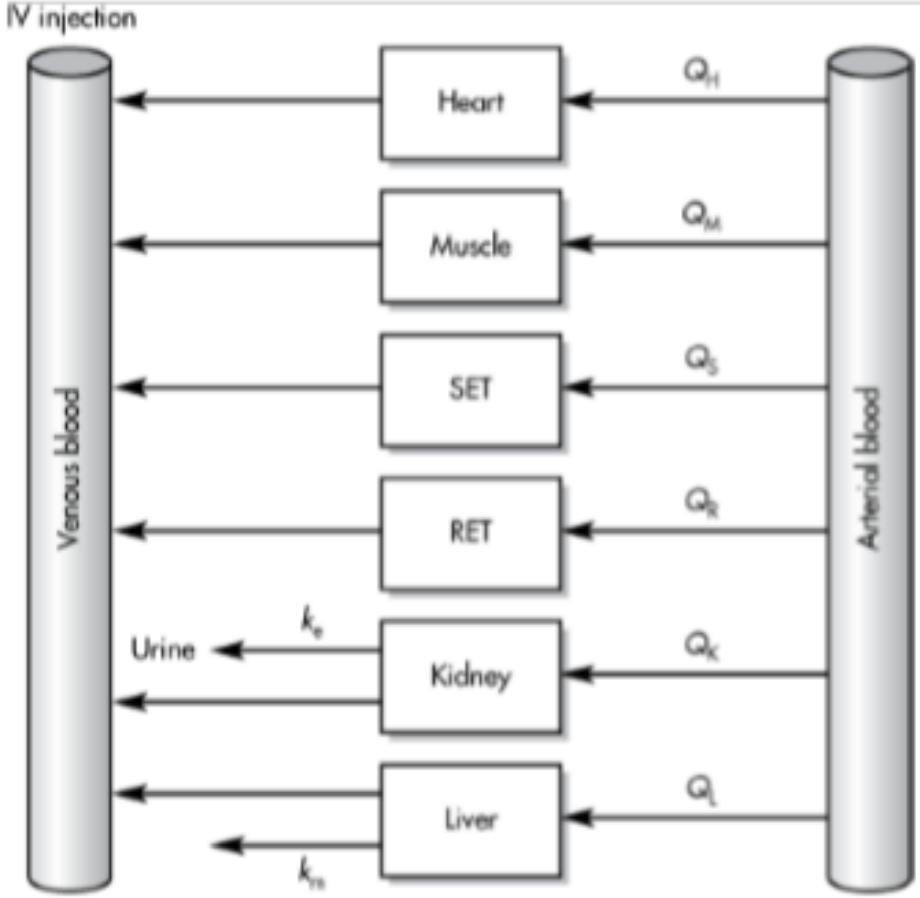
# Physiologic Pharmacokinetic Model (Flow Model)

- Physiologic pharmacokinetic models, also known as blood flow or perfusion models, are pharmacokinetic model based on known anatomic and physiologic data.
- The models describe the data kinetically, with the consideration that blood flow is responsible for distributing drug to various parts of the body.
- Uptake of drug into organs is determined by the binding of drug in these tissues.

- Tissue volume of distribution, the actual tissue volume is used.
- Because there are many tissue organs in the body, each tissue volume must be obtained and its drug concentration described. The model would potentially predict realistic tissue drug concentrations, which the two-compartment model fails to do.
- Unfortunately, much of the information required for adequately describing a physiologic pharmacokinetic model are experimentally difficult to obtain. In spite of this limitation, the physiologic pharmacokinetic model does provide much better insight into how physiologic factors may change drug distribution from one animal species to another.
- Other major differences are described below.

- First, no data fitting is required in the perfusion model. Drug concentrations in the various tissues are predicted by organ tissue size, blood flow, and experimentally determined drug tissueâ€“blood ratios (ie, partition of drug between tissue and blood).
- Second, blood flow, tissue size, and the drug tissueâ€“blood ratios may vary due to certain pathophysiologic conditions. Thus, the effect of these variations on drug distribution must be taken into account in physiologic pharmacokinetic models.
- Third, and most important of all, physiologically based pharmacokinetic models can be applied to several species, and, for some drugs, human data may be extrapolated. Extrapolation from animal data is not possible with the compartment models, because the volume of distribution in such models is a mathematical concept that does not relate simply to blood volume and blood flow. To date, numerous drugs (including digoxin, lidocaine, methotrexate, and thiopental) have been described with perfusion models. Tissue levels of some of these drugs cannot be predicted successfully with compartment models, although they generally describe blood levels well. An example of a perfusion model is shown in Figure 1-7 .

**Figure 1-7.**

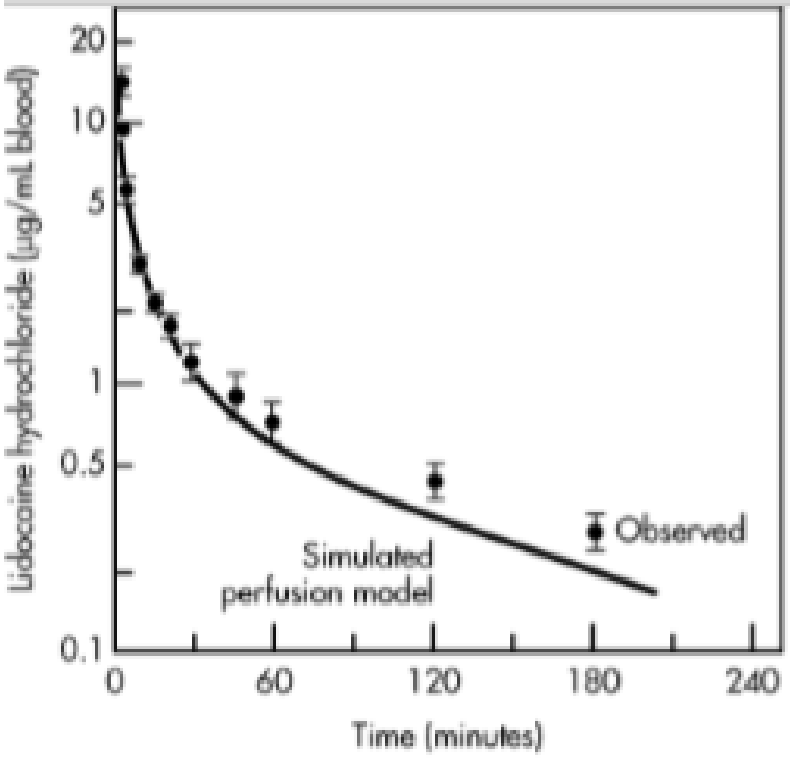





Pharmacokinetic model of drug perfusion. The $k$'s represent kinetic constants: $k_e$ is the first-order rate constant for urinary drug excretion and $k_m$ is the rate constant for hepatic elimination. Each "box" represents a tissue compartment. Organs of major importance in drug absorption are consid-ered separately, while other tissues are grouped as RET (rapidly equilibrating tissue) and SET (slowly equilibrating tissue). The size or mass of each tissue compartment is determined physiologically rather than by mathematical estimation. The concentration of drug in the tissue is determined by the ability of the tissue to accumulate drug as well as by the rate of blood perfusion to the tissue, represented by $Q$ .

- The number of tissue compartments in a perfusion model varies with the drug. Typically, the tissues or organs that have no drug penetration are excluded from consideration. Thus, such organs as the brain, the bones, and other parts of the central nervous system are often excluded, as most drugs have little penetration into these organs. To describe each organ separately with a differential equation would make the model very complex and mathematically difficult. A simpler but equally good approach is to group all the tissues with similar blood perfusion properties into a single compartment.
- A perfusion model has been used successfully to describe the distribution of lidocaine in blood and various organs. In this case, organs such as lung, liver, brain, and muscle were individually described by differential equations, whereas other tissues were grouped as RET (rapidly equilibrating tissue) and SET (slowly equilibrating tissue), asshown in Figure 1-8. shows that the blood concentration of lidocaine declines biexponentially and was well predicted by the physiologic model based on blood flow. The tissue lidocaine level in the lung, muscle, and adipose and other organs is shown in Figure 1-9.

**Figure 1-8.**

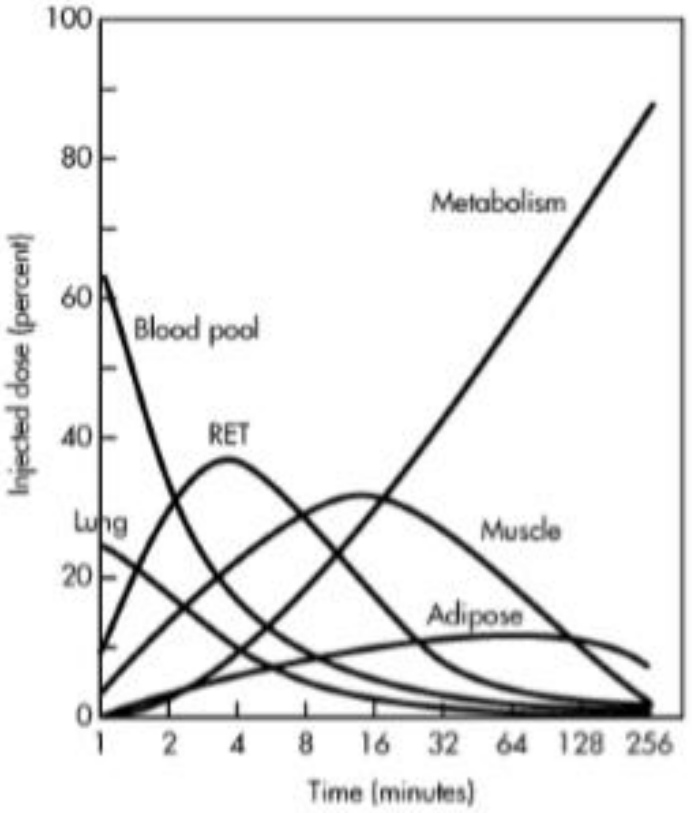





Observed mean (•) and simulated (â€") arterial lidocaine blood concentrations in normal volunteers receiving 1 mg/kg per min constant infusion for 3 minutes.

(, with permission; data from Tucker GT, Boas RA: *Anesthesiology* **34:** 538, 1971.)

# Figure 1-9.






Perfusion model simulation of the distribution of lidocaine in various tissues and its elimination from humans following an intravenous infusion for 1 minute.

(From , with permission.)

- The real significance of the physiologically based model is the potential application of this model in the prediction of human pharmacokinetics from animal data ().
- The mass of various body organs or tissues, extent of protein binding, drug metabolism capacity, and blood flow in humans and other species are often known or can be determined. Thus, physiologic and anatomic parameters can be used to predict the effects of drugs on humans from the effects on animals in cases where human experimentation is difficult or restricted.

# FREQUENTLY ASKED QUESTIONS

1. Why is plasma or serum drug concentration, rather than blood concentration, used to monitor drug concentration in the body?
2. What are reasons to use a multicompartment model instead of a physiologic model?
3. At what time should plasma drug concentration be taken in order to best predict drug response and side effects?

# LEARNING QUESTIONS

1. What is the significance of the plasma levelâ€“time curve? How does the curve relate to the pharmacologic activity of a drug?
2. What is the purpose of pharmacokinetic models?
3. Draw a diagram describing a three-compartment model with first-order absorption and drug elimination from compartment 1.
4. The pharmacokinetic model presented in represents a drug that is eliminated by renal excretion, biliary excretion, and drug metabolism. The metabolite distribution is described by a one-compartment open model. The following questions pertain to .

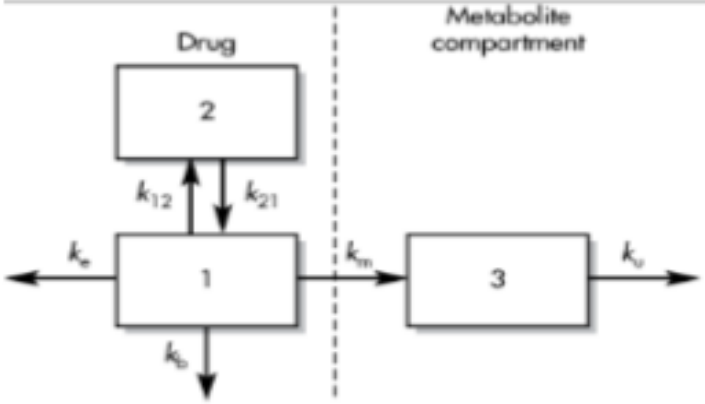
a. How many parameters are needed to describe the model if the drug is injected intravenously (ie, the rate of drug absorption may be neglected)?

b. Which compartment(s) can be sampled?

c. What would be the overall elimination rate constant for elimination of drug from compartment 1?

d. Write an expression describing the rate of change of drug concentration in compartment 1 (dC 1 /dt ).

**Figure 1-10.**






Pharmacokinetic model for a drug eliminated by renal and biliary excretion and drug metabolism. $k_m$ = rate constant for metabolism of drug; $k_u$ = rate constant for urinary excretion of metabolites; $k_b$ = rate constant for biliary excretion of drug; and $k_e$ = rate constant for urinary drug excretion.

**5.** Give two reasons for the measurement of the plasma drug concentration, $C_p$ assuming (a) the $C_p$ relates directly to the pharmacodynamic activity of the drug and (b) the $C_p$ does not relate to the pharmacodynamic activity of the drug.

**6.** Consider two biologic compartments separated by a biologic membrane. Drug A is found in compartment 1 and in compartment 2 in a concentration of $c_1$ and $c_2$, respectively.

**a.** What possible conditions or situations would result in concentration $c_1 > c_2$ at equilibrium?

**b.** How would you experimentally demonstrate these conditions given above?

**c.** Under what conditions would $c_1 = c_2$ at equilibrium?

**d.** The total amount of Drug A in each biologic compartment is $A_1$ and $A_2$, respectively. Describe a condition in which $A_1 > A_2$, but $c_1 = c_2$ at equilibrium.

Include in your discussion, how the physicochemical properties of Drug A or the biologic properties of each compartment might influence equilibrium conditions.