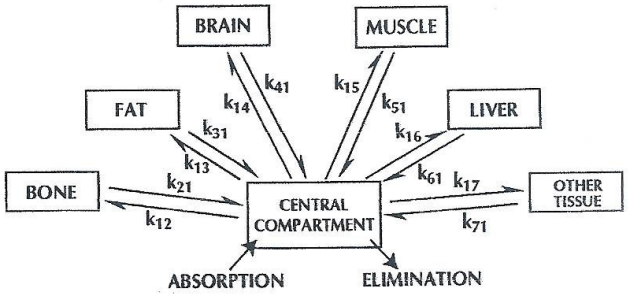


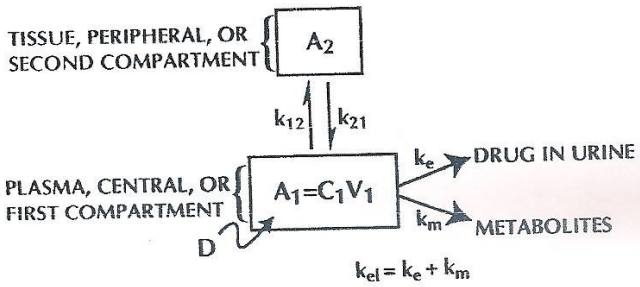

SCHEME 17.1 Distribution of drug between a central compartment and various body tissues and fluids.

simultaneously, or drug could conceivably be eliminated exclusively from the second, or tissue, compartment (3). However, the model in Scheme 17.2 is the most common and makes good anatomical sense. Intravenous dosage always delivers drug directly into the plasma compartment. Similarly, drug elimination occurs principally via the liver or kidney, and these organs are intimately associated with, if not part of, the plasma compartment because of rapid blood flow through these organs and rapid equilibrium of substances between these organs and blood. Each compartment has three names. The plasma compartment is also called the central or first compartment. Similarly, the tissue compartment is also known as the peripheral or second compartment. These names are largely self-explanatory and are synonymous within each compartment.

## The Two-Compartment Model with Bolus Intravenous Injection

As shown in Chapter 13, in the one-compartment model drug equilibrates rapidly into those fluids and tissues that constitute the distribution volume. Thus, a plot of drug concentration versus time following intravenous dosage yields a simple monoexponential curve, and a plot of the logarithm of drug concentration versus time yields a straight line. With the two-compartment model, a distinctive curve is obtained that readily distinguishes the two-compartment model from the one-compartment model.

The sequence of events in the two-compartment model, as depicted in Scheme 17.2, is as follows: After drug is introduced into the first compartment by bolus intravenous injection, initial and rapid distribution into those fluids and tissues that constitute the first compartment occurs. At the same time, drug starts to disperse into the less accessible and more slowly equilibrating tissues and fluids that constitute the second compartment. Of course, drug is simultaneously being eliminated from the first compartment. Because drug is not only being eliminated (excreted or metabolized) but also being taken up by second-compartment tissues and fluids during the early postdose period, rapid net loss of drug from the first compartment, and a rapid decline in plasma concentrations, occurs. This period of rapidly falling drug concentrations due to the combined effects of tissue uptake and elimination is called the $\alpha$ phase. After a certain time period depending on the




Two-compartment open model with rapid intravenous injection.

SCHEME 17.2

magnitude of "microscopic" rate constants between the compartments, $k_{12}$ and $k_{21}$, drug will equilibrate between the various tissues and fluids, and net loss of drug from the first compartment due to distribution will no longer occur. Even though equilibrium is reached between the two compartments at the end of the α phase, the concentration of drug is not necessarily equal in the two compartments. The concentration of drug in tissues may be less or greater than that in the first compartment, but the concentrations will nonetheless be at equilibrium. Because the second compartment usually comprises several organs and tissues, the concentration of drug in this compartment is unlikely to be homogeneous.

Once equilibrium is reached between the two compartments, the rate of drug loss from the bloodstream is reduced. This period of more slowly declining blood levels is the β phase. The type of drug profile that occurs in this situation is shown in Figure 17.1, which shows rapid decline of drug concentrations during the α phase and relatively slow decline during the β phase.

## Interpretation of Drug-Concentration Profiles in Plasma To Obtain Parameter Estimates

Having established the kinetic model in Scheme 17.2, and having described the type of blood level curve that occurs in Figure 17.1, it is now possible to derive the appropriate equations that describe the drug profile in plasma.

The rates of change in the amounts of drug in the first and second compartments, and also the cumulative amount of drug voided in urine with respect to time, are given by equations 17.1 through 17.3.

$$\frac{dA_1}{dt} = k_{21}A_2 - (k_{12} + k_{el})A_1 \qquad (17.1)$$

$$\frac{dA_2}{dt} = k_{12}A_1 - k_{21}A_2 \qquad (17.2)$$

$$\frac{dA_u}{dt} = k_eA_1 \qquad (17.3)$$

These equations can be solved simultaneously to obtain

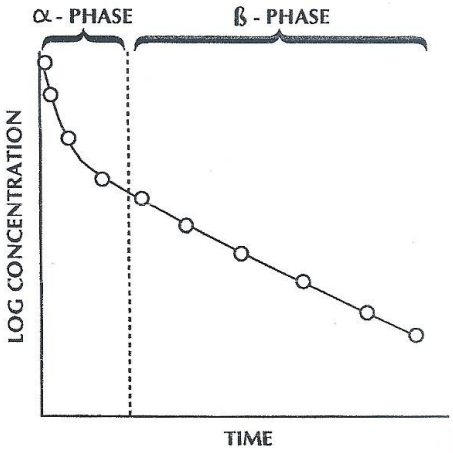



**FIGURE 17.1** Blood levels of a drug that obeys two-compartment model kinetics following bolus intravenous injection.

$$A_1 = \left(\frac{D}{\alpha - \beta}\right)\left[(k_{21} - \beta)e^{-\beta t} - (k_{21} - \alpha)e^{-\alpha t}\right] \tag{17.4}$$

$$A_2 = \left(\frac{Dk_{12}}{\alpha - \beta}\right)\left(e^{-\beta t} - e^{-\alpha t}\right) \tag{17.5}$$

$$A_u - A_u^{\infty}\left[1 - \frac{k_{el}}{\alpha - \beta}\left(\frac{k_{21} - \beta}{\beta}e^{-\beta t} - \frac{k_{21} - \alpha}{\alpha}e^{-\alpha t}\right)\right] \tag{17.6}$$

which represent the quantity of drug in the first compartment, the quantity of drug in the second compartment, and the quantity of drug cumulatively excreted unchanged in urine, respectively. The parameters $\alpha$ and $\beta$ are complex rate constants that are related to the "microscopic" constants $k_{12}$, $k_{21}$, and $k_{el}$ as shown in equations 17.7 and 17.8.

$$\alpha = 0.5\{(k_{12} + k_{21} + k_{el}) + [(k_{12} + k_{21} + k_{el})^2 - 4k_{21}k_{el}]^{1/2}\} \tag{17.7}$$

$$\beta = 0.5\{(k_{12} + k_{21} + k_{el}) - [(k_{12} + k_{21} + k_{el})^2 - 4k_{21}k_{el}]^{1/2}\} \tag{17.8}$$

The only difference in the right sides of these two equations is the sign separating the parenthetical term and the root function. These equations appear complex, but careful examination will show that the combined equations 17.7 and 17.8 can be written

$$X = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \tag{17.9}$$

This equation represents the two possible values of $X$ in the quadratic equation:

$$aX^2 + bX + c = 0 \tag{17.10}$$

Equation 17.9 thus represents the two possible roots of equation 17.10. In exactly the same way, the values $\alpha$ and $\beta$ are the two possible roots of a quadratic function that one reaches when obtaining simultaneous solutions for the rate equations 17.1, 17.2, and 17.3.

The values $\alpha$ and $\beta$ are therefore intimately related to the values of $k_{12}$, $k_{21}$, and $k_{el}$, and both $\alpha$ and $\beta$ are influenced by all three rate constants. If $k_{12}$ is very high, then drug will distribute rapidly into peripheral tissue. Detecting a distribution phase in this case will be difficult, and the drug will tend to exhibit simple one-compartment model kinetics. The lower $k_{12}$ becomes relative to the other microscopic constants, the slower the distribution phase, and the more two-compartment character is evident in the drug plasma profile.

Relationships between the values of $\alpha$ and $\beta$ and the magnitude of the elimination rate constant, $k_{el}$, are interesting. For example, if values of $k_{12}$ and $k_{21}$ are held constant, and the value of the elimination rate constant is varied over a fairly wide range, then for very high values of $k_{el}$, with very fast intrinsic elimination, the value of $\alpha$ will approach $k_{el}$. For very low values of $k_{el}$ relative to the other microscopic constants, $\alpha$ approaches the sum of $k_{12}$ and $k_{21}$. Because of the negative sign in equation 17.8, the value of $\beta$ is affected differently by changes in $k_{el}$. For instance, at high values of $k_{el}$, when elimination is rapid relative to $k_{12}$ and $k_{21}$, the value of $\beta$ approaches $k_{21}$. At very low values of $k_{21}$, $\beta$ approaches zero.

Having established the basic equations associated with this model, the next task is to obtain estimates of the rate constants and other parameters from the drug profile in plasma. Equation 17.4 can be rewritten in concentration form as

$$C = \frac{D}{V_1(\alpha - \beta)}\left[(k_{21} - \beta)e^{-\beta t} - (k_{21} - \alpha)e^{-\alpha t}\right] \tag{17.11}$$

where $V_1$ is the volume of the first compartment. Equation 17.11 can be expressed in shorthand notation as

$$C = Ae^{-\alpha t} + Be^{-\beta t} \tag{17.12}$$

In this equation, the values $A$ and $B$ relate to the parameters in equation 17.4, as shown in equations 17.13 and 17.14.

$$A = \frac{D(k_{21} - \alpha)}{V_1(\alpha - \beta)} \tag{17.13}$$