PHARMAKOKINETIKA – PRŮHYB LÉKU PO PODÁNÍ
DYNAMIKA – EFEKT LÉKU

13

The One-Compartment Open Model with Intravenous Dosage

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In order to understand the mathematical approaches used throughout this book, a basic knowledge of calculus is needed. Initially some kinetic expressions will be derived. However, with some exceptions, mathematical derivation will be kept to a minimum. Helpful integrating procedures, such as the Laplace transform, must be used to solve rate equations for complex pharmacokinetic expressions. However, the intent of this book is not to teach mathematics but to provide a basic understanding of pharmacokinetics and its uses. Therefore, only minor emphasis will be placed on derivations, and major emphasis will be placed on the meaning and application of pharmacokinetic principles.

Drug input, elimination, and transfer between pharmacokinetic compartments will be assumed to be first-order and linear. This assumption is consistent with the modeling approach. In later chapters, departures from this general approach will be described, but the principal arguments will be developed assuming first-order, nonsaturable, and either reversible kinetics (e.g., between spatial compartments) or irreversible kinetics (e.g., between chemical compartments, and also absorption and elimination).

To reiterate a comment in Chapter 1, the pharmacokinetic compartment can be used to describe both spatial and chemical states. For example, if a drug appears to distribute in a heterogeneous manner in the body so that overall drug distribution can be described in terms of two distinct body volumes, then the concentration of drug in these volumes and its distribution between them are described in terms of two spatial compartments. On the other hand, if a drug forms a metabolite, particularly if the metabolite is active, which makes it of interest, then the metabolite is considered to be a separate chemical compartment regardless of whether the metabolite occupies the same or different body fluids and tissues as the parent drug. Spa-

tial and chemical compartments can coexist in the same kinetic model. For an drug that is metabolized, coexistence is necessarily the case.

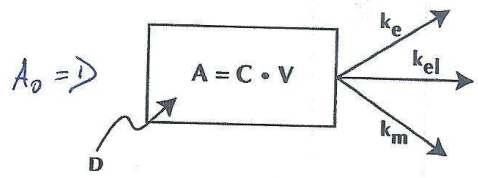
Consider the simplest model of all, the one-compartment open model Despite its associated simplifications and assumptions, this model is the mos common for describing drug profiles in blood, plasma, serum, or urine after oral o intramuscular doses. Following intravenous bolus doses, an additional drug distri bution phase is often more readily discernible. This situation will be discussed i more detail later. In the simple one-compartment model, however, the drug i assumed to rapidly distribute into a homogeneous fluid volume in the body regardless of the route of administration (*1*, *2*).

Pharmacokinetic rate constants are based on transfer of amounts of drugs Rate constants are subsequently applied to concentration changes by dividing the expressions by the appropriate distribution volumes. Also, on a microscopic basis, most pharmacokinetic rate constants describe a multiplicity of events. For example, an absorption rate constant is possibly influenced by dissolution, stomach emptying, splanchnic blood flow, and a variety of other factors. However, despite the gross simplifications involved, observed rate constants describe the overall rate-limiting process, be it absorption, distribution, metabolism, or excretion. How much more mechanistic information can be obtained from such rate constants depends on the drug and the enthusiasm and ingenuity of the investigator.

The One-Compartment Open Model with Bolus Intravenous Injection

This model, which has been summarized by Gibaldi and Perrier (*3*), is depicted in Scheme 13.1. Because of the generally heterogeneous nature of the body, and the impact of this on drug distribution, this model is relatively rare. However, examples in the literature include plasma concentrations of prednisolone following bolus intravenous administration to a kidney transplant patient (*4*), and of tritium following intravenous administration of tritiated Hirulog 1 (BG 8967), a synthetic thrombin inhibitor (*5*, *6*).

The box, or compartment, represents the drug distribution volume, and other values and rate constants are defined in the caption. The value k_{el} is equal to the sum of all elimination rate constants, including those for drug eliminated via sweat, bile, lungs, etc. However, in this example only two routes of elimination are assumed, urinary excretion and metabolism. The curved arrow leading into the compartment represents instantaneous introduction of drug.



SCHEME 13.1 One-compartment open model with bolus intravenous injection: *D* is the dose, *A* is the amount of drug in the body, *C* is the concentration of drug in body fluids, and *V* is the drug distribution volume.

Using this model, equation 13.1 can be written in the following form.

$$\frac{dA}{dt} = -(k_e + k_m)A = -k_{el}A \qquad (13.1)$$

where A is the amount of drug in the body, t is time, k_e is the rate constant for urinary excretion, and k_m is the rate constant for metabolism. Equation 13.1 describes the rate of loss of drug from the body. This equation is rearranged to

$$\frac{dA}{A} = -k_{el}dt \qquad (13.2)$$

Equation 13.2, when integrated between the limits of zero and finite time, with the value of A varying from A_0, the initial amount of drug in the body, to some value less than A_0, becomes

$$\ln A - \ln A_0 = -k_{el}t \qquad (13.3)$$

The natural logarithms appear in this expression because the integral of the reciprocal of any single value X is equal to the natural logarithm of X. Rearrangement of equation 13.3 yields

$$\ln\left(\frac{A}{A_0}\right) = -k_{el}t \qquad (13.4)$$

If both sides of equation 13.4 are made a power of e, as in equation 13.5, equation 13.6 is obtained.

$$e^{\ln\left(\frac{A}{A_0}\right)} = e^{-k_{el}t} \qquad (13.5)$$

$$\frac{A}{A_0} = e^{-k_{el}t} \quad \text{or} \quad A = A_0e^{-k_{el}t} \qquad (13.6)$$

Equation 13.5 converts to equation 13.6 because e to the power of the natural logarithm of X is equal to X ($e^{\ln X} = X$). This is analogous to logarithms to the base 10. To use a numerical example, the logarithm to the base 10 of 100 is equal to 2, and 10^2 is 100. Thus, 10 raised to the power of the logarithm of 100 is equal to 100, or 10 raised to the power of the logarithm of X is equal to X.

Equation 13.6 can be converted into concentration terms by dividing both sides of the expression by the distribution volume, V, as in equation 13.7, to yield equation 13.8.

$$\frac{A}{V} = \left(\frac{A_0}{V}\right)e^{-k_{el}t} \qquad (13.7)$$

$$C = C_0 e^{-k_{el}t} \tag{13.8}$$

where C is the concentration of drug in the body and C_0 is the initial concentration of drug at zero time. Equation 13.3 can similarly be converted to concentration form as in

$$\ln C = \ln C_0 - k_{el}t \quad \text{or} \quad \log C = \log C_0 - \frac{k_{el}t}{2.3} \tag{13.9}$$

Conversion from natural logarithms to logarithms to the base 10 in equation 13.9 is obtained from the simple relationship that $\ln X = 2.3 \log X$.

What information can be obtained about a drug by using some of these expressions? From equations 13.8 and 13.9, a plot of the logarithm of drug concentration against time will be linear. Logarithms to the base 10 will be used in this book because logarithmic graph paper is printed that way, and it is thus more convenient.

In Figure 13.1, the slope of the line, which will be linear if the data fit the model, gives the elimination rate constant k_{el}, and the extrapolated intercept at time zero gives C_0. Actually, the intercept is the logarithm of C_0, but as the actual concentration values are plotted on semilogarithmic graph paper, the paper converts actual values into logarithmic values. Actual concentration values can therefore be read directly from the plots.

The elimination half-life of the drug can also be obtained from the relationship in equation 13.10.

$$t_{1/2} = \frac{\ln 2}{k_{el}} = \frac{0.693}{k_{el}} \tag{13.10}$$

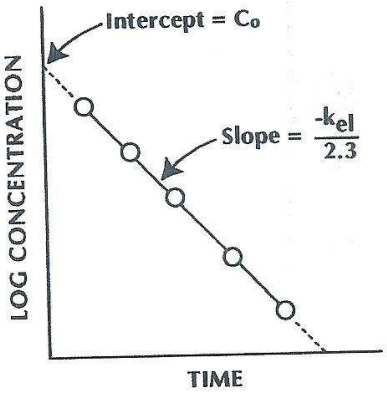


FIGURE 13.1 Plot of logarithm of drug concentration vs. time following intravenous bolus injection.

Equation 13.10 is valid for any first-order rate constant. However, instead of finding the elimination rate constant and then calculating the half-life, obtaining these values in reverse order is usually more convenient when analyzing data graphically. For example, the elimination half-life can be obtained by selecting any time interval during which the value of C is reduced by one-half. Whichever values of C are used, the time interval for C to be reduced by one-half will be the same. The value of k_{el} is then obtained from equation 13.10.

If the administered dose D is divided by the extrapolated value C_0, and if the reasonable assumption is made that all of the injected dose was absorbed, then the drug distribution volume is obtained from

$$V = \frac{D}{C_0} \tag{13.11}$$

A word of caution is appropriate here. During this and subsequent exercises, the simplifying assumption is made that drugs are not bound, or are bound to only a negligible extent, to plasma and tissue proteins or other macromolecules. This assumption saves considerable time and keeps the mathematics relatively simple. However, if binding does occur, then appropriate adjustments may be made to such parameters as distribution volume, as described in Chapter 8.

The drug elimination half-life, overall elimination rate constant k_{el}, and its distribution volume have now been calculated from the data in Figure 13.1. Multiplying the distribution volume, V, by the elimination rate constant, k_{el}, as in equation 13.12, yields the plasma clearance, Cl_p.

$$Cl_p = Vk_{el} \tag{13.12}$$

Knowing also the renal clearance and differentiating it from other clearance processes would be useful information. This information cannot be obtained from plasma data alone because the information in Figure 13.1 indicates only how rapidly drug is leaving the body. The figure provides no information regarding the route of elimination. However, if all the drug that is excreted in unchanged form in the urine, A_u^∞, were collected, then the renal clearance can be obtained from

$$\frac{Cl_r}{Cl_p} = \frac{k_e V}{k_{el} V} = \frac{k_e}{k_{el}} = \frac{A_u^\infty}{D} \tag{13.13}$$

where Cl_p is the plasma clearance, Cl_r is the renal clearance, and A_u^∞ is the total amount of drug excreted in urine.

The renal clearance is thus related to plasma clearance in direct proportion to the ratio of total urinary recovery of unchanged drug to the administered dose. As discussed previously, renal clearance may be equal to or less than plasma clearance, but never greater. That is, k_e can never be greater than k_{el}. Once k_e is obtained, k_m can be calculated simply by subtracting k_e from k_{el}, as in equation 13.14.

$$k_m = k_{el} - k_e \tag{13.14}$$

Another useful pharmacokinetic parameter that can be obtained from intravenous data, or from any other data for that part, is the area under the plasma level curve, AUC.

The total area under the plasma curve, that is, the area from zero to infinite time, is obtained mathematically by integrating the terms in equation 13.8 between zero and infinite time. This integration, after appropriate cancellations, yields

$$\begin{aligned} \text{AUC}^{0\to\infty} &= \int_0^\infty C = C_0 \int_0^\infty e^{-k_{el}t} dt \\ &= -\frac{C_0}{k_{el}}\left(e^{-k_{el}\infty} - e^{-k_{el}0}\right) \\ &= -\frac{C_0}{k_{el}}(0-1) = \frac{C_0}{k_{el}} \end{aligned} \tag{13.15}$$

Because C_0 can be expressed as D/V, equation 13.15 can be written as equation 13.16.

$$\text{AUC}^{0\to\infty} = \frac{D}{Vk_{el}} = \frac{D}{Cl_p} \tag{13.16}$$

This expression shows that the area under the plasma curve is equal to the dose divided by plasma clearance. Perhaps more importantly, plasma clearance can be obtained by dividing the dose by the AUC. However, the area must be the total area. If a truncated area is used, and this is frequently all that can be determined by direct observation of the data, overestimation of the plasma clearance will result.

Renal clearance can also be obtained with this approach, provided urinary recovery of unchanged drug is known. Renal clearance is readily obtained from

$$Cl_r = \frac{A_u^t}{\text{AUC}^{0\to t}} \tag{13.17}$$

Equation 13.17 is analogous to a rearranged form of equation 13.16. Thus, renal clearance is calculated by dividing the quantity of drug recovered in urine up to a certain time by the area under the plasma curve up to the same time. (This time can be infinity but need not be.) The calculation for renal clearance has the advantage over calculation for plasma clearance in that truncated areas and partial urine collections can be used. If the values in equation 13.17 are extrapolated to infinity, then equation 13.18 results.

$$Cl_r = \frac{A_u^\infty}{\text{AUC}^{0\to\infty}} \tag{13.18}$$

Equation 13.8 shows that renal clearance and plasma clearance differ only in terms of the difference between the administered dose and urinary recovery of unchanged drug, A_u^∞.

The Trapezoidal Rule

Equations 13.15 and 13.16 describe the area under the plasma curve following bolus intravenous injection. In many cases, however, area values are measured directly from the data, for example, in model-independent kinetics, and several methods are available to do this. These include the trapezoidal rule and the log trapezoidal rule. The simple trapezoidal rule is described here because it is most commonly used. The trapezoidal rule is quick and accurate. The accuracy of the method is directly related to the number of data points used in its calculation.

A trapezoid is a four-sided figure with two sides parallel and two sides nonparallel. When the length of one of the sides is reduced to zero, the trapezoid becomes a triangle. If plasma data are plotted on regular graph paper, the area under the plasma profile can be divided into a series of trapezoids, and the areas of the individual trapezoids can be calculated and summed.

The data in Table 13.1 constitute a typical drug profile that might be obtained following bolus intravenous injection of a drug that has a biological half-life of 1 h. If these data are plotted on regular graph paper, and if the data points are joined by straight lines, a series of trapezoids is obtained, terminating with a triangle for the 8–12 h interval. Calculating the area for each segment of the curve and cumulatively adding each successive segment yield the trapezoidal area shown in the third column of the table. In this example, the sampling time has been extended until no detectable drug remains in the plasma. Unfortunately, this situation does not usually occur in practice. In most cases, the plasma sampling time is not extended for a sufficiently long period to allow plasma drug levels to decline to zero, so that the area calculated by the trapezoidal rule is the area from time zero to some time t when drug levels are still present. Thus, a truncated area is obtained, as in Figure 13.2. The 4-h plasma sample still contains drug, so the total area under the plasma level curve cannot be calculated.

The truncated area is useful for many types of calculations, but the complete area under the curve is more useful. For example, the area from time zero to infinity is required to calculate plasma clearance and total absorption and to construct Wagner–Nelson absorption plots, which will be discussed shortly. So it is important to be able to extend the truncated area to infinite time.

TABLE 13.1 **A Typical Drug Profile Following Bolus IV Injection**

Time (h)	*Concentration (μg/mL)*	*Cumulative AUC (μg · h/mL)*
0	25.0	
0.25	21.0	5.75
0.50	17.6	10.58
1.0	12.5	18.11
2.0	6.25	27.49
3.0	3.13	32.18
4.0	1.56	34.53
6.0	0.40	36.49
8.0	0.10	36.99
12.0	0.0	37.19

NOT BOLUS BUT DRUG WITH ABSORPTION !!!

další parameter k_0

$$D \xrightarrow{k_0} \boxed{A = C \cdot V} \xrightarrow{k_{el}} A_u + M + \ldots$$

SCHEME 13.2 One-compartment open model with zero-order absorption and first-order elimination: k_0 is the zero-order rate constant for drug administration.

infuse - k_0

$$\frac{dA}{dt} = k_0 - k_{el}A$$

$A_0 = 0$

rozmíšení k_0 !!!

obeys first-order kinetics, as in the bolus intravenous case. The elimination rate is dependent on the product of the rate constant, k_{el}, and the amount of drug in the body, A.

During the initial period of zero-order input, the amount of drug in the body, A, will be small. Thus the product, $k_{el}A$, will also be small, the rate of drug input will exceed the rate of drug output, and the quantity of drug in the body will increase. As the value of A increases, the product $k_{el}A$ will also increase, so the overall rate of drug elimination will approach and eventually become equal to the rate of input. A steady state is then achieved in which the rate of absorption equals the rate of elimination.

The infusion may be stopped either before or after the amount of drug in the body has reached steady state. During the resulting postabsorption phase, drug levels will decline at a first-order rate as in the intravenous bolus case. The two possible situations are shown in Figure 13.4.

Integration of equation 13.32 yields equation 13.33, which in concentration terms becomes equation 13.34.

$$A = \frac{k_0}{k_{el}}(1 - e^{-k_{el}t}) \tag{13.33}$$

$$C = \left(\frac{k_0}{V} \cdot k_{el}\right)(1 - e^{-k_{el}t}) \tag{13.34}$$

=

Although two rate constants are involved in the overall drug profile, only one time-dependent function, $e^{-k_{el}t}$, is involved. If t=0, $e^{-k_{el}t}$ becomes unity and $C = 0$. As the time after the start of infusion increases, the value $e^{-k_{el}t}$ becomes progressively smaller, the value $(1 - e^{-k_{el}t})$ increases, and the accumulation curve in Figure 13.3 is obtained. If the infusion is continued for a sufficiently long period so that $e^{-k_{el}t}$ approaches or becomes zero, then the parenthetical term becomes unity, and $C = k_0/Vk_{el}$ as in

$$C_{ss} = \frac{k_0}{Vk_{el}} \tag{13.35}$$

Because the steady-state concentration is described, C is now expressed as C_{ss}.

Thus, at steady state, as in Figure 13.4a, the concentration of drug in the distribution volume is equal to the infusion rate, k_0, divided by the plasma clearance,

má být konec ?!

Vk_{el}. Because the constant k_0 has units of mass per unit time, and because plasma clearance is commonly expressed in terms of volume per unit time, C_{ss} has units of mass per volume, or concentration.

The relationship in equation 13.35 provides considerable information. For example, knowledge of plasma clearance and drug infusion rate permits calculation of the steady-state drug concentration in plasma. Alternatively, if k_0 and C_{ss} are known, then plasma clearance can be calculated. Similarly, if k_0, C_{ss}, and the elimination $t_{1/2}$ are known, then the distribution volume can be calculated.

If both sides of equation 13.35 are multiplied by the distribution volume, V, equation 13.36 is obtained.

$$A_{ss} = \frac{k_0}{k_{el}} \tag{13.36}$$

This equation describes the amount of drug in the body at steady state, A_{ss}, in terms of the absorption and elimination rate constants. Thus, the total body drug load can be determined by dividing the zero-order infusion rate constant by the first-order elimination rate constant. A_{ss} can therefore be determined without knowing C_{ss}.

As previously noted from equations 13.34 and 13.35, steady-state drug levels are dependent on both the infusion and elimination rate constants. Faster infusion yields higher blood levels; faster elimination yields lower blood levels. However, from equation 13.34, the time dependency of the accumulation process is clearly dependent only on the elimination rate constant, k_{el}. No matter how fast a drug is infused, the time to reach steady state is governed exclusively by the elimination rate constant. How long it will take for a drug level to reach steady state can be determined from equation 13.34. Because this equation is exponential, steady state will theoretically take a very long time to achieve. However, because pharmacokineticists have to consider practicalities, 95% of steady state may be considered a reasonable approximation given the normal variability of biological data. How long does a drug need to be infused before drug levels in the blood reach 95% of

$95 = 100\left[1 - e^{-k_{el}t}\right]$

$t = 4.3\, t_{1/2}$

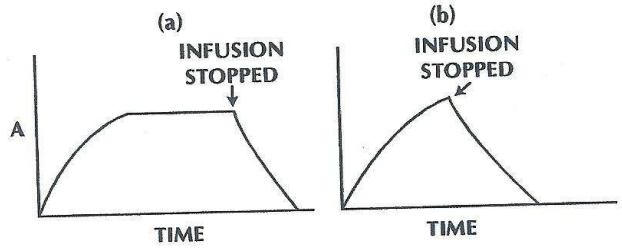
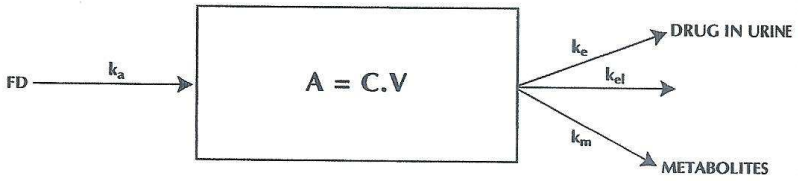


FIGURE 13.4

Time course of the quantity of Drug A in the body during and following zero-order infusion. In (a), drug levels had reached steady state before the infusion was stopped, and in (b), the levels had not reached steady state.

FIRST-ORDER ABSORPTION – ORALLY or intramuscular



k_a – konstanta F – fraction of the dose that is absorbed

SCHEME 14.1 One-compartment open model with first-order absorption and elimination, where F is the fraction of the dose, D, absorbed from the dosage site into the systemic circulation, and k_a is the first-order rate constant for drug absorption.

After intravenous injection, the parameter F is not pertinent because the availability of administered drug is almost always 100%; therefore, F is equal to unity. However, after oral doses, and also after intramuscular doses in some cases, bioavailability is not always 100%. Complete absorption from oral doses tends to be the exception rather than the rule. Incomplete absorption might be expected because of limited dissolution, degradation or metabolism occurring in the gastrointestinal (GI) tract, incomplete membrane penetration, and also presystemic hepatic clearance. After intramuscular doses, more efficient absorption might be expected, but this is not always the case. Incomplete absorption from intramuscular doses may result from degradation of drug at the intramuscular site, drug precipitation, or slow release of a portion of the drug giving rise to low and perhaps undetectable drug levels during prolonged periods. Intramuscularly dosed phenobarbital has been shown to be only 80% bioavailable compared to oral doses in humans (*1*), and intramuscularly dosed promethazine has been shown to be approximately 70–80% bioavailable in dogs compared to intravenously dosed drug (*2*). All of the above factors may influence the magnitude and interpretation of the absorption rate constant, k_a.

jen "absorption" – k_a

Suppose that a drug is at the absorption site and is simultaneously being absorbed at a rate governed by an intrinsic absorption rate constant, k_{ab}, and being enzymatically degraded at the absorption site at a rate governed by a rate constant, k_d. The overall rate of drug loss from the absorption site is then governed by the sum of k_{ab} and k_d. Because k_a is used to describe the overall loss of drug from the absorption site, the amount of drug, X, remaining at the absorption site at any time is described by

$$X = FDe^{-(k_{ab}+k_d)t} = FDe^{-k_a t} \qquad (14.1)$$

In Chapter 13 the apparent rate constant for appearance of intravenously dosed drug in the urine was shown to be equal to the overall elimination rate constant, k_{el}. Similarly, the apparent rate constant for appearance of orally or intramuscularly dosed drug into the circulation is equal to the overall rate constant for loss of drug from that absorption site by all processes. In other words, the rate constant that is obtained from the drug-concentration curve in plasma is not necessarily the intrinsic absorption rate constant but may be a constant related to overall loss of drug from the absorption site. An observed k_a may actually be the sum of k_{ab}, k_d,

and any other rate constant that contributes to loss of drug from the absorption site. Note that the absorption half-life, $t_{½\{abs\}}$, is obtained from $t_{½\{abs\}} = 0.693/k_a$.

An interesting analogy can be drawn with ocular drug administration [3]. When a drug solution is applied to the surface of the eye, for example from an eye dropper, more than 95% of the drug is washed from the eye surface by tear movement and is washed down the nasolachrymal duct. Thus, the overall rate of loss of drug from the absorption site at the surface of the eye is high. Absorption of drug into the eye will continue only as long as drug is available at the absorption site. Because overall loss of drug from the eye surface is approximately a first-order process, the apparent rate constant for drug penetration into the eye is very fast, and the absorption rate constant calculated from drug levels within the eye may overestimate the actual intrinsic absorption rate constant by a factor of 20 or more. This concept is worth remembering when considering drug absorption kinetics.

From Scheme 14.1, equation 14.2 can be written to describe the rate of change in the amount of drug, A, in the body.

$$\frac{dA}{dt} = k_a X - k_{el} A \qquad (14.2)$$

In this equation, X is the amount of drug remaining to be absorbed as described in equation 14.1. By substituting for X from equation 14.1 and then integrating, equation 14.3 is obtained.

$$A = FD\frac{k_a}{k_a - k_{el}}\{e^{-k_{el}t} - e^{-k_a t}\} \qquad (14.3)$$

This equation can then be converted to describe time-dependent drug concentrations by dividing both sides by the distribution volume, V, to obtain equation 14.4, which describes the drug profile shown in Figure 14.1.

$$C = \frac{FD}{V}\left(\frac{k_a}{k_a - k_{el}}\right)\{e^{-k_{el}t} - e^{-k_a t}\} \qquad (14.4)$$

Now that the kinetic parameters associated with the one-compartment model with first-order absorption and elimination have been identified, the next step is to understand how numerical values are assigned to these parameters from a drug-concentration profile. Understanding the variable relationship between k_a, the absorption rate constant, and k_{el}, the elimination rate constant, is important. Three different situations can occur:

1. k_a may be greater than k_{el}.
2. k_a may be less than k_{el}.
3. The two constants may have the same, or approximately the same, numerical value.