Appendix A

Method of Laplace Transforms

Rate equations that describe apparent zero-order or first-order processes are termed linear equations. The Laplace transform is used for solving linear differential equations and hence is applicable to the solution of many equations used for pharmacokinetic analysis. A rigorous mathematical development of the Laplace transform method will not be provided herein. However, the basic idea of the method and its application in solving relatively simple differential equations in pharmacokinetics will be examined. For a more detailed treatment, the reader is referred to several books [1–3] and particularly to a programmed text [4] that should prove useful.

Essentially what the Laplace transform does is replace the time domain of a rate expression by the complex domain of the Laplace operator s. This is achieved by eliminating the independent variable (in pharmacokinetics this variable is always time) and replacing it with the Laplace operator. The Laplace transform enables complex rate expressions to be manipulated easily by conventional algebraic techniques once the time variable has been replaced by the Laplace operator s. Since most problems fall into certain patterns, the transformed expression may be rearranged into a form that can generally be found in a table of Laplace transforms. Values for initial conditions may be included in the transformed expression. Consequently, upon transformation back into the time domain, the complete solution to the differential equation is obtained.

The means by which a time-dependent expression is transformed into the s domain is given by the Laplace integral Lf(t), which is defined by

$$Lf(t) = \int_0^\infty e^{-st} f(t)\, dt \qquad (A.1)$$

where f(t) is the time-dependent function. Thus the function is multiplied by e^{-st}, and this product is evaluated by integration from time zero to time infinity.

The Laplace transform of several expressions will be derived using the Laplace integral simply to illustrate how the transforms are obtained. However, once certain transformed functions that are used repeatedly in pharmacokinetics are established, the use of the integral may be dispensed with for future transformations simply by constructing an appropriate table of transforms and referring to this table for the transform of the desired time-dependent expression. For example, to obtain the transform of a constant A, the Laplace integral can be applied:

$$L(A) = \int_0^\infty e^{-st} A \, dt \tag{A.2}$$

which when integrated becomes

$$L(A) = A\left(-\frac{1}{s}\right)e^{-st}\Big|_0^\infty \tag{A.3}$$

Evaluation of this equation between the limits of time zero and infinity yields

$$L(A) = \frac{A}{s} \tag{A.4}$$

Thus the transform of any constant will take the form given in Eq. (A.4). The transform of the constant k_0, for example, will simply be k_0/s. Initially, derivation of the transform of a function requires some knowledge of integral calculus. However, once these transforms are known, no integration is required.

The transformation of an exponential function is also readily accomplished. Proceeding as before, the Laplace integral may be applied to the function e^{-at}:

$$L(e^{-at}) = \int_0^\infty e^{-st}(e^{-at})\, dt = \int_0^\infty e^{-(s+a)t}\, dt \tag{A.5}$$

which when integrated yields

$$L(e^{-at}) = -\frac{1}{s+a}e^{-(s+a)t}\Big|_0^\infty = \frac{1}{s+a} \tag{A.6}$$

If this exponential is multiplied by a constant, for example Ae^{-at}, the resulting transform is found to be $A/(s + a)$.

A function that is used quite often is the derivative expression $df(t)/dt$. The Laplace integral is

$$L\frac{df(t)}{dt} = \int_0^\infty e^{-st}\frac{df(t)}{dt}\, dt \tag{A.7}$$

Solving this integral by integration by parts yields

$$\int_0^\infty e^{-st}\frac{df(t)}{dt}\,dt = e^{-st}f(t)\Big|_0^\infty - \int_0^\infty -se^{-st}f(t)\,dt \qquad (A.8)$$

since

$$\int_a^b h(x)\frac{dg(x)}{dx}dx = h(x)g(x)\Big|_a^b - \int_a^b \frac{dh(x)}{dx}g(x)\,dx \qquad (A.9)$$

and

$$\frac{de^{-st}}{dt} = -se^{-st} \qquad (A.10)$$

Equation (A.8) may be simplified to

$$\int_0^\infty e^{-st}\frac{df(t)}{dt}\,dt = -f(0) + \int_0^\infty e^{-st}f(t)\,dt \qquad (A.11)$$

In this equation $\int_0^\infty e^{-st}f(t)\,dt$ equals $Lf(t)$ [see (A.1)]. Therefore,

$$\int_0^\infty e^{-st}\frac{df(t)}{dt}\,dt = -f(0) + sLf(t) \qquad (A.12)$$

Hence the Laplace transform of $df(t)/dt$ is given by

$$L\frac{df(t)}{dt} = sLf(t) - f(0) \qquad (A.13)$$

where $f(t)$ is the time-dependent function we are interested in finding, $df(t)/dt$ is the derivative of this function (as in a rate expression, for example dC/dt), and $f(0)$ is the value of the function at time zero (initial condition).

The approach outlined above has been used in determining the Laplace transforms of many functions. Some of the most useful of these are presented in Table A.1. On the left side of the table are the time-domain functions that are commonly encountered in rate expressions. The corresponding, s-domain, Laplace transforms are shown on the right side of Table A.1, opposite their time functions.

There are examples throughout Chap. 1 illustrating the use of the method of Laplace transforms for solving linear differential equations. The derivation of the expression describing the time course of the amount of drug in the body during zero-order intravenous infusion will be presented here to illustrate the steps that should be followed in solving such equations. Initially, the rate expression for the species of interest should be written. In this example the rate expression is

$$\frac{dX}{dt} = k_0 - KX \qquad (A.14)$$

Table A.1 Laplace Transforms of Some Common Functions

Function, F(t)	Laplace Transform, f(s)
1	$\frac{1}{s}$
A	$\frac{A}{s}$
t	$\frac{1}{s^2}$
t^m	$\frac{m!}{s^{m+1}}$
Ae^{-at}	$\frac{A}{s+a}$
Ate^{-at}	$\frac{A}{(s+a)^2}$
$\frac{A}{a}(1-e^{-at})$	$\frac{A}{s(s+a)}$
$\frac{A}{a}e^{-(b/a)t}$	$\frac{A}{as+b}$
$\frac{(B-Aa)e^{-at}-(B-Ab)e^{-bt}}{b-a}$ $(b \neq a)$	$\frac{As+B}{(s+a)(s+b)}$
$\frac{A}{b-a}(e^{-at}-e^{-bt})$	$\frac{A}{(s+a)(s+b)}$
$e^{-at}[A+(B-Aa)t]$	$\frac{As+B}{(s+a)^2}$
$-\frac{1}{PQR}[P(Aa^2-Ba+C)e^{-at}$ $+Q(Ab^2-Bb+C)e^{-bt}+R(Ac^2-Bc+C)e^{-ct}]$ $(P=b-c,\ Q=c-a,\ R=a-b)$	$\frac{As^2+Bs+C}{(s+a)(s+b)(s+c)}$
$A\left[\frac{1}{ab}+\frac{1}{a(a-B)}e^{-at}-\frac{1}{b(a-b)}e^{-bt}\right]$	$\frac{A}{s(s+a)(s+b)}$
$\frac{A}{a}t-\frac{A}{a^2}(1-e^{-at})$	$\frac{A}{s^2(s+a)}$
$\frac{B}{ab}-\frac{Aa-B}{a(a-b)}e^{-at}+\frac{Ab-B}{b(a-b)}e^{-bt}$	$\frac{As+B}{s(s+a)(s+b)}$
$\frac{B}{ab}-\frac{a^2-Aa+B}{a(b-a)}e^{-at}+\frac{b^2-Ab+B}{b(b-a)}e^{-bt}$	$\frac{s^2+As+B}{s(s+a)(s+b)}$

From Ref. 5.

where X is the amount of drug in the body, k_0 the zero-order infusion rate, and K the apparent first-order rate constant for elimination of drug from the body. Taking the Laplace transform of each term yields

$$sLf(X) - X(0) = \frac{k_0}{s} - KLf(X) \tag{A.15}$$

For simplicity in writing such transformed expressions, the following convention will be employed. A bar will be placed over the dependent variable that is being transformed. Thus

$$s\bar{X} - X(0) = \frac{k_0}{s} - K\bar{X} \tag{A.16}$$

This greatly facilitates representation of transformed expressions.

The symbol X_0 or D (dose) rather than X(0) is generally employed for the initial amount of X present at time zero. In the present example X_0 equals zero since there is no drug in the body at time zero. Setting X(0) equal to zero in (A.16) and solving for $\bar{X}$ yields

$$\bar{X} = \frac{k_0}{s(s + K)} \tag{A.17}$$

which is the transform of the desired quantity X. An expression identical in form to the right-hand side of (A.17) may be found under the column for Laplace transforms in Table A.1. This expression is $A/s(s + a)$.

The time-dependent function F(t) for this transform is $A(1 - e^{-at})/a$ (see Table A.1). Since k_0 is A and K is a, the expression for the amount of drug in the body X as a function of time following intravenous infusion may be readily written

$$X = \frac{k_0}{K}(1 - e^{-Kt}) \tag{A.18}$$

This equation is the complete solution to the differential equation given in (A.14).

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Appendix B

Method for Solving Linear Mammillary Models

A method is available which permits, by means of some very simple general treatments, the derivation of equations for any linear mammillary compartment model with any first- or zero-order, or bolus (instantaneous) input process. This is accomplished by the use of (1) general input and disposition functions, (2) a method for solving partial fractions to obtain solutions to Laplace transforms, and (3) a multiple-dosing function. The input function and the disposition function are defined such that the product of these two functions yields the Laplace transform of the equation describing the time course of a drug in a model compartment. A disposition function defines the model necessary to describe drug levels in the body or a compartment thereof. Disposition describes everything that happens to a drug (i.e., distribution and elimination through all possible routes) when input into the system occurs instantaneously. Input functions describe the processes necessary to get the drug into the body. They may either describe an intravenous bolus injection, an intravenous infusion, or first- or zero-order absorption from a site such as the gastrointestinal tract or a muscle.

The following general equation has been empirically derived to describe the Laplace transform for the disposition function of the central compartment in a linear N-compartment mammillary model where elimination of drug from any compartment is allowed:

$$d_{s,c} = \frac{\prod_{i=2}^{N} (s + E_i)}{\prod_{i=1}^{N} (s + E_i) - \sum_{j=2}^{N} \left[k_{1j} k_{j1} \prod_{\substack{m=2 \\ m \neq j}}^{N} (s + E_m) \right]} \qquad \text{(B.1)}$$

In this equation:

$d_{s,c}$ = disposition function for compartment 1, the central compartment; it is a function of s, the Laplace operator (see Appendix A)

Π = continued product where any term is defined as equal to 1 when the index takes a forbidden value; that is, i = 1 in the numerator or m = j in the denominator

Σ = continued summation where any term is defined as equal to zero when the index takes a forbidden value

k_{1j}, k_{j1} = first-order intercompartmental transfer rate constants

E_i, E_m = sum of the exit rate constants out of compartments i or m

N = number of driving force compartments in the disposition model (i.e., compartments having exit rate constants)

This equation has been employed in the text for the determination of disposition functions for several multicompartment models.

The following input functions describe the usual ways drugs get to the systemic circulation: intravenous bolus, in_s = dose; first-order absorption, $in_s = k_a \text{ dose}/(s + k_a)$, where k_a is the first-order absorption rate constant. The input function for absorption may describe absorption from any site but will usually be used for either oral or intramuscular dosing. The term "dose" in this input function refers to the amount of drug that actually gets into the system as such. Frequently, an F may appear in equations describing oral dosing, where F is the systemic availability of the drug. For intravenous infusion or zero-order absorption, $in_s = k_0(e^{-t_0 s} - e^{-Ts})s$, where k_0 is the zero-order infusion rate in units of amount per time and t_0 and T are the times when infusion begins and ends, respectively. In most cases, the intravenous infusion begins at time zero ($t_0 = 0$) and, therefore, the input function for intravenous infusion is generally $in_s = k_0(1 - e^{-Ts})/s$. This input function may be used to define zero-order input from the gastrointestinal tract as well as constant rate intravenous infusion. Input functions may also be combined if a drug is given by more than one route of administration. For example, it is common to given an intravenous bolus injection of a drug to produce therapeutic blood levels quickly followed by a zero-order infusion so that these blood levels may be maintained. In this case, the input function in_s would equal dose + $k_0(1 - e^{-Ts})/s$ if the infusion began at the same time that the bolus injection was administered.

The product of the input and disposition functions yields the Laplace transform for the amount of drug in the central compartment, $a_{s,c}$:

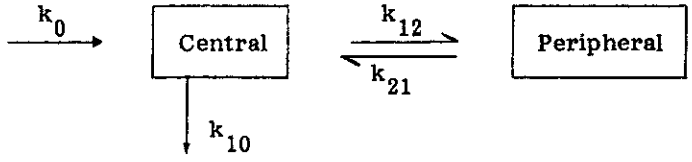
$$a_{s,c} = in_s d_{s,c} \tag{B.2}$$

The anti-Laplace of the resulting transform may be found in an extensive table of Laplace transforms. However, the method of partial fractions is generally easier to apply. The use of a general partial fraction theorem for obtaining inverse Laplace transforms, denoted L^{-1}, has been described [1]. If the quotient of two polynomials $P(s)/Q(s)$ is such that $Q(s)$ has a higher degree and contains the factor $s - \Lambda_i$, which is not repeated, then

$$L^{-1}\frac{P(s)}{Q(s)} = \sum_{i=1}^{N} \frac{P(\Lambda_i)}{Q_i(\Lambda_i)} e^{\Lambda_i t} \tag{B.3}$$

where Λ_i's are the roots of the polynomial $Q(s)$. $Q_i(\Lambda_i)$ is the value of the denominator when Λ_i is substituted for all s terms except for the term originally containing Λ_i, this term being omitted. The $P(\Lambda_i)$ terms are obtained by substitution of the appropriate root for every value of s in the numerator. If a repeating function appears in the denominator, an alternative approach discussed in Ref. 2 must be used. The complex symbolism of Eq. (B.3) will be clarified in the following illustration.

To illustrate the application of this approach for solving linear differential equations, a two-compartment model with zero-order input will be employed. This model is represented by the following scheme:



where k_0 is the zero-order infusion rate constant, k_{12} and k_{21} are apparent first-order intercompartmental rate constants, and k_{10} is the apparent first-order elimination rate constant from the central compartment. The disposition function for the central compartment can readily be written by setting N equal to 2, in Eq. (B.1), since there are two driving force compartments in a two-compartment model. Hence

$$d_{s,c} = \frac{s + E_2}{(s + E_1)(s + E_2) - k_{12}k_{21}} \tag{B.4}$$

where E_1 and E_2 are the sum of the exit rate constants from the central and peripheral compartments, respectively, that is, $E_1 = k_{10} + k_{12}$ and $E_2 = k_{21}$.

A term with s to the second power appears in the denominator of Eq. (B.4), since there are two driving force compartments in the model. As a result, the equation describing the disposition function for the central compartment is biexponential. Therefore, Eq. (B.4) may be rewritten

$$d_{s,c} = \frac{s + E_2}{(s + \lambda_1)(s + \lambda_2)} \tag{B.5}$$

The constants λ_1 and λ_2 may be expressed in terms of the individual rate constants when the denominators of (B.4) and (B.5) are expanded in terms of the coefficients of the powers of s.

Multiplication of this disposition function by the input function for an intravenous infusion beginning at time zero [i.e., $in_s = k_0(1 - e^{-Ts})/s$] yields the following Laplace transform for the amount of drug in the central compartment:

$$a_{s,c} = \frac{k_0(s + E_2)(1 - e^{-Ts})}{s(s + \lambda_1)(s + \lambda_2)} \tag{B.6}$$

The two polynomials in this equation fulfill the requirements for the use of (B.3). Hence the solution for the amount of drug in the central compartment X_c as a function of time may be readily written

$$X_c = \frac{k_0(E_2 - \lambda_1)(1 - e^{\lambda_1 T})}{-\lambda_1(\lambda_2 - \lambda_1)} e^{-\lambda_1 t} + \frac{k_0(E_2 - \lambda_2)(1 - e^{\lambda_2 T})}{-\lambda_2(\lambda_1 - \lambda_2)} e^{-\lambda_2 t} \tag{B.7}$$

Note that even though there are three roots (0, $-\lambda_1$, and $-\lambda_2$) in the denominator of (B.6), there are only two terms in (B.7). This is because the numerator of (B.6) becomes zero when the root zero is substituted for every value of s. It should also be noted that (B.7), a single equation, describes the amount of drug in the central compartment as a function of time while infusion is being carried out and after infusion stops. While infusion is continuing, T = t and varies with time. However, when infusion ceases, T becomes a constant corresponding to the time infusion was stopped.

Haborak et al. [3] have pointed out that although the constant rate infusion input function leads to a correct equation for the time course of drug in the central compartment [Eq. (B.7)], the approach is technically incorrect because the presence of the term $1 - e^{-Ts}$ in the numerator of (B.6) destroys the polynomial character of the numerator. Benet [4] acknowledges this discrepancy but suggests that apparently the restriction concerning the polynomial character of the

numerator may be relaxed when exponential functions appear in the numerator due to the inclusion of a zero-order input function. The approach outlined above gives the correct equations for the usual multicompartment pharmacokinetic models with zero-order input into the central or peripheral compartments.

A mammillary model may also be solved for compartments other than the central compartment. For example, to obtain an equation that would describe the time course of drug in the peripheral compartment of a two-compartment model following intravenous infusion, the following approach can be employed. The differential equation describing the peripheral compartment is

$$\frac{dX_p}{dt} = k_{12}X_c - k_{21}X_p \tag{B.8}$$

where X_p is the amount of drug in the peripheral compartment and k_{12}, k_{21}, and X_c are as defined previously. Taking the Laplace transform of (B.8) yields

$$s(a_{s,p}) = k_{12}a_{s,c} - k_{21}a_{s,p} \tag{B.9}$$

where $a_{s,p}$ is the Laplace transform for the amount of drug in the peripheral compartment. Solving this equation for $a_{s,p}$ and substituting the value of $a_{s,c}$ as given in (B.6) into the resulting equation yields the following expression for $a_{s,p}$:

$$a_{s,p} = \frac{k_{12}k_0(s + E_2)(1 - e^{-Ts})}{s(s + k_{21})(s + \lambda_1)(s + \lambda_2)} \tag{B.10}$$

Since E_2 equals, k_{21}, Eq. (B.10) reduces to

$$a_{s,p} = \frac{k_{12}k_0(1 - e^{-Ts})}{s(s + \lambda_1)(s + \lambda_2)} \tag{B.11}$$

This equation can be readily solved for the amount of drug in the peripheral compartment employing the method of partial fractions [i.e., Eq. (B.3)]. Hence

$$X_p = \frac{k_{12}k_0(1 - e^{\lambda_1 T})}{-\lambda_1(\lambda_2 - \lambda_1)} e^{-\lambda_1 t} + \frac{k_{12}k_0(1 - e^{\lambda_2 T})}{-\lambda_2(\lambda_1 - \lambda_2)} e^{-\lambda_2 t} \tag{B.12}$$

It has been shown [5] that any equation describing the time course of drug in a driving force compartment after a single dose may be changed into a multiple-dose equation by multiplying each exponential term containing t (time), $e^{-k_i t}$, by the function

$$\frac{e^{(n-1)k_i\tau} - e^{-k_i\tau}}{1 - e^{-k_i\tau}}$$

where τ is the constant dosing interval, k_i is the apparent first-order rate constant in each exponential term, and n equals the number of doses. It can be demonstrated that

$$\frac{e^{(n-1)k_i\tau} - e^{-k_i\tau}}{1 - e^{-k_i\tau}} e^{-k_i t} = \frac{1 - e^{-nk_i\tau}}{1 - e^{-k_i\tau}} e^{-k_i[t-(n-1)\tau]}$$

$$= \frac{1 - e^{-nk_i\tau}}{1 - e^{-k_i\tau}} e^{-k_i t'} \qquad \text{(B.13)}$$

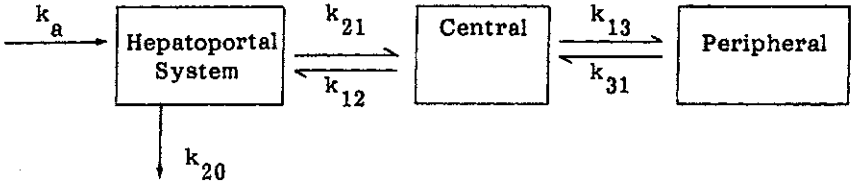
where $t' = t - (n-1)\tau$, the time since the last dose was given (i.e., the time during a dosing interval where $0 \leq t' \leq \tau$). The application of the function

$$\frac{1 - e^{-nk_i\tau}}{1 - e^{-k_i\tau}}$$

for converting single-dose equations to multiple-dose equations is discussed in Chap. 3.

In addition to the material covered in this appendix, a situation where one mammillary model serves as an input function into a second mammillary model has also been considered [2].

A model that has appeared in the pharmacokinetic literature and may not be solved employing the techniques presented in this appendix is depicted in the following scheme:



In this model k_{12}, k_{21}, k_{13}, and k_{31} are apparent first-order intercompartmental rate constants, k_a is an apparent first-order absorption rate constant, and k_{20} is the apparent first-order elimination rate constant of drug from the hepatoportal system. This particular model has been employed to describe the disposition of a drug subject to first-pass metabolism following oral drug administration. Since drug

enters the body via the hepatoportal compartment, this model behaves mathematically like a catenary rather than a mammillary system. The method of Laplace transforms (Appendix A) can be used to obtain a solution. A general treatment of simultaneous input into and elimination from a peripheral compartment has been described by Vaughan and Trainor [6].

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Appendix C
Method of Residuals

The method of residuals is a commonly used technique in pharmacokinetics for resolving a curve into its various exponential components. The terms feathering, peeling, and stripping are also used to describe this technique. Application of the method of residuals is probably most clearly illustrated by employing specific numerical examples. Hence four examples have been selected to demonstrate the application of this technique.

The first example is the case where a drug administered orally is absorbed by apparent first-order kinetics and confers the characteristics of a one-compartment model on the body. The following equation has been employed to describe the time course of such a drug in the body:

$$C = \frac{k_a F X_0}{V(k_a - k)} (e^{-Kt} - e^{-k_a t}) \qquad (C.1)$$

where C is the plasma concentration of drug at any time t following the administration of dose X_0, V is the apparent volume of distribution, F is the fraction of the orally administered dose which is absorbed, and k_a and K are the apparent first-order absorption and elimination rate constants, respectively. Assuming that $k_a > K$, the term $e^{-k_a t}$ in (C.1) will approach zero, whereas the term e^{-Kt} retains a finite value. At some time (C.1) will reduce to

$$C = \frac{k_a F X_0}{V(k_a - K)} e^{-Kt} \qquad (C.2)$$

which can be written in terms of common logarithms as follows:

$$\log C = \log \frac{k_a F X_0}{V(k_a - K)} - \frac{Kt}{2.303} \qquad (C.3)$$

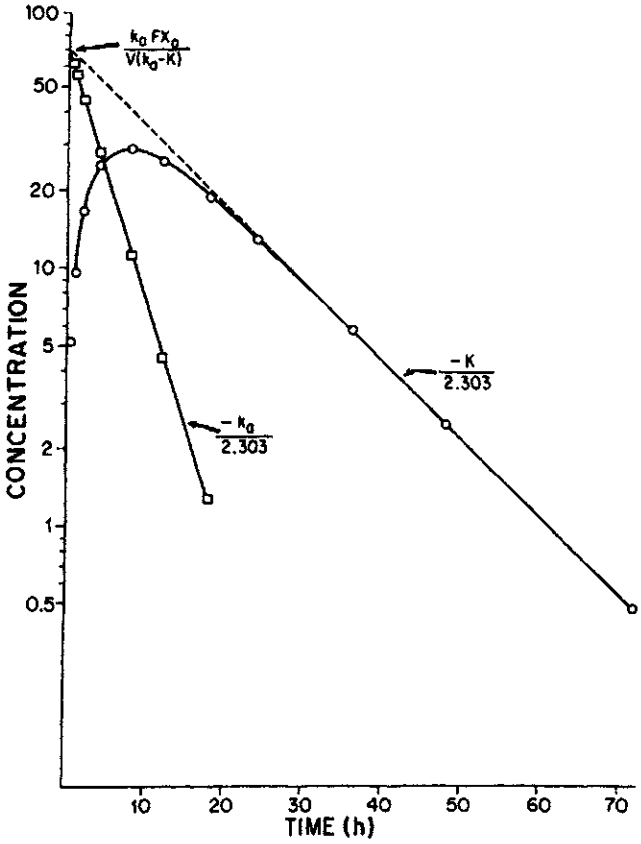

Fig. C.1 Drug concentration in plasma (O) after oral administration of a drug (see Table C.1). Residual values are denoted by (□). See Eqs. (C.1) to (C.5).

Based on these relationships, a plot of the logarithm of plasma drug concentration versus time following oral administration will be biexponential with a terminal linear phase having a slope of $-K/2.303$ (see Fig. C.1, which is a plot of the concentration-time data presented in Table C.1). Since the terminal linear phase is described by (C.3), extrapolation of this straight line to time zero will yield an intercept equal to log $[k_a FX_0/V(k_a - K)]$.

Subtraction of the true plasma drug concentration-time values in the absorptive phase from the corresponding concentration-time values on the extrapolated line yields a series of residual concentration values (see Table C.1). These residual values are described by the following equation, which is obtained by subtracting (C.1) from (C.2):

Table C.1 Application of the Method of Residuals to Data Obtained After Oral Administration of a Drug

Time (h)	Plasma Concentration (μg/ml)	Extrapolated Concentration (μg/ml)	Residual Concentration (μg/ml)
0.5	5.36	69.0	63.64
1.0	9.95	66.5	56.55
2.0	17.18	62.5	45.32
4.0	25.78	54.0	28.22
8.0	29.78	41.2	11.42
12.0	26.63	31.2	4.57
18.0	19.40	20.7	1.30
24.0	13.26		
36.0	5.88		
48.0	2.56		
72.0	0.49		

Notes: First-order absorption and a one-compartment model are assumed. $K = 0.0693\ h^{-1}$, $k_a = 0.231\ h^{-1}$, $V = 10$ liters, $X_0 = 500$ mg, $F = 1$.

$$C_r = \frac{k_a F X_0}{V(k_a - K)} e^{-k_a t} \tag{C.4}$$

where C_r is the residual plasma concentration. In terms of common logarithms Eq. (C.4) becomes

$$\log C_r = \log \frac{k_a F X_0}{V(k_a - K)} - \frac{k_a t}{2.303} \tag{C.5}$$

Hence a plot of the logarithm of the residual concentrations versus time will yield a straight line with a slope of $-k_a/2.303$ and a zero-time intercept equal to $\log [k_a F X_0/V(k_a - K)]$. Application of the method of residuals has enabled resolution of the plasma level-time curve in Fig. C.1 into its two exponential components.

A second example is the resolution of a plasma concentration-time curve obtained following intravenous administration of a drug that confers multicompartment characteristics on the body. To illustrate this type of curve, a two-compartment model is employed. The resulting curve can be described by the following biexponential equation:

$$C = Ae^{-\alpha t} + Be^{-\beta t} \tag{C.6}$$

where α and β are the apparent first-order fast and slow disposition rate constants, respectively, and A and B are the corresponding zero-time intercepts. Since α is larger than β, by definition, the term $Ae^{-\alpha t}$ will approach zero more rapidly than will the term $Be^{-\beta t}$, and Eq. (C.6) will then reduce to

$$C = Be^{-\beta t} \tag{C.7}$$

which in terms of common logarithms is

$$\log C = \log B - \frac{\beta t}{2.303} \tag{C.8}$$

This equation describes the terminal linear phase of the curve resulting from a plot of the logarithm of plasma concentration versus time. This terminal linear phase has a slope of $-\beta/2.303$, and when extrapolated to zero yields an intercept of log B (see Fig. C.2).

By subtracting the concentration-time values on the extrapolated line from the corresponding true plasma concentration-time values, a series of residual concentration-time values will be obtained (see Table C.2). These residual concentrations C_r are described by

Table C.2 Application of the Method of Residuals to Data Obtained After Intravenous Administration of a Drug

Time (h)	Plasma Concentration (μg/ml)	Extrapolated Concentration (μg/ml)	Residual Concentration (μg/ml)
0.165	65.03	4.65	60.38
0.5	28.69	4.26	24.43
1.0	10.04	3.73	6.31
1.5	4.93	3.30	1.63
3.0	2.29		
5.0	1.36		
7.5	0.71		
10.0	0.38		

Notes: An instantaneous intravenous bolus dose and a two-compartment open model are assumed. A = 95 μg/ml, B = 4.85 μg/ml, $\alpha = 2.718\ h^{-1}$, $\beta = 0.254\ h^{-1}$, $X_0 = 1$ g.

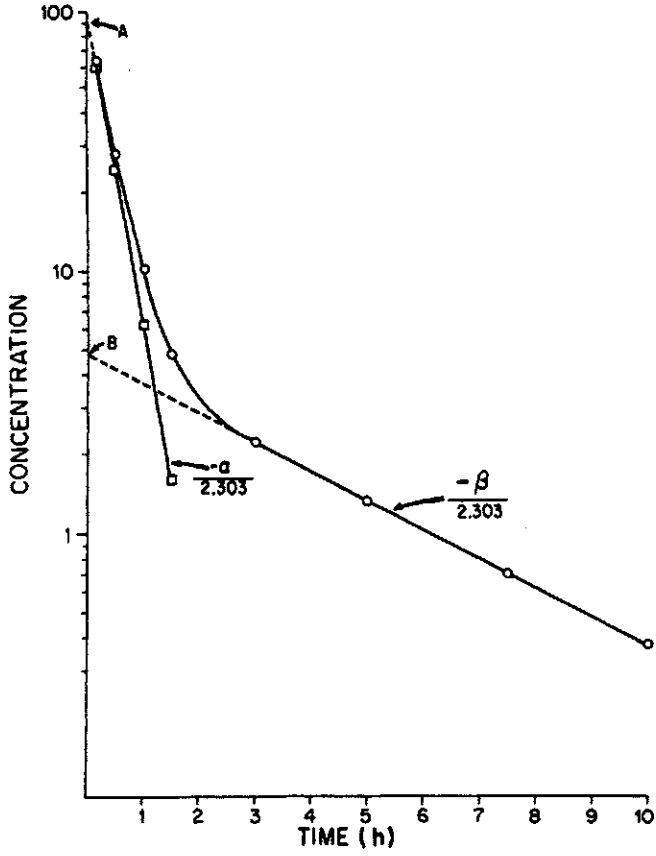

Fig. C.2 Drug concentration in plasma (O) after intravenous administration of a drug (see Table C.2). Residual values are denoted by (□). See Eqs. (C.6) to (C.10).

$$C_r = Ae^{-\alpha t} \tag{C.9}$$

which is arrived at by subtracting (C.7) from (C.6). When expressed as common logarithms, Eq. (C.9) becomes

$$\log C_r = \log A - \frac{\alpha t}{2.303} \tag{C.10}$$

Therefore, a plot of the logarithm of the residual concentration values versus time will yield a straight line with a slope of $-\alpha/2.303$ and a zero-time intercept of log A (see Fig. C.2). Resolution of the biexponential curve thereby enables the determination of all parameters in Eq. (C.6), which will in turn permit the estimation of the two-

compartment model parameters k_{12}, k_{21}, k_{10}, and V_c (see Chap. 2). The method of residuals can also be employed to resolve plasma-level curves which require more than two exponentials for their description.

Urinary excretion data can also be resolved employing the method of residuals. For example, following the oral administration of a drug that confers the characteristics of a one-compartment model on the body, the urinary excretion of unchanged drug can be evaluated employing the sigma-minus method according to the equation

$$X_u^\infty - X_u = \frac{X_u^\infty}{k_a - K}(k_a e^{-Kt} - Ke^{-k_a t}) \tag{C.11}$$

In this equation X_u^∞ and X_u are the cumulative amounts of unchanged drug excreted in the urine to time infinity (i.e., at least seven half-lives) and time t, respectively. The constants k_a and K are as defined previously in this appendix.

Absorption is generally assumed to occur at a faster rate than elimination. Therefore, the term $Ke^{-k_a t}$ will approach zero while the term $k_a e^{-Kt}$ has a finite value resulting in Eq. (C.11) reducing to

$$X_u^\infty - X_u = \frac{X_u^\infty k_a}{k_a - K} e^{-Kt} \tag{C.12}$$

Writing this equation in common logarithms yields

$$\log (X_u^\infty - X_u) = \log \frac{X_u^\infty k_a}{k_a - K} - \frac{Kt}{2.303} \tag{C.13}$$

Based on these relationships, if urine samples were collected at sufficiently frequent intervals immediately following oral administration, a plot of $\log (X_u^\infty - X_u)$ versus time should result in a biexponential curve with a terminal linear phase having a slope of $-K/2.303$. Extrapolation of this terminal phase to time zero will yield an intercept of $\log [X_u^\infty k_a/(k_a - K)]$ (see Fig. C.3, which is a plot of the data presented in Table C.3).

Subtracting the true $X_u^\infty - X_u$ values from the values on the extrapolated line at the same time period [i.e., (C.12) minus (C.13)] yields a series of residual $X_u^\infty - X_u$ values (Table C.3) which can be described by the equation

$$(X_u^\infty - X_u)_r = \frac{X_u^\infty K}{k_a - K} e^{-k_a t} \tag{C.14}$$

In this equation $(X_u^\infty - X_u)_r$ is the residual sigma-minus value. Writing Eq. (C.14) in terms of common logarithms yields

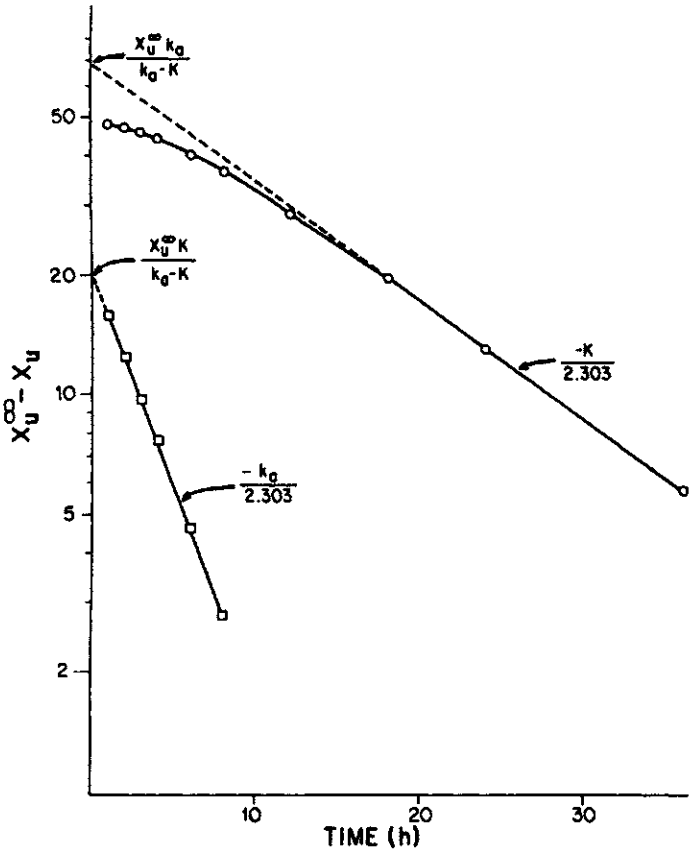

Fig. C.3 Amount of drug remaining to be excreted (O) after oral administration (see Table C.3). Residual values are denoted by (□). See Eqs. (C.11) to (C.15).

$$\log (X_u^\infty - X_u)_r = \log \frac{X_u^\infty K}{k_a - K} - \frac{k_a t}{2.303} \qquad (C.15)$$

Therefore, by plotting the logarithm of the residual $X_u^\infty - X_u$ values [$\log (X_u^\infty - X_u)_r$] versus time, a straight line with a slope of $-k_a/2.303$ and an intercept of $\log [X_u^\infty K/(k_a - K)]$ would result (see Fig. C.3). The method of residuals, therefore, permits the resolution of a sigma-minus plot into its exponential components.

A final example illustrating the application of the method of residuals is the resolution of the plasma concentration-time curve of a

Table C.3 Application of the Method of Residuals to Urinary Excretion Data Obtained After Oral Administration of a Drug

Time (h)	X_u[a] (mg)	$X_u^\infty - X_u$ (mg)	Extrapolated $X_u^\infty - X_u$ (mg)	Residual $X_u^\infty - X_u$ (mg)
1.0	0.36	49.64	65.8	16.16
2.0	1.32	48.68	61.5	12.82
3.0	3.70	47.30	57.3	10.0
4.0	4.37	45.63	53.5	7.87
6.0	8.23	41.77	46.5	4.73
8.0	12.35	37.65	40.5	2.85
12.0	20.24	29.76		
18.0	29.82	20.18		
24.0	36.55	13.45		
36.0	44.11	5.90		
∞	50.00			

[a]Cumulative amount of drug in the urine.

Notes: The data are analyzed using the sigma-minus method. First-order absorption and a one-compartment model are assumed. $K = 0.0693\ h^{-1}$, $k_a = 0.231\ h^{-1}$, $V = 10$ liters, $X_0 = 500$ mg, $F = 1$.

drug which when administered orally confers the pharmacokinetic characteristics of a two-compartment model on the body. The equation describing such a curve is

$$C = Ne^{-k_a t} + Le^{-\alpha t} + Me^{-\beta t} \tag{C.16}$$

where k_a, α, and β are as defined previously in this appendix and L, M, and N are coefficients.

Since α is by definition larger than β, and since k_a is generally assumed to be larger than β, the terms $Ne^{-k_a t}$ and $Le^{-\alpha t}$ will approach zero while the term $Me^{-\beta t}$ will retain some finite value. Equation (C.16) will then reduce to

$$C = Me^{-\beta t} \tag{C.17}$$

This equation can be written in terms of common logarithms as follows:

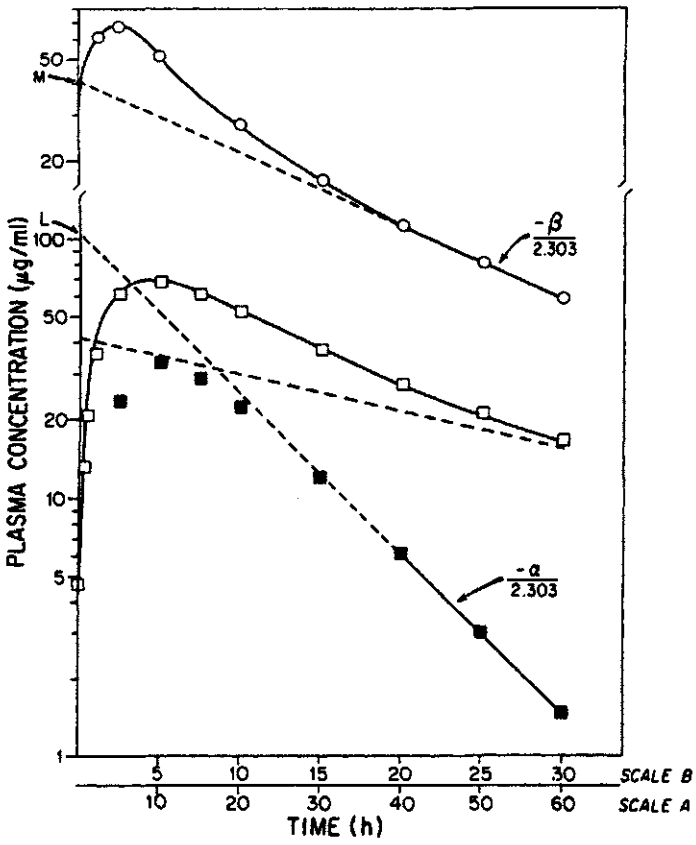

Fig. C.4 Drug concentration in plasma (O, time scale A; □, time scale B) after oral administration of a drug (see Table C.4). First residual values are denoted by (■) and are plotted on time scale B. See Eqs. (C.16) to (C.21).

$$\log C = \log M - \frac{\beta t}{2.303} \tag{C.18}$$

which describes the terminal lines phase of the curve resulting from a plot of the logarithm of the plasma concentration versus time. The slope of this terminal linear phase is $-\beta/2.303$, and when extrapolated to time zero yields an intercept of log M (see Fig. C.4).

Subtraction of the concentration-time values on the extrapolated line from the corresponding true plasma concentration-time values produces a series of residual concentration-time values (see Table C.4). The equation describing the time course of these residual concentrations C_{r1} is obtained by subtracting (C.17) from (C.16):

Table C.4 Application of the Method of Residuals to Data Obtained After Oral Administration of a Drug

Time (h)	Plasma Concentration, C (μg/ml)	$Me^{-\beta t}$ (μg/ml)	C_{r1} (μg/ml)	$Le^{-\alpha t}$ (μg/ml)	C_{r2} (μg/ml)
0.1	4.7	41.2	−36.5	104.0	140.5
0.3	13.2	40.9	−27.7	101.0	128.7
0.5	20.8	40.6	−19.8	98.2	118.0
1	36.3	40.0	−3.7	91.5	95.2
2.5	61.4	38.0	23.4	74.0	50.6
5	68.1	35.0	33.1	51.9	18.8
7.5	61.1	32.2	28.9	36.5	7.6
10	52.1	29.7	22.4	25.6	3.2
15	37.3	25.2	12.1		
20	27.5	21.3	6.2		
25	21.1	18.1	3.0		
30	16.9	15.4	1.5		
40	11.4				
50	8.2				
60	5.9				

Notes: First-order absorption and a two-compartment open model are assumed. It is assumed further that $k_a > \alpha > \beta$. See Eqs. (C.16) to (C.23). $L = 105.0$ μg/ml, $M = 41.3$ μg/ml, $N = -146.3$ μg/ml, $\alpha = 0.141\ h^{-1}$, $\beta = 0.033\ h^{-1}$, $k_a = 0.40\ h^{-1}$, $X_0 = 1$ g, $V_c = 10$ liters, $F = 1$.

$$C_{r1} = Ne^{-k_a t} + Le^{-\alpha t} \tag{C.19}$$

A plot of the positive residual concentration values versus time will yield a biexponential curve (see Fig. C.4). Assuming that k_a is greater than α, the term $Ne^{-k_a t}$ will approach zero while the term $Le^{-\alpha t}$ still has a finite value, and (C.19) will then reduce to

$$C_{r1} = Le^{-\alpha t} \tag{C.20}$$

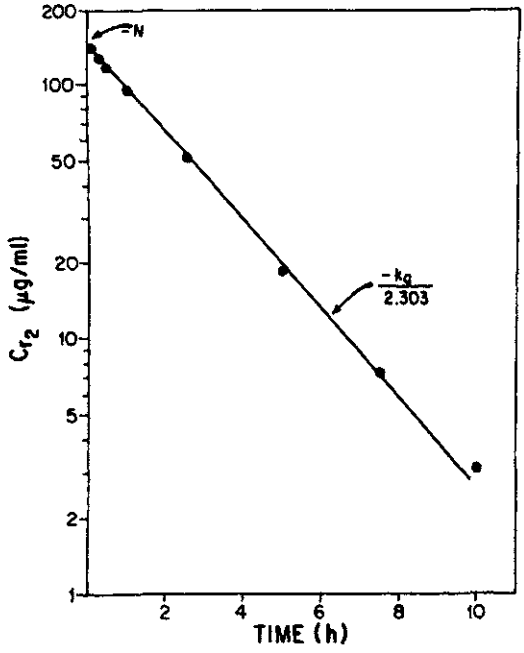

Fig. C.5 Plot of second residual values (see Table C.4) to estimate the apparent first-order absorption rate constant. See Eqs. (C.22) and (C.23).

which in terms of common logarithms is

$$\log C_{r1} = \log L - \frac{\alpha t}{2.303} \tag{C.21}$$

This equation describes the terminal linear phase of the residual curve resulting from a plot of log C_{r1} versus time. The slope of the resulting straight line will be $-\alpha/2.303$, and when extrapolated to time zero will yield an intercept of log L (see Fig. C.4).

This residual curve can be resolved further. Subtracting the residual concentration values C_{r1} from the corresponding concentration-time values on the extrapolated residual line yields a second series of residual concentration-time values (see Table C.4). These residual concentrations C_{r2} are described by the following equation, which is obtained by subtracting (C.19) from (C.20):

$$C_{r2} = -Ne^{-k_a t} \tag{C.22}$$

which when transformed to common logarithms becomes

$$\log C_{r2} = \log (-N) - \frac{k_a t}{2.303} \qquad (C.23)$$

Hence a plot of the logarithm of C_{r2} versus time will yield a straight line with a slope of $-k_a/2.303$ and a zero-time intercept of log $(-N)$ (see Fig. C.5). Application of the method of residuals thus permits the resolution of Eq. (C.16) into its three exponential components, and hence estimation of the parameters k_a, α, β, N, L, and M.

The method of residuals is a useful technique for resolving essentially any multiexponential curve encountered in pharmacokinetic analysis into the individual exponential components.

Appendix D
Estimation of Areas

The estimation of areas under blood level-time curves is often required for pharmacokinetic analysis. These areas are usually estimated by employing an approximate integration formula. The trapezoidal rule is one such formula. This particular method involves the description of a given plasma concentration-time curve by a function that depicts the curve as a series of straight lines, thereby enabling the area under the curve to be divided into a number of trapezoids (see Fig. D.1). The area of each trapezoid is easily calculated, and the sum of all the areas of all the trapezoids yields an estimate of the true area under the curve.

We will let f(t) be a function that describes a given plasma concentration-time curve and $\phi(t)$ be a second function that coincides with f(t) but is linear between two consecutive blood level-time points (see Fig. D.1). Consequently, the area under the curve described by the function $\phi(t)$ [i.e., $\int_{t_0}^{t_n} \phi(t)\, dt$] will only be an approximation of the true area under the curve, $\int_{t_0}^{t_n} f(t)\, dt$.

The integral $\int_{t_0}^{t_n} \phi(t)\, dt$ can be expressed as the sum of n integrals, where n equals the number of trapezoids into which the curve is divided. Hence

$$\int_{t_0}^{t_n} \phi(t)\, dt = \int_{t_0}^{t_1} \phi(t)\, dt + \int_{t_1}^{t_2} \phi(t)\, dt + \cdots + \int_{t_{n-1}}^{t_n} \phi(t)\, dt \qquad (D.1)$$

Since each integral on the right side of this equation is the area of a trapezoid, it follows that

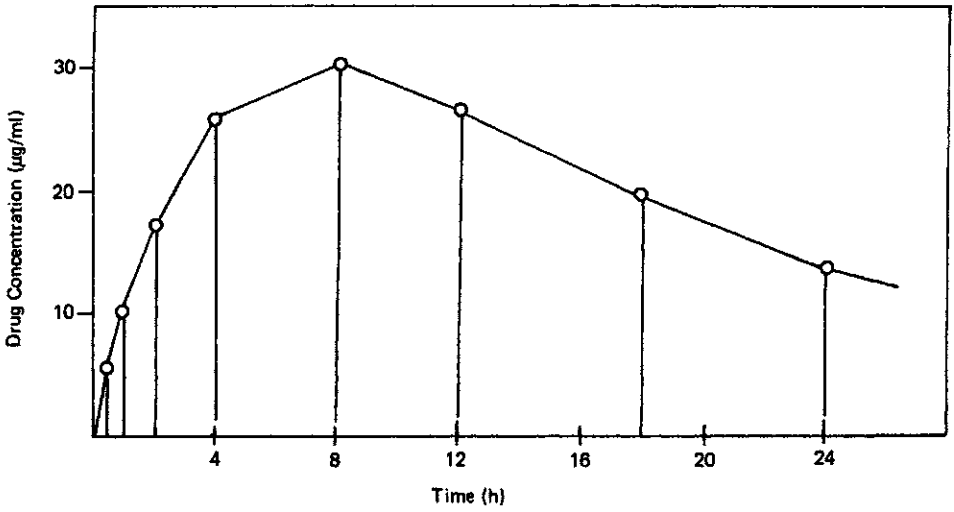

Fig. D.1 Representation of drug concentration in plasma-time profile after oral administration for the application of linear trapezoidal method to estimate areas. See Table D.1.

$$\int_{t_0}^{t_1} \phi(t)\, dt = \frac{t_1 - t_0}{2} (C_0 + C_1) \qquad (D.2)$$

where C_0 and C_1 are the plasma concentrations at times t_0 and t_1, respectively. After a single oral dose of a drug, C_0 is usually zero. C_0 has a positive value following a single intravenous dose of drug and during a dosing interval of a multiple-dose regimen. By the same token,

$$\int_{t_1}^{t_2} \phi(t)\, dt = \frac{t_2 - t_1}{2} (C_1 + C_2) \qquad (D.3)$$

and

$$\int_{t_{n-1}}^{t_n} \phi(t)\, dt = \frac{t_n - t_{n-1}}{2} (C_{n-1} + C_n) \qquad (D.4)$$

Therefore, Eq. (D.1) can be rewritten

$$\int_{t_0}^{t_n} \phi(t)\, dt = \frac{t_1 - t_0}{2}(C_0 + C_1) + \frac{t_2 - t_1}{2}(C_1 + C_2) + \cdots + \frac{t_n - t_{n-1}}{2}(C_{n-1} + C_n) \qquad (D.5)$$

If the time intervals between sampling of the plasma were the same,

$$\int_{t_0}^{t_n} \phi(t)\, dt = \frac{\Delta t}{2}(C_0 + 2C_1 + 2C_2 + \cdots + 2C_{n-1} + C_n) \qquad (D.6)$$

where Δt is the sampling time interval. However, sampling intervals are often different and a more general expression such as Eq. (D.5) must usually be employed. This equation can be written more consisely as follows:

$$\int_{t_0}^{t_n} \phi(t)\, dt = \sum_{i=0}^{n-1} \frac{t_{i+1} - t_i}{2}(C_i + C_{i+1}) \qquad (D.7)$$

The use of the trapezoidal rule as a method for approximating the area under a plasma concentration-time curve is probably best illustrated by employing a numerical example. The data from which the plasma concentration versus time curve in Fig. D.1 was constructed will be used. These data were generated by assuming first-order absorption and a one-compartment model (see Table D.1). In this particular example, 11 plasma samples were obtained after drug administration for the characterization of the curve; hence n equals 11. The approximate area under the curve can be estimated by determining the area under the 11 trapezoids and then summing these areas. The total area under the curve from zero to 72 h [$\int_0^{72} \phi(t)\, dt$] was found to be 724 μg-h/ml, which is in reasonable agreement with the true area under the curve [$\int_0^{72} f(t)\, dt$], 714 μg-h/ml.

The accuracy to which this method approximates the true area under a curve depends on the number of plasma concentration-time points within the time interval t_0 to t_n. The larger the number of samples within a given time interval, the more closely will $\int_{t_0}^{t_n} \phi(t)\, dt$ estimate $\int_{t_0}^{t_n} f(t)\, dt$, since the straight-line function $\phi(t)$ will be a more exact representation of the true function, f(t). For example, if plasma samples had been taken only at times 1, 4, 12, 24, 48, and 72 h, the estimated area would be 734 μg-h/ml, which is a poorer approximation of the true area than when the plasma was sampled more frequently.

As we have noted in the text, the *total* area under the drug concentration in blood or plasma versus time curve from t = 0 to t = ∞

Table D.1 Drug Concentration in Plasma Following Oral Administration of a Fully Absorbed 500 mg Dose, and Areas Under the Curve During Successive Time Intervals Calculated According to the Linear Trapezoidal Method

i	Time (h)	Concentration (μg/ml)	Area Under[a] Trapezoid (μg-h/ml)
0	0	0	
1	0.5	5.4	1.3
2	1.0	10.0	3.9
3	2.0	17.2	13.6
4	4.0	25.8	43.0
5	8.0	29.8	111.1
6	12.0	26.6	112.8
7	18.0	19.4	138.1
8	24.0	13.3	98.0
9	36.0	5.9	114.8
10	48.0	2.6	50.6
11	72.0	0.5	36.6
		$\int_{t_0}^{t_n} \phi(t)dt$ =	723.8

[a]Determined employing Eq. (D.7).

Note: Data generated by assuming first-order absorption (k_a = 0.231 h^{-1}) and a one-compartment model (V = 10 liters) with first-order elimination (K = 0.0693 h^{-1}).

following a single dose is calculated by combining the area to t_n, estimated by the trapezoidal rule, to the area from t_n to ∞, estimated by assuming log-linear decline. Under these conditions, this residual area is given by C_n/K or C_n/λ_n.

Yeh and Kwan [1] have noted that the linear interpolation between data points that is required to apply the trapezoidal rule tends to overestimate or underestimate the area, depending on the concavity of the curve. In cases where changes in curvature between data points are pronounced or there are long intervals between

data points, large errors are known to occur. In some instances, area estimates can be obtained by linear interpolation of logarithmically transformed data. In the log trapezoidal method the area is given by [1]

$$AUC\Big|_{t_1}^{t_2} = \frac{(C_1 - C_2)(t_2 - t_1)}{\ln C_1 - \ln C_2} \tag{D.8}$$

Equation (D.8) is most appropriate when applied to data that appear to decline exponentially. However, the method may produce large errors when used in an ascending curve, near a peak, or in a steeply descending polyexponential curve. Furthermore, the method cannot be used if either concentration is zero or if the two values are equal. Despite these limitations, the log trapezoidal method can be used advantageously in combination with a second method, such as the linear trapezoidal rule, to yield optimal estimates.

Two alternative algorithms based on known interpolating functions have been devised for area calculation. In the Lagrange method, the linear interpolations are replaced by cubic polynomial interpolations. In the spline method, the cubic functions are modified so that the fitted curves are smooth. The advantages and disadvantages of the Lagrange and spline methods relative to the trapezoidal or log trapezoidal method are discussed by Yeh and Kwan [1].

REFERENCE

1. K. C. Yeh and K. C. Kwan. A comparison of numerical integrating algorithms by trapezoidal, Lagrange, and spline approximations. *J. Pharmacokinet. Biopharm.* 6:79 (1978).

Appendix E

Prediction of Drug Concentrations on Mutliple Dosing Using the Principle of Superposition

Assuming that a drug may be characterized by linear pharmacokinetics, concentrations in blood or plasma on multiple dosing can be predicted from the corresponding concentrations after a single dose. The usual approach requires computer fitting of the data to a particular compart-

Table E.1 Predicting Drug Concentrations During Multiple Dosing Using the Principle of Superposition

Dose Number	Time (h)	Dose 1	Dose 2	Dose 3	Dose 4	Drug Concentration
1	0	0				0
	1	59				59
	2	70				70
	4	58				58
2	6	42	0			42
	7	35	59			94
	8	30	70			100
	10	21	58			79
3	12	15	42	0		57
	13	13	35	59		107
	14	10	30	70		110
	16	7	21	58		86
4	18	5	15	42	0	62
	19	4	13	35	59	111
	20	4	10	30	70	114
	22	3	7	21	58	89
	24	2	5	15	42	64

Note: It is assumed that a constant dose is given every 6 h. From Ref. 2.

Table E.2 Predicting Drug Concentrations During Multiple Dosing Using the Principle of Superposition

Dose Number	Time (h)	Dose 1	Dose 2	Dose 3	Dose 4	Drug Concentration
1	0	0				0
	1	59				59
	2	70				70
2	4	58	0			58
	5	50	59			109
	6	42	70			112
3	8	30	58	0		88
	9	25	50	59		134
	10	21	42	70		133
4	12	15	30	58	0	103
	13	13	25	50	59	147
	14	10	21	42	70	143
	16	7	15	30	58	110
	17	6	13	25	50	94
	18	5	10	21	42	78
	20	4	7	15	30	56
	21	3	6	13	25	47
	22	3	5	10	21	39
	24	2	4	7	15	28

Note: It is assumed that the same dose of drug is given four times a day (i.e., at 9 a.m., 1 p.m., 5 p.m., and 9 p.m.).

mental model and some necessarily simplistic assumption concerning the absorption kinetics of the drug. An alternative approach that requires no assumptions regarding a pharmacokinetic model or absorption kinetics is based on the principle of superposition and employs an overlay technique [1,2]. This method merely requires the assumptions that each dose of drug, in essence, acts independently of every other dose, that the rate and extent of absorption and average systemic clearance are the same for each dosing interval, and that linear pharmacokinetics apply so that a change in dose during the multiple dosing regimen can be accommodated. The overlay technique also requires a rather complete characterization of the concentration-time profile after a single dose.

In the example shown in Table E.1, it is assumed that one wishes to predict the drug concentrations in blood on multiple dosing when the same dose is taken every 6 h. The concentration data in the column

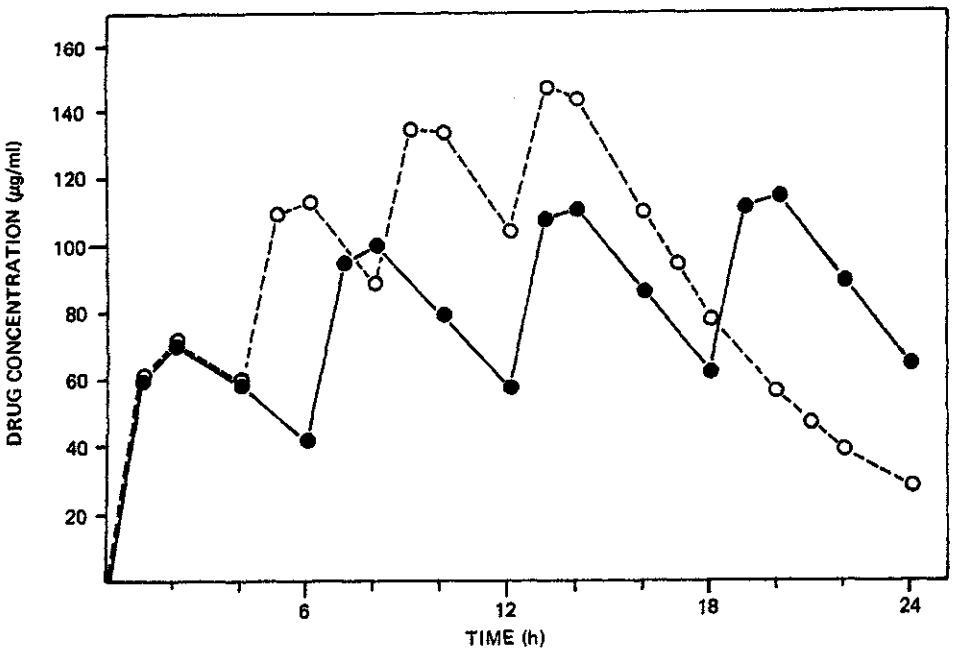

Fig. E.1 Drug concentrations in blood during multiple dosing of a constant dose given every 6 h (●) or four times a day (○). Data from Tables E.1 and E.2.

labeled "Dose 1" was either determined after a single dose, or interpolated or extrapolated from such data. The values are repeated under each "dose" column at the appropriate time. The drug concentration at any time during multiple dosing is predicted by simply adding all the concentration values in a given row. The drug concentration 2 h after the fourth dose is equal to the sum of the drug concentration 2 h after a single dose and all residual concentrations resulting from doses preceding the fourth dose.

A particular advantage of this overlay technique is that it permits one to almost as easily predict drug concentrations during multiple dosing using unequal dosing intervals, unequal doses, or both. In the example shown in Table E.2, it is assumed that one wishes to predict drug concentrations during multiple dosing when the same dose of drug is given four times a day (i.e., at 9 a.m., 1 p.m., 5 p.m., and 9 p.m.) rather than every 6 h. The example in Table E.3 is similar to that shown in Table E.1 except that a loading dose that is twice the usual dose is given. Note that drug concentrations after dose 1 are doubled to account for the dosing change.

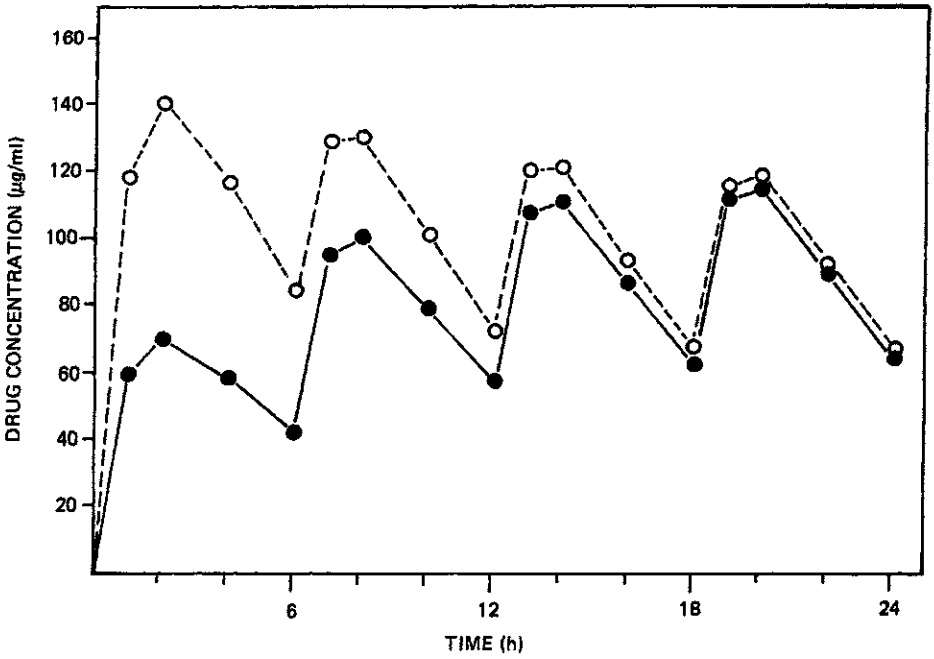

Fig. E.2 Drug concentrations in blood during multiple dosing of a constant dose given every 6 h with (O) or without (●) a loading dose. Data from Tables E.1 and E.3.

Figure E.1 compares the data from Tables E.1 and E.2. It is evident that dosing a drug four times a day results in a different drug concentration profile than that produced by dosing the drug every 6 h. Assuming a therapeutic concentration range of 60 to 140 µg/ml, it is evident that dosing the drug every 6 h results in therapeutic concentrations shortly after the second dose which are maintained throughout the course of therapy. On the other hand, dosing the drug four times a day results in rather high concentrations following the last dose of each day and subtherapeutic concentrations for several hours preceding the first dose of each day of therapy.

Figure E.2 compares the data from Tables E.1 and E.3. As we have noted in the text, an appropriate loading dose can safely allow more rapid attainment of therapeutic concentrations.

In those cases where the same dose of drug is given at constant dosing intervals and where the dosing interval is sufficiently large so that drug concentrations reflect the postabsorptive and postdistributive phase of the concentration-time profile, it is possible to describe the overlay technique by simple equations that are readily solved by means of a calculator.

Table E.3 Predicting Drug Concentrations During Multiple Dosing Using the Principle of Superposition

Dose Number	Time (h)	Dose 1	Dose 2	Dose 3	Dose 4	Drug Concentration
1	0	0				0
	1	118				118
	2	140				140
	4	116				116
2	6	84	0			84
	7	70	59			129
	8	60	70			130
	10	42	58			100
3	12	30	42	0		72
	13	26	35	59		120
	14	20	30	70		120
	16	14	21	58		93
4	18	10	15	42	0	67
	19	8	13	35	59	115
	20	8	10	30	70	118
	22	6	7	21	58	92
	24	4	5	15	42	66

Note: It is assumed that the same dose is given every 6 h but that the first dose is a loading dose (i.e., twice the usual dose).

To predict the drug concentration at time t (where $0 < t < \tau$) during the nth dosing interval [i.e., $C_n(t)$] under these conditions, the following approach can be used. Drug concentration at time t following the first dose is defined as $C_1(t)$. At t hours after the second dose, drug concentration is given by

$$C_2(t) = C_1(t) + Be^{-\lambda_n(t+\tau)} \tag{E.1}$$

where B and λ_n are as defined in Fig. E.3. Similarly, drug concentration at t hours after the third dose is given by

$$C_3(t) = C_1(t) + Be^{-\lambda_n(t+\tau)} + Be^{-\lambda_n(t+2\tau)} \tag{E.2}$$

The first term on the right-hand side of Eq. (E.2) is contributed by the third dose, the second term by the second dose, and the third term by the first dose.

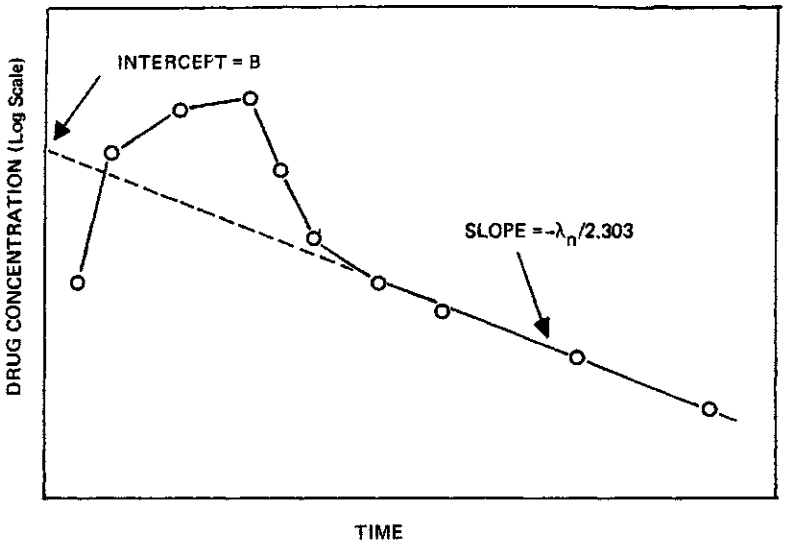

Fig. E.3 Drug concentration-time profile on semilogarithmic coordinates following a single oral dose.

It follows that drug concentration after the nth dose is given by

$$C_n(t) = C_1(t) + Be^{-\lambda_n(t+\tau)} + Be^{-\lambda_n(t+2\tau)} + \cdots + Be^{-\lambda_n[t+(n-1)\tau]} \qquad \text{(E.3)}$$

which can be simplified to

$$C_n(t) = C_1(t) + Be^{-\lambda_n\tau}[1 + e^{-\lambda_n\tau} + e^{-2\lambda_n\tau} + \cdots + e^{-(n-2)\lambda_n\tau}]e^{-\lambda_n t} \qquad \text{(E.4)}$$

The term in brackets can be shown to be equal to

$$\frac{1 - e^{-(n-1)\lambda_n\tau}}{1 - e^{-\lambda_n\tau}}$$

Therefore, Eq. (E.4) can be written as follows:

$$C_n(t) = C_1(t) + \frac{Be^{-\lambda_n \tau}\left[1 - e^{-(n-1)\lambda_n \tau}\right]e^{-\lambda_n t}}{1 - e^{-\lambda_n \tau}} \qquad (E.5)$$

At steady-state the term in brackets approaches one and Eq. (E.5) may be simplified to

$$C_{ss}(t) = C_1(t) + \frac{(Be^{-\lambda_n \tau})(e^{-\lambda_n t})}{1 - e^{-\lambda_n \tau}} \qquad (E.6)$$

where $C_{ss}(t)$ is the drug concentration at any time t during a dosing interval at steady state.

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Appendix F

Estimation of Rates

It is not possible experimentally to determine instantaneous rates of change of drug or metabolite concentrations in any body compartment. Hence it becomes necessary to approximate instantaneous rates by estimating average rates over finite periods of time. Possible limitations of employing average rates have been discussed [1]. We will illustrate this method by employing the equations for the excretion of unchanged drug in the urine following the intravenous administration of a drug, assuming a one-compartment model with first-order elimination.

The expression for the instantaneous rate of appearance of unchanged drug in the urine, dX_u/dt, is given as follows:

$$\frac{dX_u}{dt} = k_e X \tag{F.1}$$

where k_e is the apparent first-order excretion rate constant, X_u the cumulative amount of unchanged drug eliminated in the urine to time t, and X the amount of drug in the body at time t. Since the time course of drug in the body following intravenous administration in a one-compartment model is given by the equation

$$X = X_0 e^{-Kt} \tag{F.2}$$

the following expression for dX_u/dt can be written by substituting this value of X into Eq. (F.1):

$$\frac{dX_u}{dt} = k_e X_0 e^{-Kt} \tag{F.3}$$

which in terms of common logarithms is

$$\log \frac{dX_u}{dt} = \log k_e X_0 - \frac{Kt}{2.303} \tag{F.4}$$

In this equation K is the apparent first-order elimination rate constant for the drug and X_0 is the intravenous dose. Integration of Eq. (F.3) yields the following expression for the cumulative amount of unchanged drug in the urine as a function of time:

$$X_u = \frac{k_e X_0}{K}(1 - e^{-Kt}) \tag{F.5}$$

Hence the cumulative amount of drug in the urine at two consecutive sampling times t_1 and t_2 is given by

$$(X_u)_{t_1} = \frac{k_e X_0}{K}(1 - e^{-Kt_1}) \tag{F.6}$$

and

$$(X_u)_{t_2} = \frac{k_e X_0}{K}(1 - e^{-Kt_2}) \tag{F.7}$$

respectively. If Δt equals t_2 minus t_1 and t^* is the time at the midpoint of t_2 and t_1 [i.e., $t^* = (t_2 + t_1)/2$], then

$$t_1 = t^* - \Delta t/2 \tag{F.8}$$

and

$$t_2 = t^* + \Delta t/2 \tag{F.9}$$

Substitution of these values of t_1 and t_2 into Eqs. (F.6) and (F.7), respectively, yields

$$(X_u)_{t_1} = \frac{k_e X_0}{K}[1 - e^{-K(t^*-\Delta t/2)}] \tag{F.10}$$

and

$$(X_u)_{t_2} = \frac{k_e X_0}{K}[1 - e^{-K(t^*+\Delta t/2)}] \tag{F.11}$$

The amount of unchanged drug eliminated in the urine during the time interval Δt (i.e., ΔX_u) would be equal to $(X_u)_{t_2}$ minus $(X_u)_{t_1}$. Hence ΔX_u is given by the difference between Eqs. (F.11) and (F.10):

$$\Delta X_u = \frac{k_e X_0}{K}[e^{-K(t^*-\Delta t/2)} - e^{-K(t^*+\Delta t/2)}] \tag{F.12}$$

which can be simplified to

$$\Delta X_u = \frac{k_e X_0}{K} e^{-Kt^*}(e^{K\Delta t/2} - e^{-K\Delta t/2}) \qquad (F.13)$$

Since the amount of drug in the body X at time t* equals $X_0e^{-Kt^*}$, according to Eq. (F.2), substitution of X for $X_0e^{-Kt^*}$ in Eq. (F.13) yields

$$\Delta X_u = \frac{k_e X}{K}(e^{K\Delta t/2} - e^{-K\Delta t/2}) \qquad (F.14)$$

Dividing both sides of Eq. (F.14) by Δt gives the average rate of appearance of unchanged drug in the urine over a finite period of time, $\Delta X_u/\Delta t$, which is an approximation of the instantaneous rate dX_u/dt:

$$\frac{\Delta X_u}{\Delta t} = \frac{k_e X}{K\ \Delta t}(e^{K\Delta t/2} - e^{-K\Delta t/2}) \qquad (F.15)$$

To account for any difference between $\Delta X_u/\Delta t$ and the instantaneous rate, the factor λ will be introduced such that

$$\frac{\Delta X_u}{\Delta t} = \lambda \frac{dX_u}{dt} \qquad (F.16)$$

Solving this equation for λ yields

$$\lambda = \frac{\Delta X_u/\Delta t}{dX_u/dt} \qquad (F.17)$$

Substituting for $\Delta X_u/\Delta t$ and dX_u/dt according to Eqs. (F.15) and (F.1), respectively, and canceling common terms results in the following expression for λ:

$$\lambda = \frac{e^{K\Delta t/2} - e^{-K\Delta t/2}}{K\ \Delta t} \qquad (F.18)$$

Therefore, λ is a constant that depends on the values of K and Δt. A plot of the logarithm of $\Delta X_u/\Delta t$ versus t* would be linear and parallel to a plot of the logarithm of dX_u/dt versus t provided that Δt is the same for each point plotted. Consequently, no error will arise in the calculation of the elimination rate constant K from the slope (i.e., slope = $-K/2.303$) of a log $(\Delta X_u/\Delta t)$ versus t* plot if the sampling intervals are the same.

By expressing Δt in terms of the biologic half-life $t_{1/2}$ of a drug such that

$$\Delta t = \theta t_{1/2} \qquad (F.19)$$

and since

Table F.1 Relationship Between Average Excretion Rates Calculated over Varying Time Intervals and Instantaneous Excretion Rates

Δt [a]	$\frac{\Delta X_u/\Delta t}{dX_u/dt}$ [b]
0.25	1.001
0.5	1.005
1.0	1.020
2.0	1.082
3.0	1.190

[a] Expressed as a multiple of the elimination half-life of the drug, that is, values of θ, where $\theta = \Delta t/t_{1/2}$.
[b] The value of λ, that is, the extent of departure of $\Delta X_u/\Delta t$ from dX_u/dt.

$$t_{1/2} = \frac{\ln 2}{K} \tag{F.20}$$

then

$$\Delta t = \frac{\theta \ln 2}{K} \tag{F.21}$$

Substituting this value for Δt in Eq. (F.18) and canceling common terms yields

$$\lambda = \frac{e^{\theta(\ln 2)/2} - e^{-\theta(\ln 2)/2}}{\theta \ln 2} = \frac{2^{\theta/2} - 2^{-\theta/2}}{\theta \ln 2} \tag{F.22}$$

Based on this equation, the extent to which a semilogarithmic plot of $\Delta X_u/\Delta t$ versus the midpoint in time (i.e., t^*) deviates from an instantaneous rate plot can be readily calculated. The larger the value of Δt, relative to the half-life, the greater will be the displacement of the log $(\Delta X_u/\Delta t)$ plot above the log (dX_u/dt) plot (see Table F.1). If urine is collected, however, at intervals that are not larger than one half-life of the drug, there is only a 2% shift upward (i.e., $\lambda = 1.020$), which is insignificant.

Usually, urinary excretion rate plots are not based on constant time intervals. As can be seen from Table F.1, the error caused by employing unequal time intervals does not become significant until one of these intervals is at least twice the half-life of a drug. A problem may arise with drugs having very short half-lifes where urine col-

lection intervals equal to or less than one half-life may be difficult to attain. With this type of drug the use of equal time intervals is suggested.

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Appendix G
Selective Derivations

MICHAELIS-MENTEN EQUATION

Based on the scheme

$$E + C \underset{k_1}{\overset{k_{-1}}{\rightleftharpoons}} EC \xrightarrow{k_2} E + M$$

the differential equation for EC is

$$\frac{dEC}{dt} = k_1(E)(C) - (k_{-1} + k_2)EC \tag{G.1}$$

where E, C, EC, and M are the concentrations of enzyme, drug, enzyme-drug complex, and metabolite, respectively. The constants k_{-1} and k_2 are first-order rate constants and k_1 is a second-order rate constant. Assuming that dEC/dt = 0 (steady-state assumption), the right-hand side of (G.1) can be rearranged to yield

$$\frac{k_{-1} + k_2}{k_1} = \frac{(E)(C)}{EC} \tag{G.2}$$

since

$$k_1(E)(C) - (k_{-1} + k_2)\,EC = 0 \tag{G.3}$$

The ratio (E)(C)/EC is denoted as K_m, the Michaelis constant.

The following differential equation can be written for C:

$$-\frac{dC}{dt} = k_1(E)(C) - k_{-1}(EC) \tag{G.4}$$

Expansion of Eq. (G.3) and rearrangement yields

$$k_1(E)(C) - k_{-1}(EC) = k_2(EC) \tag{G.5}$$

Substitution of $k_2(EC)$ for $k_1(E)(C) - k_{-1}(EC)$ in (G.4) produces the following expression for $-dC/dt$:

$$-\frac{dC}{dt} = k_2(EC) \tag{G.6}$$

The total concentration of enzyme in the system, E_T, equals the sum of the concentrations of free and bound enzyme, E and EC, respectively. Therefore,

$$E_T = E + EC \tag{G.7}$$

Since there is only a finite amount of enzyme present in the system, all of the enzyme will exist as EC complex at a sufficiently high drug concentration. At this point the enzyme will be completely saturated with drug, and the rate of change in C will occur at a maximum rate. This maximum rate V_m will equal k_2ET. Therefore, at high drug concentrations

$$-\frac{dC}{dt} = k_2(EC) = k_2E_T = V_m \tag{G.8}$$

Taking the ratio of $V_m/(-dC/dt)$, where V_m equals k_2E_T and $-dC/dt$ is given by Eq. (G.6) yields

$$\frac{V_m}{-dC/dt} = \frac{k_2E_T}{k_2(EC)} = \frac{E_T}{EC} \tag{G.9}$$

As stated previously,

$$K_m = \frac{(E)(C)}{EC} \tag{G.10}$$

Substitution of $(E_T - EC)$ for E [according to a rearrangement of (G.7)] in (G.10) results in the relationship

$$K_m = \frac{(E_T - EC)(C)}{EC} \tag{G.11}$$

Dividing both sides of this equation by C and solving for the ratio E_T/EC gives

$$\frac{E_T}{EC} = \frac{K_m}{C} + 1 = \frac{K_m + C}{C} \tag{G.12}$$

Substituting the value of E_T/EC in (G.12) for E_T/EC in (G.9) and solving for $-dC/dt$ produces the Michaelis-Menten equation

$$-\frac{dC}{dt} = \frac{V_m C}{K_m + C} \tag{G.13}$$

TIME TO REACH A FRACTION OF STEADY STATE FOR A DRUG ELIMINATED BY PARALLEL FIRST-ORDER AND CAPACITY-LIMITED PROCESSES

Assuming a one-compartment model, consider the following situation: drug is administered by a constant rate (k_0) intravenous infusion and eliminated by parallel first-order and Michaelis-processes. The rate of change of drug concentration during infusion is given by

$$\frac{dC}{dt} = \frac{k_0}{V} - K'C - \frac{V_m C}{K_m + C} \tag{G.14}$$

where K' is the sum of the rate constants for the first-order elimination processes. Expansion and rearrangement of (G.14) yields

$$\frac{K_m}{-K'C^2 + [(k_0/V) - K'K_m - V_m]C + k_0K_m/V}\,dC + \frac{C}{-K'C^2 + [(k_0/V) - K'K_m - V_m]C + K_0K_m/V}\,dC = dt \tag{G.15}$$

This equation is of the form

$$\frac{g}{fx^2 + bx + a}\,dx + \frac{x}{fx^2 + bx + a}\,dx = dt \tag{G.16}$$

where

$$a = \frac{k_0K_m}{V} \tag{G.17}$$

$$b = \frac{k_0}{V} - K'K_m - V_m \tag{G.18}$$

$$f = -K' \tag{G.19}$$

$$g = K_m \tag{G.20}$$

The integral of (G.16) is [1]

$$\frac{g}{\sqrt{-q}} \ln \frac{2fx + b - \sqrt{-q}}{2fx + b + \sqrt{-q}} + \frac{1}{2f} \ln (a + bx + fx^2) - \frac{b}{2f} \frac{1}{\sqrt{-q}} \ln \frac{2fx + b - \sqrt{-q}}{2fx + b + \sqrt{-q}} = t + i \tag{G.21}$$

where

$$-q = b^2 - 4af = b^2 + 4aK' \tag{G.22}$$

Equation (G.21) can be simplified to

$$\frac{1}{2f} \ln (a + bx + fx^2) + \left(\frac{g}{\sqrt{-q}} - \frac{b}{2f\sqrt{-q}} \right) \ln \frac{2fx + b - \sqrt{-q}}{2fx + b + \sqrt{-q}} = t + i \tag{G.23}$$

At $t = 0$, $x = 0$ and therefore

$$i = \frac{1}{2f} \ln a + \left(\frac{g}{\sqrt{-q}} - \frac{b}{2f\sqrt{-q}} \right) \ln \frac{b - \sqrt{-q}}{b + \sqrt{-q}} \tag{G.24}$$

Substitution of the value of i in (G.24) into (G.21), setting x equal to C (i.e., drug concentration), substitution of $-K'$ for f and K_m for g according to (G.19) and (G.20), respectively, followed by rearrangement yields

$$t = \frac{1}{\sqrt{-q}} \left(K_m + \frac{b}{2K'} \right) \ln \left(\frac{-2K'C + b - \sqrt{-q}}{-2K'C + b + \sqrt{-q}} \right) \left(\frac{b + \sqrt{-q}}{b - \sqrt{-q}} \right) - \frac{1}{2K'} \ln \frac{a + bC - K'C^2}{a} \tag{G.25}$$

The steady-state concentration of a drug eliminated by parallel first-order and saturable pathways is given by

$$C_{ss} = \frac{k_0}{Cl_s} = \frac{k_0}{[VV_m/(K_m + C_{ss})] + K'V} \tag{G.26}$$

where Cl_s at steady state is given by (7.53). Rearranging (G.26) produces the following quadratic equation:

$$-K'C_{ss}^2 + \left(\frac{k_0}{V} - VK'K_m - V_m \right) C_{ss} + \frac{k_0 K_m}{V} = 0 \tag{G.27}$$

or in terms of a and b where these values are given by (G.17) and (G.18), respectively.

$$-K'C_{ss}^2 + bC_{ss} + a = 0 \tag{G.28}$$

The solution for C_{ss} is

$$C_{ss} = \frac{b \pm \sqrt{b^2 + 4aK'}}{2K'} \tag{G.29}$$

The term $\sqrt{b^2 + 4aK'}$ will always be greater than b; therefore, the sign between these two terms must always be positive since C_{ss} must be positive. Consequently,

$$C_{ss} = \frac{b + \sqrt{b^2 + 4aK'}}{2K'} = \frac{b + \sqrt{-q}}{2K'} \tag{G.30}$$

Substitution of $2K'C_{ss}$ for $b + \sqrt{-q}$ in (G.25) yields

$$t = \frac{1}{\sqrt{-q}}\left(K_m + \frac{b}{2K'}\right) \ln \frac{-2K'C + b - \sqrt{-q}}{-2K'C + 2K'C_{ss}} \frac{2K'C_{ss}}{b - \sqrt{-q}}$$

$$- \frac{1}{2K'} \ln \frac{a + bC - K'C^2}{a} \tag{G.31}$$

or

$$t = \frac{1}{\sqrt{-q}}\left(K_m + \frac{b}{2K'}\right) \ln \frac{-2K'C + b - \sqrt{-q}}{b - \sqrt{-q}} \frac{1}{1 - C/C_{ss}}$$

$$- \frac{1}{2K'} \ln \frac{a + bC - K'C^2}{a} \tag{G.32}$$

The fraction of a given steady-state concentration, f_{ss}, equals C/C_{ss}. Therefore, substitution of f_{ss} for C/C_{ss} and rearrangement gives

$$t = \frac{1}{\sqrt{-q}}\left(K_m + \frac{b}{2K'}\right) \ln\left(\frac{-2K'C}{b - \sqrt{-q}} + 1\right) \frac{1}{1 - f_{ss}}$$

$$- \frac{1}{2K'} \ln \left(1 + \frac{bC - K'C^2}{a}\right) \tag{G.33}$$

Two limiting cases of Eq. (G.33) can be considered: the time to reach a certain fraction of steady state when there is a very high or a very low rate of drug administration. When the rate of drug administration is very low (i.e., $k_0 \simeq 0$) and hence $C \simeq 0$, Eqs. (G.18) and (G.22) can be approximated by

$$b \simeq -K'K_m - V_m \tag{G.34}$$

and

$$-q \simeq b^2 \simeq (K'K_m + V_m)^2 \tag{G.35}$$

respectively. Substitution of these values of b and $-q$ and the value of a as given by (G.17) into (G.33) yields

$$t = \frac{1}{K'K_m + V_m}\left(K_m - \frac{K'K_m + V_m}{2K'}\right)\ln\left(\frac{-2K'C}{b - \sqrt{-q}} + 1\right)\frac{1}{1 - f_{ss}}$$

$$- \frac{1}{2K'}\ln\left(1 - \frac{(K'K_m + V_m)VC + K'VC^2}{k_0K_m}\right) \qquad (G.36)$$

Recognizing that $-2K'C \simeq 0$ and $(K'K_m + V_m)VC >> K'VC^2$, and factoring out $1/2K'$ produces the following expression for t:

$$t = \frac{1}{2K'}\left(\frac{2K'K_m - K'K_m - V_m}{K'K_m + V_m}\ln\frac{1}{1 - f_{ss}}\right.$$

$$\left. - \ln\left\{1 - \frac{[K' + (V_m/K_m)]VC}{k_0}\right\}\right) \qquad (G.37)$$

At a low rate of administration Eq. (G.26) reduces to

$$C_{ss} = \frac{k_0}{[K' + (V_m/K_m)]V} \qquad (G.38)$$

since $K_m >> C_{ss}$.

Substitution of $1/C_{ss}$ for $[K' + (V_m/K_m)]V/k_0$ in (G.37), and recognizing that $C/C_{ss} = f_{ss}$, yields

$$t = \frac{-1}{2K'}\left[\frac{K'K_m - V_m}{K'K_m + V_m}\ln(1 - f_{ss}) + \ln(1 - f_{ss})\right] \qquad (G.39)$$

which, when $\ln(1 - f_{ss})$ is factored out, becomes

$$t = -\frac{1}{2K'}\left(\frac{K'K_m - V_m}{K'K_m + V_m} + 1\right)\ln(1 - f_{ss}) \qquad (G.40)$$

Equation (G.27) can be further simplified to give

$$t = -\frac{1}{K' + (V_m/K_m)}\ln(1 - f_{ss}) \qquad (G.41)$$

When the rate of drug administration is very high and the resulting value of C approaches infinity, Eqs. (G.18) and (G.22) can be approximated by

$$b \simeq \frac{k_0}{V} \qquad (G.42)$$

and

$$-q \simeq b^2 \simeq \left(\frac{k_0}{V}\right)^2 \tag{G.43}$$

respectively. Substitution of these values of b and $-q$ and the value of a as given by (G.17) into (G.33) yields

$$t = \frac{1}{k_0/V}\left(K_m + \frac{k_0/V}{2K'}\right)\ln\left(\frac{-2K'C}{b - \sqrt{-q}} + 1\right)\frac{1}{1 - f_{ss}} - \frac{1}{2K'}\ln\left[1 + \frac{(k_0/V)C - K'C^2}{k_0K_m/V}\right] \tag{G.44}$$

Since $(k_0/V)/2K' \gg K_m$, $-2K'C/(b - \sqrt{-q}) \gg 1$, and $[(k_0/V)C - K'C^2]/(k_0K_m/V) \gg 1$, Eq. (G.44) can be simplified to

$$t = \frac{1}{2K'}\ln\frac{-2K'C}{b - \sqrt{-q}}\frac{1}{1 - f_{ss}} - \frac{1}{2K'}\ln\frac{k_0C - K'VC^2}{k_0K_m} \tag{G.45}$$

Factoring out $1/2K'$ and simplifying the resulting expression gives

$$t = \frac{1}{2K'}\ln\frac{1}{1 - f_{ss}}\frac{-2K'k_0K_m}{(b - \sqrt{-q})(k_0 - K'VC)} \tag{G.46}$$

Further simplification requires that the term $b - \sqrt{-q}$ be evaluated. Substitution of the values of a and b as given by Eqs. (G.17) and (G.18), respectively, into Eq. (G.22) yields

$$-q = \left(\frac{k_0}{V} - K'K_m - V_m\right)^2 + \frac{4k_0K_mK'}{V} \tag{G.47}$$

Expansion, collection of common terms, and further simplification results in the following relationship:

$$-q = \left(\frac{k_0}{V}\right)^2 + 2\frac{k_0}{V}(K'K - V_m) - (K'K_m + V_m)^2 \tag{G.48}$$

Factoring out $(k_0/V)^2$ produces

$$-q = \left(\frac{k_0}{V}\right)^2\left[1 + 2\frac{V}{k_0}(K'K_m - V_m) - \left(\frac{V}{k_0}\right)^2(K'K_m + V_m)^2\right] \tag{G.49}$$

the square root of which is given by

$$\sqrt{-q} = \frac{k_0}{V}\left[1 + 2\frac{V}{k_0}(K'K_m - V_m) - \left(\frac{V}{k_0}\right)^2 (K'K_m + V_m)^2\right]^{1/2} \tag{G.50}$$

This is of the form

$$\sqrt{-q} = \frac{k_0}{V}(1 + x)^n \tag{G.51}$$

where n = 1/2, and therefore

$$(1 + x)^{1/2} = \left[1 + 2\frac{V}{k_0}(K'K_m - V_m) - \left(\frac{V}{k_0}\right)^2 (K'K_m + V_m)^2\right]^{1/2} \tag{G.52}$$

The binomial expansion [1] of $(1 + x)^{1/2}$ is

$$(1 + x)^{1/2} = 1 + 1/2x - \frac{1}{8}x^2 + \frac{1}{16}x^3 + \cdots \tag{G.53}$$

or

$$(1 + x)^{1/2} = 1 + \left[\frac{V}{k_0}(K'K_m - V_m) - 1/2\left(\frac{V}{k_0}\right)^2 (K'K_m + V_m)^2\right] - \frac{1}{8}\left[2\frac{V}{k_0}(K'K_m - V_m) - \left(\frac{V}{k_0}\right)^2 (K'K_m + V_m)^2\right]^2 + \frac{1}{16}\cdots \tag{G.54}$$

Since k_0 is very large, an approximation of $(1 + x)^{1/2}$ is

$$(1 + x)^{1/2} \simeq 1 + \frac{V}{k_0}(K'K_m - V_m) \tag{G.55}$$

Substitution of this value of $(1 + x)^n$ into (G.51) and simplification yields

$$\sqrt{-q} = \frac{k_0}{V} + K'K_m - V_m \tag{G.56}$$

The resulting expression for $b - \sqrt{-q}$, where b and $\sqrt{-q}$ are given by (G.18) and (G.56), respectively, is

$$b - \sqrt{-q} = \frac{k_0}{V} - K'K_m - V_m - \left(\frac{k_0}{V} + K'K_m - V_m\right) \tag{G.57}$$

which can be further reduced to give

$$b - \sqrt{-q} = -2K'K_m \tag{G.58}$$

The following relationship for t results when this value of $b - \sqrt{-q}$ is substituted into (G.46) and common terms are canceled:

$$t = \frac{1}{2K'} \ln \frac{1}{1 - f_{ss}} \frac{k_0}{k_0 - K'VC} \tag{G.59}$$

At a high rate of drug administration steady-state concentration is given by

$$C_{ss} \simeq \frac{k_0}{K'V} \tag{G.60}$$

since under this condition K'V in (G.26) becomes $>> VV_m/(K_m + C_{ss})$. Substituting k_0/C_{ss} for K'V in (G.59), canceling common terms, and recognizing that C/C_{ss} is f_{ss} produces

$$t = \frac{1}{2K'} \ln \left(\frac{1}{1 - f_{ss}} \right)^2 \tag{G.61}$$

or

$$t = -\frac{1}{K'} \ln(1 - f_{ss}) \tag{G.62}$$

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Appendix H

Computer Programs

The corresponding appendix in the first edition of this book emphasized simulation programs and nonlinear least-squares regression programs for use in large computers. In the intervening period, pharmacokinetic analysis has undergone a distinct change and the advances in computer technology have been nothing short of revolutionary.

The principal purpose of a pharmacokinetic analysis today is to gain information regarding the clearance, renal clearance, volume of distribution, metabolic disposition, accumulation characteristics on multiple dosing, and absorption of a drug. As we have indicated throughout this text, model-independent methods are now available to attain these ends. There is very much less interest in characterizing the pharmacokinetics of a drug in terms of model-dependent constants. Thus there is far less need for nonlinear least-squares regression analysis. This type of analysis remains useful to estimate the slope of the terminal exponential phase of a polyexponential curve and the half-life of the drug, but such estimates can usually be carried out with sufficient accuracy by logarithmic conversion of the data and the application of linear regression. Moreover, a relatively simple method termed direct linear plotting has recently been described [1] which may be more robust than nonlinear least-squares regression (weighted or unweighted), particularly when the assumption of equal variance for all experimental data points is incorrect. This method can be implemented using a programmable calculator or microcomputer [2].

Pharmacokinetic analysis based on curve-fitting is still best carried out by means of nonlinear estimation programs such as BMDP [3], NONLIN [4], and SAAM [5], which are designed for use with large computers. These and similar programs have been discussed by Metzler [6]. Although relatively little has been written concerning nonlinear least-squares regression programs for microcomputers, considerable development may take place over the next decade. Peck and Barrett [7] have surveyed the available nonlinear regression programs

and found several written in BASIC, of which at least two [8,9] have been successfully run on microcomputers with BASIC capability and 8K bytes of random access memory (RAM). These programs have been found under certain conditions to perform at least as well as NONLIN and BMDP but have several serious limitations, including limited accuracy and insufficient documentation [7]. More recently, Muir [10] has described two programs for programmable calculators allowing nonlinear least-squares fits to data conforming to the one-compartment oral (first-order absorption) and the two-compartment intravenous pharmacokinetic models.

Mathematical description of polyexponential curves by exponential stripping [11] is easily implemented using a microcomputer or programmable calculator. Several programs have been described, including ESTRIP [12] and STRIPACT [13]. This method, however, is widely acknowledged to provide an insufficiently definitive analysis. The value of such programs is viewed in terms of improvement in accuracy of final parameter estimates (e.g., avoiding unreasonable final estimates arising from bad initial estimates) when used in conjunction with a nonlinear regression program. Koup [2] has recently described an exponential stripping program for a microcomputer which is based on the method of direct linear plotting. This approach may prove to be more robust than previously described stripping methods.

Although the need for curve-fitting has decreased considerably, the importance of simulation techniques in pharmacokinetics remains high. However, these techniques may now be implemented with microcomputers. Koup and Benjamin [14] have described BASIC programs for use with the Apple II Plus microcomputer which generate graphic and hard copy simulations of various linear and Michaelis-Menten pharmacokinetic models. The programs numerically integrate sets of differential equations for appropriate models. Multiple oral, intramuscular, intravenous bolus, or intravenous infusion doses may be simulated in any combination. Doses as well as pharmacokinetic parameters may be changed at the end of each simulated dosing interval.

It requires no great prescience to suggest that the computational aspects of pharmacokinetic analysis will be substantially further simplified in the years ahead.

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