General Treatment of Linear Mammillary Models with Elimination from Any Compartment as Used in Pharmacokinetics

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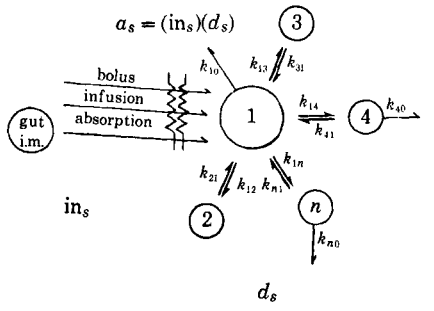
Abstract □ This paper presents some very simplified general treatments which will allow workers to derive equations for any linear mammillary compartment model with any first- or zero-order or impulse input process. This is done through the use of general input and disposition functions, the method of partial fractions for solving Laplace transforms, and the use of a multiple-dosing function. A disposition function defines the model necessary to describe accurately drug body concentrations after the drug has entered the blood circulation. A general equation is presented to describe the disposition function in Laplace operators for the central compartment of a linear mammillary model having n driving force compartments with elimination occurring from any of the compartments. Input functions describing intravenous bolus injection, zero-order infusion, or GI absorption and first-order processes for oral dosing and intramuscular injection are presented. The Laplace transform for the amount of drug in the central compartment is given by the products of the input and disposition functions. These Laplace transforms may usually be solved in one step using the method of partial fractions, without the necessity of referring to extensive tables. By using a multiple-dosing function, general equations may be derived covering the entire dosage regimen of a drug in a patient.

Keyphrases □ Mammillary models (linear), with first- or zero-order input process—equations, general treatment □ Pharmacokinetics—general treatment of linear mammillary models with elimination from any compartment □ Compartment elimination—general equations for linear mammillary models, first- or zero-order input process

During the past decade, the pharmacokinetic treatment of plasma and urine drug concentrations has progressed through a number of modeling sophistications as the ability to analyze drug concentration levels has improved. A large number of papers have appeared in the pharmaceutical literature describing the treatment of data, at first for the one-compartment body model, then for the two-compartment model, and now for various permutations of the three-compartment body model. In each paper, a major portion of the published material deals with the derivation of the equations as particularly suited to the adaptation the author wishes to emphasize. This paper intends to present some very simplified general treatments which will allow workers to derive equations for any linear mammillary compartment model with any first- or zero-order input process. This will be done through the use of general input and disposition functions, the method of partial fractions for solving Laplace transforms, and the use of a multiple-dosing function.



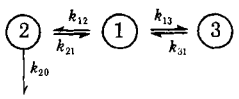
Scheme I—A general mammillary model with elimination allowed from every compartment. The disposition function, d_s, *describes the model necessary to describe accurately drug body concentrations after the drug has gotten into the blood circulation. Input functions* (in_s) *describe the process or processes necessary to get the drug into the bloodstream. The products of the input and disposition functions yield the Laplace transform for the equation describing the time course of the amount of drug in a compartment* (a_s).

THEORETICAL CONSIDERATIONS

Input and Disposition Functions—Rescigno and Segre (1) introduced the use of transfer functions in the derivation of pharmacokinetic models. Riggs (2) also demonstrated their use with respect to linear functions describing plasma concentrations of drugs. They have received little use in the work of pharmaceutical scientists beyond one application by Loo and Riegelman (3) in a recent derivation involving postinfusion blood curves.

A general model describing input and disposition functions is presented in Scheme I. The input functions (in_s) and the disposition function (d_s) are defined such that the product of the two functions yields the Laplace transform of the equation describing the time course of a drug in a particular compartment (a_s). In this work, a disposition function (d_s) defines the model necessary to describe accurately drug body concentrations *after* the drug has entered the blood circulation. That is, disposition describes everything that happens to a drug (*i.e.*, distribution, metabolism, and unidirectional elimination through all possible routes) as if all input into the circulation occurred instantaneously. This definition of the disposition function follows that introduced by Riegelman *et al.* (4) for disposition rate constants. Input functions (in_s) describe the process necessary to get the dose into the bloodstream. They may either describe an intravenous bolus injection, an intravenous infusion, a first- or zero-order absorption from a site such as the gut or a muscle, or any combination of these methods of input.

General Disposition Equation for the Central Compartment—Rescigno and Segre (1) presented general equations for the treatment of systems with strongly connected compartments (*i.e.*, every compartment is connected by a rate constant with every other compartment) and for reversible and irreversible catenary systems. They adapted these general equations for use in a mammillary model as was studied by Matthews (5) in the investigation of the kinetics of protein metabolism. Their general treatment applies to a system of a central compartment connected with $n - 1$ other compartments, where *all* elimination from the system takes place from the central compartment. This type of elimination would be analogously described by rate constant k_{10} in the model depicted in Scheme I. Sheppard (6) also introduced general equations to treat the mam-



Scheme II—A three-compartment disposition model as proposed by Nagashima et al. (7) *to describe the pharmacokinetics of dicumarol. Note that elimination does not take place from the central compartment.*

millary model as already defined. However, recently a number of papers appeared in which unidirectional elimination was hypothesized for compartments other than the central compartment (7–9), such as through pathways described by k_{40} and k_{n0}.

Therefore, the following general equation was empirically derived to describe the Laplace transform for the disposition function of the central compartment in a linear mammillary model where elimination of drug from any compartment is allowed:

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

where:

$d_{s,1}$ = disposition function for Compartment 1, the central compartment; it is a function of s, an auxiliary variable introduced with the Laplace transforms

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

k_{1j} = first-order rate constant describing transfer from Compartment 1 to Compartment j; *i.e.*, in Scheme I, k_{14} describes transfer from Compartment 1 into Compartment 4

E_i = sum of the exit rate constants out of Compartment i (9); for example, in Scheme I, $E_4 = k_{41} + k_{40}$ and $E_1 = k_{10} + k_{12} + k_{13} + k_{14} + k_{1n}$

n = number of driving force compartments in the disposition model, that is, compartments having exit rate constants.

As an example of the use of Eq. 1, consider the three-compartment model (Scheme II) proposed by Nagashima *et al.* (7) to describe the pharmacokinetics of dicoumarol[1]. Note that elimination does not occur from the central compartment but rather from Compartment 2. Realizing that there are three driving force compartments ($n = 3$) and that $E_1 = k_{12} + k_{13}$, $E_2 = k_{20} + k_{21}$, and $E_3 = k_{31}$, one may immediately write down the disposition function for the central compartment:

$$d_{s,1} = \frac{(s + E_2)(s + E_3)}{(s + E_1)(s + E_2)(s + E_3) - k_{12}k_{21}(s + E_3) - k_{13}k_{31}(s + E_2)} \quad \text{(Eq. 2)}$$

The numerator is the continued product as i varies from 2 to 3. The first term in the denominator is the continued product as i varies from 1 to 3. The second term in the denominator is a result of the first time through the sum, *i.e.*, $j = 2$. Note that even though the continued product term in the sum in Eq. 1 is stated as varying from 2 to n, there is no $(s + E_2)$ term in the second term of the denominator of Eq. 2 since $m = j$ is forbidden. The third term in the denominator is a result of the second and final time through the sum, *i.e.*, $j = n = 3$.

Since a term with s to the third power appears in the denominator of Eq. 2 (*i.e.*, since there are three driving force compartments in the model), the equation describing the disposition function for the central compartment is triexponential. Therefore, Eq. 2 may be rewritten as:

$$d_{s,1} = \frac{(s + E_2)(s + E_3)}{(s + \alpha)(s + \beta)(s + \gamma)} \quad \text{(Eq. 3)}$$

where α, β, and γ may be expressed in terms of the individual rate constants when the denominator of Eq. 2 is expanded in terms of the coefficients of the powers of s.

Number of Solvable Rate Constants in a Mammillary Disposition Model—Five rate constants describe the disposition of dicumarol in the model (Scheme II) proposed by Nagashima *et al.* (7). By sampling the central compartment, the authors were able to solve for these rate constants. However, one should realize that in any linear mammillary model for a single drug, where only the central compartment is available for sampling, the maximum number of solvable rate constants, R, is given by Eq. 4 and only one of the R rate constants may unambiguously describe elimination of drug from the model[2]:

$$R = 2(n - 1) + 1 \quad \text{(Eq. 4)}$$

where:

R = maximum number of solvable terms or rate constants in a mammillary model with elimination allowed from any compartment

n = number of driving force compartments in the disposition model, that is, the number of compartments with rate constants coming out of them.

Thus, if either one or two elimination rate constants (k_{10} and/or k_{30}) were added to the model in Scheme II, it would still be only possible to solve for five terms, even though the model would pictorially show six or seven rate constants. In fact, as the authors (7) mention, it is impossible to ascertain from the data available whether the model should have elimination from one, two, or three compartments. This point was raised with respect to the number of eliminating compartments in the two-compartment model by Rowland *et al.* (9). As stated previously, only one of the R rate constants may unambiguously describe elimination of drug from the model. Thus, if k_{10} was added to the model in Scheme II, E_2 would become one of the five solvable terms, but the relative sizes of k_{20} and k_{21} could not be determined. Nagashima *et al.* (7) assumed that elimination occurred from the more rapidly accessible peripheral compartment and showed that different numerical constants were obtained if alternate assumptions were made. This only means that the definitions of E_2, E_3, and E_1, given in Eqs. 2 and 3, change depending on the model hypothesized. However, as Eq. 4 points out, there is no evidence from the data as to which is the correct model.

It should be emphasized that Eq. 4 was defined with respect to the number of solvable rate constants when only the central compartment (a driving force compartment) is sampled. The ability to sample unchanged drug in additional nondriving force compartments such as the urine or expired air would allow one to determine additional rate constants. However, in most cases these additional rate constants will only be a part of a previously hypothesized elimination rate constant and will not allow the investigator to determine the validity of the hypothesized model. For example, if urinary excretion of unchanged drug is also examined for a compound hypothesized to follow the model in Scheme II, the rate constant k_{2u} may be determined from the urinary data. However, unless all of the injected drug is eliminated unchanged in the urine, the investigator has no additional information as to the validity of one particular three-compartment model. A future publication will deal in greater detail with the results and implications obtainable when more than one compartment in the model may be sampled and when it is possible to input drug into the model by routes that bypass the central compartment.

Equation 4 applies only to a drug in a single mammillary model. Rowland *et al.* (9) pointed out how it is possible to solve additional rate constants when both a drug and its metabolite are injected and followed in the plasma. However, in this case, one is really dealing with two mammillary models, one for the drug and one for its metabolite. As described in a following section, the mammillary model for the unchanged drug may be considered an input function for the metabolite model.

Common Input Functions—The following input functions, pictured in Scheme I, describe the usual methods utilized to get drug into the central compartment.

For an intravenous bolus:

$$\text{in}_s = \text{dose} \quad \text{(Eq. 5)}$$

For intravenous infusion or zero-order absorption:

$$\text{in}_s = k^0(e^{-as} - e^{-bs})/s \quad \text{(Eq. 6)}$$

where k^0 = zero-order infusion rate in units of amount per time,

[1] Formerly bishydroxycoumarin.

[2] Although Eq. 4 could be more simply expressed as $R = 2n - 1$, this form was chosen to emphasize the fact that for each compartment beyond the first, two additional terms describing either distribution or a combination of distribution and elimination may be determined; yet it is still only possible to determine one elimination constant unambiguously.

a = time when infusion begins, and b = time when infusion ends. In most cases, the intravenous infusion begins at time zero ($a = 0$) and, therefore, Eq. 6*a* is the more usual input function for intravenous infusion:

$$\text{in}_s = k^0(1 - e^{-bs})/s \qquad \text{(Eq. 6a)}$$

Equations 6 and 6*a* may also be used to define zero-order input from the GI tract or a pellet implant.

For first-order absorption:

$$\text{in}_s = k_a \text{ dose}/(s + k_a) \qquad \text{(Eq. 7)}$$

where k_a = first-order absorption rate constant. This input function may describe absorption from any site but will usually be used in either oral or intramuscular dosing equations. Dose in Eq. 7 refers to the dose that actually gets into the central compartment as unchanged drug, and very often an F may appear in equations describing oral dosing, where F is the availability of the drug. [Availability is defined (10) as the extent to which an administered material reaches the point of measurement.]

Input functions may also be combined if a drug is given by more than one route of administration. For example, it is common to give a patient an intravenous bolus injection of a drug in order to reach therapeutic blood levels quickly, followed by a zero-order infusion so that blood levels may be maintained. Under this condition the input function would be the sum of Eqs. 5 and 6, where a would equal zero if the infusion began at the same time as the bolus injection was administered but would more likely be equal to a value consistent with beginning the infusion after the bolus injection.

DISCUSSION

Solving the Mammillary Model Using the Input and Disposition Functions and the Method of Partial Fractions—The Laplace transform for the amount of drug in Compartment 1, $a_{s,1}$, is given by the product of the input and disposition functions:

$$a_{s,1} = (\text{in}_s)(d_{s,1}) \qquad \text{(Eq. 8)}$$

Let us now consider the dicumarol model (Scheme II) with an intravenous bolus injection. The input function for an intravenous bolus is exactly equal to dose. Therefore, multiplying the disposition function (Eq. 3) by dose, D, yields the Laplace transform for the amount of drug in the central compartment:

$$a_{s,1} = \frac{(s + E_2)(s + E_3)D}{(s + \alpha)(s + \beta)(s + \gamma)} \qquad \text{(Eq. 9)}$$

The anti-Laplace of Eq. 9 could be found in an extensive table of Laplace transforms, but the general method of partial fractions is much easier and is applicable in the majority of cases. Recently, Benet and Turi (11) described the use of a general partial fraction theorem for obtaining inverse Laplace transforms in pharmacokinetic analysis as is detailed here.

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:

$$L^{-1}\left\{\frac{P(s)}{Q(s)}\right\} = \sum_{i=1}^{n} \frac{P(\lambda_i)}{Q_i(\lambda_i)} e^{\lambda_i t} \qquad \text{(Eq. 10)}$$

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 the s terms except for the term originally containing λ_i, this term being omitted; and s is the standard notation used in Laplace operations (12). Since the two polynomials in Eq. 9 fulfill the requirements listed for use of Eq. 10 (*i.e.*, there are no repeated factors in the denominator, and the denominator contains a higher degree in s than the numerator), the answer for the amount of drug in Compartment 1, A_1, may be immediately written:

$$A_1 = \frac{(E_2 - \alpha)(E_3 - \alpha)D}{(\beta - \alpha)(\gamma - \alpha)} e^{-\alpha t} + \frac{(E_2 - \beta)(E_3 - \beta)D}{(\alpha - \beta)(\gamma - \beta)} e^{-\beta t} + \frac{(E_2 - \gamma)(E_3 - \gamma)D}{(\alpha - \gamma)(\beta - \gamma)} e^{-\gamma t} \qquad \text{(Eq. 11)}$$

Although the following facts need never be written, they are implicitly considered in going from Eq. 9 to Eq. 11. That is, the roots of the polynomial, $Q(s)$, are $\lambda_1 = -\alpha$, $\lambda_2 = -\beta$, and $\lambda_3 = -\gamma$. Therefore, the following definitions of $Q_i(\lambda_i)$ are used. When:

$$i = 1 \quad Q_i(\lambda_i) = (\lambda_1 + \beta)(\lambda_1 + \gamma) = (\beta - \alpha)(\gamma - \alpha)$$
$$i = 2 \quad Q_i(\lambda_i) = (\lambda_2 + \alpha)(\lambda_2 + \gamma) = (\alpha - \beta)(\gamma - \beta)$$
$$i = 3 \quad Q_i(\lambda_i) = (\lambda_3 + \alpha)(\lambda_3 + \beta) = (\alpha - \gamma)(\beta - \gamma)$$

The $P(\lambda_i)$ terms are obtained by substitution of the appropriate root for every value of s in the numerator of Eq. 9.

Let us review the procedure. When the factor $(s + \alpha)$ is omitted from the denominator (*i.e.*, when the root $\lambda_1 = -\alpha$ is used), all values of s in Eq. 9 are substituted by $-\alpha$ and this root appears in the exponential term ($e^{-\alpha t}$). Next, the factor $(s + \beta)$ is omitted when the root $\lambda_2 = -\beta$, *etc.* In practice, an easy way to carry out the taking of the anti-Laplace is to cover the factors in the denominator one by one with a finger, while substituting the root of the covered factor for all the remaining s terms. If a single s term appears in the denominator, as when zero-order infusion equations are derived, the root for this factor is zero. The above solution may not appear worth learning in view of the fact that the anti-Laplace might be found in an extensive table. However, consider the above model with an intravenous infusion input. The resulting products of the input (Eq. 6*a*) and disposition (Eq. 3) functions yield:

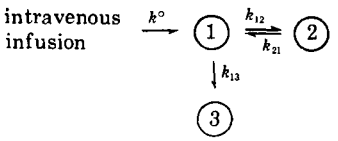
$$a_{s,1} = \frac{k^0(s + E_2)(s + E_3)(1 - e^{-bs})}{s(s + \alpha)(s + \beta)(s + \gamma)} \qquad \text{(Eq. 12)}$$

Realizing that $\lambda_1 = 0$, one may immediately write the solution:

$$A_1 = \frac{k^0(E_2 - \alpha)(E_3 - \alpha)(1 - e^{\alpha b})}{-\alpha(\beta - \alpha)(\gamma - \alpha)} e^{-\alpha t} + \frac{k^0(E_2 - \beta)(E_3 - \beta)(1 - e^{\beta b})}{-\beta(\alpha - \beta)(\gamma - \beta)} e^{-\beta t} + \frac{k^0(E_2 - \gamma)(E_3 - \gamma)(1 - e^{\gamma b})}{-\gamma(\alpha - \gamma)(\beta - \gamma)} e^{-\gamma t} \qquad \text{(Eq. 13)}$$

Note that even though there are four roots in Eq. 12, there are only three terms in Eq. 13 since the numerator of Eq. 12 becomes zero when the root zero is substituted for every value of s. It is also important to realize that the single equation (Eq. 13) describes the amount of drug in Compartment 1, while infusion is going on and after infusion stops. While infusion is continuing, $b = t$ and varies with time. When infusion ceases, b becomes a constant corresponding to the time infusion was stopped. Equation 13 can be used in a computer fit of all the data obtained from an intravenous infusion of a drug, but it requires the use of two independent variables: the variable describing clock time t from the beginning of the experiment and the other equal to the value of b. (A third independent variable corresponding to a in Eq. 6 must be added if the infusion begins at a time different than zero, as discussed previously for the combined intravenous bolus and infusion inputs.) All the least-squares nonlinear fitting programs usually utilized in pharmacokinetic treatments have the ability to fit data to Eq. 13 and should be used since data points taken before the infusion stops are extremely important in characterizing the fast disposition rate constants in multicompartment models.

Two restrictions were placed on the use of the general partial fraction theorem for obtaining inverse Laplace transforms as explained previously and in *Reference 11*. The first restriction, that the denominator in the Laplace transform function contain a higher degree of s than the numerator, will never be violated when deriving equations involving mammillary model disposition functions and the normal input functions described in this paper. However, pharmacokinetic equations involving the second restriction, *i.e.*, repeated functions in the denominator, are often found in pharmacokinetic derivations involving the time course for the amount of drug found in a nondriving force compartment such as the urine. If there is a repeating function in the denominator (*e.g.*, s^2), then the use of Eq. 10 will give the incorrect answer. It is then necessary either to rewrite the function in parts, where the repeating function is separated from the rest of the equation, or to use a general equation for repeated functions as described in the *Appendix*. An example of a solution of this type is presented in the next section.



Scheme III—A two-compartment disposition model with elimination from the central compartment into Compartment 3, a nondriving force compartment such as the urine. Input into the model is by zero-order intravenous infusion.

Solving the Mammillary Model for Compartments Other than the Central Compartment—The general equation for the central compartment (Eq. 1) was previously described. There is no need to define a general equation for any other compartment, since in a mammillary model it is very easy to calculate the Laplace transform of any other compartment, knowing the answer for the central compartment. For example, if one wished to solve for A_3, the amount of drug in Compartment 3 in the model presented in Scheme II, following an intravenous bolus injection, one should take the following approach:

1. Determine the differential equation describing Compartment 3:

$$dA_3/dt = k_{13}A_1 - k_{31}A_3 = k_{13}A_1 - E_3A_3 \qquad \text{(Eq. 14)}$$

2. Take the Laplace transform of the differential equation:

$$s(a_{s,3}) = k_{13}a_{s,1} - E_3a_{s,3} \qquad \text{(Eq. 15)}$$

3. Solve for $a_{s,3}$ and substitute the value for $a_{s,1}$ as given in Eq. 8:

$$a_{s,3} = \frac{k_{13}a_{s,1}}{(s + E_3)} = \frac{k_{13}(s + E_2)D}{(s + \alpha)(s + \beta)(s + \gamma)} \qquad \text{(Eq. 16)}$$

4. Using the method of partial fractions, write the answer for A_3:

$$A_3 = \frac{k_{13}D(E_2 - \alpha)}{(\beta - \alpha)(\gamma - \alpha)}e^{-\alpha t} + \frac{k_{13}D(E_2 - \beta)}{(\alpha - \beta)(\gamma - \beta)}e^{-\beta t} + \frac{k_{13}D(E_2 - \gamma)}{(\alpha - \gamma)(\beta - \gamma)}e^{-\gamma t} \qquad \text{(Eq. 17)}$$

A similar approach should be followed in solving for any nondriving force compartment. Assume that one wished to derive the equation describing the output of drug into the urine following an intravenous infusion. This familiar two-compartment model is pictured in Scheme III. The following steps should be followed:

1. Determine the differential equation describing Compartment 3, the urine:

$$dA_3/dt = k_{13}A_1 \qquad \text{(Eq. 18)}$$

2. Take the Laplace transform of the differential equation:

$$s(a_{s,3}) = k_{13}(a_{s,1}) \qquad \text{(Eq. 19)}$$

3. Solve for $a_{s,3}$:

$$a_{s,3} = \frac{k_{13}(a_{s,1})}{s} \qquad \text{(Eq. 20)}$$

4. Solve for $a_{s,1}$.

The input function for an intravenous bolus beginning at time zero is given by Eq. 6*a*. By using the general equation (Eq. 1), the disposition function may immediately be written:

$$d_{s,1} = \frac{(s + E_2)}{(s + E_1)(s + E_2) - k_{12}k_{21}} = \frac{(s + E_2)}{(s + \alpha)(s + \beta)} \qquad \text{(Eq. 21)}$$

$$a_{s,1} = (\text{in}_s)(d_{s,1}) = \frac{k^0(s + E_2)(1 - e^{-bs})}{s(s + \alpha)(s + \beta)} \qquad \text{(Eq. 22)}$$

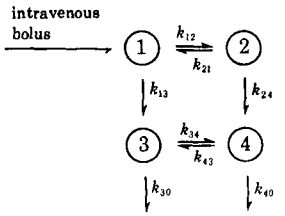
Substituting Eq. 22 into Eq. 20 yields:

$$a_{s,3} = \frac{k_{13}k^0(s + E_2)(1 - e^{-bs})}{s^2(s + \alpha)(s + \beta)} \qquad \text{(Eq. 23)}$$

5. Using the method for taking the anti-Laplace of a function having repeated terms in the denominator, as described in the *Appendix*, one may write the answer:

$$A_3 = \frac{k_{13}k^0E_2b}{\alpha\beta} + \frac{k_{13}k^0(E_2 - \alpha)(1 - e^{\alpha b})}{\alpha^2(\beta - \alpha)}e^{-\alpha t} + \frac{k_{13}k^0(E_2 - \beta)(1 - e^{\beta b})}{\beta^2(\alpha - \beta)}e^{-\beta t} \qquad \text{(Eq. 24)}$$

Equations 18–24 plus Eqs. A3–A5 in the *Appendix* encompass the entire derivation for the very complicated A_3 function using the methods described in this paper. No steps, equation rearrangements, or simplifications have been omitted.



Scheme IV—Compartmental model describing the distribution and elimination of a drug injected into Compartment 1, elimination proceeding from both the central and peripheral compartments, with a metabolite, 3, undergoing analogous disposition.

Use of One Mammillary Model as an Input Function into Another Mammillary Model—The real power of the simplified approach discussed in this paper can be seen in the solution of the model presented in Scheme IV. This model was employed by Rowland *et al.* (9) in determining the extent of metabolite formation from aspirin in the peripheral compartment. Aspirin was injected into Compartment 1, and salicylic acid was measured in the plasma corresponding to Compartment 3. In this example, we wish to solve for the amount of drug in Compartment 3 in Scheme IV where: $E_2 = k_{21} + k_{24}$; $E_4 = k_{43} + k_{40}$; $A_{13} = k_{12}k_{24}k_{40}$; α,β = fast and slow disposition constants describing an intravenous bolus injection of aspirin; and γ,δ = fast and slow disposition constants describing an intravenous bolus injection of salicylic acid.

If k_{24} is neglected initially, Scheme IV may be described as two mammillary models in series, and the disposition function for the central compartment in each model may immediately be written:

$$d_{s,1} = \frac{(s + E_2)}{(s + E_1)(s + E_2) - k_{12}k_{21}} = \frac{(s + E_2)}{(s + \alpha)(s + \beta)} \qquad \text{(Eq. 21)}$$

$$d_{s,3} = \frac{(s + E_4)}{(s + E_3)(s + E_4) - k_{34}k_{43}} = \frac{(s + E_4)}{(s + \gamma)(s + \delta)} \qquad \text{(Eq. 25)}$$

Given an intravenous bolus injection of aspirin into Compartment 1, the Laplace transform of the amount of drug in Compartment 1 is given by the products of dose, D, and Eq. 21:

$$a_{s,1} = \frac{(s + E_2)D}{(s + \alpha)(s + \beta)} \qquad \text{(Eq. 26)}$$

The input function into Compartment 3 is given by:

$$\text{in}^*_{s,3} = k_{13}(a_{s,1}) \qquad \text{(Eq. 27)}$$

where * indicates that one is neglecting the alternate route of input into the second mammillary model, *i.e.*, k_{24}. Therefore, the Laplace transform of the amount of drug in Compartment 3 is given by the products of Eqs. 25 and 27:

$$a^*_{s,3} = k_{13}(a_{s,1})(d_{s,3}) = \frac{k_{13}(s + E_2)(s + E_4)D}{(s + \alpha)(s + \beta)(s + \gamma)(s + \delta)} \qquad \text{(Eq. 28)}$$

where D must now equal the dose of salicylic acid equivalent to the injected dose of aspirin.

Equation 28 describes the Laplace transform of the amount of drug in Compartment 3 when passage from one mammillary model to the next is through a pathway connecting the central compartments of each model. This type of equation would yield a very easy solution to the six-compartment model proposed by Kaplan *et al.* (13) to describe the pharmacokinetics of chlordiazepoxide and its two pharmacologically active biotransformation products. However, if one wishes to add an alternate pathway to the model as shown in Scheme IV, it is only necessary to add the product of the alternate

pathway rate constants and the dose to the numerator of Eq. 28:

$$a_{s,3} = \frac{k_{13}(s + E_2)(s + E_4)D + A_{13}D}{(s + \alpha)(s + \beta)(s + \gamma)(s + \delta)} \quad \text{(Eq. 29)}$$

where $A_{13} = k_{12}k_{24}k_{43}$. Since there are no repeated functions in the denominator of Eq. 29, the solution may be written down in one step using the general partial fraction theorem, as was shown by Benet and Turi (11):

$$A_3 = \frac{k_{13}(E_2 - \alpha)(E_4 - \alpha)D + A_{13}D}{(\beta - \alpha)(\gamma - \alpha)(\delta - \alpha)} e^{-\alpha t} + \frac{k_{13}(E_2 - \beta)(E_4 - \beta)D + A_{13}D}{(\alpha - \beta)(\gamma - \beta)(\delta - \beta)} e^{-\beta t} + \frac{k_{13}(E_2 - \gamma)(E_4 - \gamma)D + A_{13}D}{(\alpha - \gamma)(\beta - \gamma)(\delta - \gamma)} e^{-\gamma t} + \frac{k_{13}(E_2 - \delta)(E_4 - \delta)D + A_{13}D}{(\alpha - \delta)(\beta - \delta)(\gamma - \delta)} e^{-\delta t} \quad \text{(Eq. 30)}$$

Multiple-Dosing Equations—It can be stated 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 by the function:

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

where a constant dose is given every τ hours and the rate constants in the model are time and dose independent; τ = dosing interval in the same time units as k; k_i = the appropriate first-order rate constant, where i varies from 1 to n corresponding to the number of driving force compartments; and N = number of doses. This type of multiple-dose function was first used in pharmacokinetics by Dost (14). It can easily be demonstrated that:

$$\frac{[e^{+(N-1)\tau k_i} - e^{-\tau k_i}]}{1 - e^{-\tau k_i}} e^{-k_i t} = \frac{1 - e^{-N\tau k_i}}{1 - e^{-\tau k_i}} e^{-k_i[t-(N-1)\tau]} = \frac{1 - e^{-N\tau k_i}}{1 - e^{-\tau k_i}} e^{-k_i t'} \quad \text{(Eq. 31)}$$

where $t' = t - (N - 1)\tau$, the time since the last dose was given. Thus, the equation for the amount of drug in Compartment 1 of Scheme II during multiple intravenous injections of dose D every τ hours can be obtained by multiplying each exponential term by the multiple-dosing function and rearranging:

$$A_1 = \frac{(E_2 - \alpha)(E_3 - \alpha)D(1 - e^{-N\tau\alpha})}{(\beta - \alpha)(\gamma - \alpha)(1 - e^{-\alpha\tau})} e^{-\alpha t'} + \ldots \quad \text{(Eq. 32)}$$

CONCLUSION

The general methods presented in this paper should markedly lessen the amount of work and journal pages necessary in deriving pharmacokinetic equations following linear kinetics. The use of input and disposition functions was suggested, and a general equation to describe the disposition function for the central compartment of a mammillary model with elimination allowed from any compartment was presented. The number of solvable rate constants for any mammillary model was considered. A general partial fraction theorem which allows the researcher to solve Laplace transforms in a single step was presented, and the use of a multiple-dosing function was described. Examples utilizing multicompartment models with a variety of inputs were presented so that the entire derivation could be followed by the reader with no steps omitted. Most equations for multicompartment models can be solved in four or five simple steps.

APPENDIX

When repeated functions appear in the denominator of a Laplace transform, the general partial fraction theorem, as stated in Eq. 10, may not be used. Consider the following general equation:

$$L\left\{\frac{P(s)}{Q(s)}\right\} = \frac{P(s)}{(s - \lambda_1)^{r+1}(s - \lambda_2)(s - \lambda_3)} \quad \text{(Eq. A1)}$$

where:

L = Laplace of $\{\ \}$
$P(s)$ = a polynomial in s such that $Q(s)$ has the higher degree in s (a condition that is met with all derivations involving mammillary models)
$(s-\lambda_1)$ = a repeated function in $Q(s)$; that is, r has a value greater than zero

The solution (12) to this equation is given by:

$$L^{-1}\left\{\frac{P(s)}{Q(s)}\right\} = \frac{1}{r!}\frac{\partial^r}{\partial s^r}[\Phi(s)e^{st}]_{s=\lambda_1} + \sum_{i=2}^{m}\frac{P(\lambda_i)}{Q_i(\lambda_i)}e^{\lambda_i t} \quad \text{(Eq. A2)}$$

where $\Phi(s)$ is set equal to $P(s)/Q(s)$ when the repeating function is omitted from $Q(s)$. Therefore, Eq. A1 could be rewritten as:

$$L\left\{\frac{P(s)}{Q(s)}\right\} = \frac{\Phi(s)}{(s - \lambda_1)^{r+1}} \quad \text{(Eq. A1}a\text{)}$$

Thus, the first term in Eq. A2 is the derivative of $\Phi(s)e^{st}$ with respect to s evaluated at $s = \lambda_1$. The second term is similar to Eq. 10, except that the function is not evaluated at λ_1, the root corresponding to the repeated function.

Equation 23 in this paper was solved using Eq. A2 as described here:

$$a_{s,3} = \frac{k_{13}k^0(s + E_2)(1 - e^{-bs})}{s^2(s + \alpha)(s + \beta)} \quad \text{(Eq. 23)}$$

With reference to Eqs. A1a, A2, and 23, the following terms are defined:

$$r = 1$$
$$\lambda_1 = 0$$
$$\lambda_2 = -\alpha$$
$$\lambda_3 = -\beta$$
$$\Phi(s) = \frac{k_{13}k^0(s + E_2)(1 - e^{-bs})}{(s + \alpha)(s + \beta)}$$

The derivative in Eq. A2 yields the following:

$$\frac{\partial[\Phi(s)e^{st}]}{\partial s} = \left[\frac{\partial\Phi(s)}{\partial s} + t\Phi(s)\right]e^{st} \quad \text{(Eq. A3)}$$

$$\frac{\partial\Phi(s)}{\partial s} = \frac{k_{13}k^0}{(s + \alpha)^2(s + \beta)^2}\{(s + \alpha)(s + \beta) \times [(s + E_2)(be^{-bs}) + (1 - e^{-bs})] - (s + E_2) \times (1 - e^{-bs})[(s + \alpha) + (s + \beta)]\} \quad \text{(Eq. A4)}$$

Evaluating Eq. A4 when $s = 0$ gives:

$$\frac{\partial\Phi(s)}{\partial s} = \frac{k_{13}k^0}{\alpha^2\beta^2}\{\alpha\beta[(E_2)b + 0] - E_2(1 - 1)(\alpha + \beta)\} = \frac{k_{13}k^0E_2b}{\alpha\beta} \quad \text{(Eq. A5)}$$

Since $\Phi(s) = 0$ and $e^{st} = 1$ when $s = 0$, the first term in the anti-Laplace of Eq. 23 (corresponding to the first term on the right-hand side of Eq. A2) is given by Eq. A5. The second and third terms in the anti-Laplace of Eq. 23 (corresponding to the second term on the right-hand side of Eq. A2) are found using the methods previously described for Laplace transforms involving nonrepeating functions. Thus Eq. 24 is the resulting anti-Laplace for Eq. 23.

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ACKNOWLEDGMENTS AND ADDRESSES

Received June 21, 1971, from the *Department of Pharmacy, University of California, San Francisco, CA 94122*

Accepted for publication December 15, 1971.

Presented in part to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, San Francisco meeting, March 1971.

Supported in part by Grant NIGMS 16496 from the National Institutes of Health, U. S. Public Health Service, Bethesda, MD 20014

Relationship between Dose and Plateau Levels of Drugs Eliminated by Parallel First-Order and Capacity-Limited Kinetics

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Abstract □ Repetitive administration at constant time intervals of fixed doses of drugs which are eliminated by apparent first-order kinetics will usually result in the eventual attainment of a drug level plateau in the body. If a drug is eliminated solely by capacity-limited (Michaelis–Menten) kinetics in the therapeutic dose range, it will accumulate in the body without limit when the dose exceeds a certain amount. Drugs eliminated by parallel apparent first-order and capacity-limited kinetics will attain a drug level plateau but, unlike drugs eliminated only by first-order kinetics, the ratio of plateau level–dose is not independent of dose but increases with increasing dose. The rate of this increase is particularly high in a certain dose range which, therefore, represents a "danger zone" in which an increase in dose causes a considerably more than proportional increase in plateau level. This may be the cause of some adverse and toxic effects of certain drugs, such as the salicylates, during chronic therapy.

Keyphrases □ Pharmacokinetics—dose–plateau levels relationship, parallel first-order and capacity-limited elimination kinetics □ Dose–plateau drug levels relationship—drugs eliminated by parallel first-order and capacity-limited kinetics □ Elimination kinetics, parallel first order and capacity limited—relationship between drug dose and plateau levels □ Toxicity, drugs—dose–plateau levels relationship, elimination kinetics

The most important reasons for elucidating the kinetics of absorption, distribution, and elimination of a drug are to be able to predict the time course of drug levels in the body as a function of dose and frequency of drug administration and to permit the design of safe and effective dosage regimens for long-term therapy. It is particularly important to be able to predict the plateau level of a drug in the body attained some time after repeated administration of a fixed dose at constant intervals. Many adverse reactions and intoxications are due to accumulation of drugs to excessive levels; lack of effectiveness is often the result of a dosage regimen that produces a plateau level lower than the therapeutic range.

The average amount of drug in the body ($\bar{A}_{pl}$) at the plateau is directly proportional to dose (D) provided that absorption, distribution, and elimination can be described by a set of *linear* differential equations (1). In Eq. 1, F is the fraction of the dose which is absorbed, τ is the dosing interval, and k_d is the elimination rate constant:

$$\bar{A}_{pl} = DF/\tau k_d \qquad \text{(Eq. 1)}$$

The equation holds for all linear systems, irrespective of the number of apparent compartments required to describe them (2, 3). The direct proportionality between dose and plateau level of drug in the body, represented by Eq. 1, makes it easy to adjust the plateau level by a corresponding adjustment of the maintenance dose.

It is now realized that the elimination of some important and widely used drugs cannot be described by a set of linear differential equations. Such drugs, of which salicylic acid and ethanol are prominent examples, exhibit dose-dependent kinetics (4). This dose dependence is most often due to the limited capacity of an enzyme system involved in the formation of a metabolite of the drug. In the case of salicylic acid, the formation of not one but two major metabolites is affected by the limited capacity of the respective enzyme systems, and this is evident in the therapeutic dose range in man (5). The elimination of such drugs proceeds relatively more slowly as the dose is increased (4, 6); for this reason, there is no direct, simple relationship between dose and plateau level as described by Eq. 1.

The purposes of this article are to identify the factors affecting the accumulation characteristics of drugs subject to capacity-limited elimination kinetics in the therapeutic dose range, to show the relationship between dose and plateau drug levels in the body, and to compare the nature of this relationship to that of drugs eliminated by linear processes.