Calculating Absorption Rate Constants for Drugs with Incomplete Availability

LEWIS J. LEESON[▲] and HOWARD WEINTRAUB*

Abstract □ A mathematical analysis was made of the type of results to be expected, by the classic pharmacokinetic treatment of plasma level data, when, in addition to absorption, the drug is simultaneously lost to an extravascular compartment *via* either a parallel first- or zero-order process. Equations are presented for both the presence and absence of a lag time before onset of the parallel process. A procedure is proposed which allows the true first-order absorption rate constant to be determined for some models, as well as the elucidation of the applicable model.

Keyphrases □ Drugs with incomplete availability—considerations in calculating absorption rate constants, plasma level data and simultaneous loss to extravascular compartment, equations for both presence and absence of lag time □ Absorption rate constants, drugs with incomplete availability—mathematical treatment of plasma level data and simultaneous loss to extravascular compartment, equations for both presence and absence of lag time □ Pharmacokinetics—calculation of absorption rate constants for drugs with incomplete availability, plasma level data and simultaneous loss to extravascular compartment, equations for both presence and absence of lag time

In a recent publication, Notari *et al.* (1) demonstrated that methods commonly employed to calculate absorption rate constants from the time course of drug in the blood do not result in the correct value if the drug is simultaneously lost to an extravascular compartment by a parallel first-order process. It is well recognized in chemical kinetics that the classical kinetic treatment of reaction data, in which a compound degrades *via* two or more first-order pathways, yields an apparent rate constant for loss of material which is a sum of the rate constants for the individual processes. However, to the best of these authors' knowledge, the application of this principle to pharmacokinetic considerations was not recognized prior to the publication of Notari *et al.* (1). More recently, Perrier and Gibaldi (2) expanded on Notari's concept, which deals primarily with chemical degradation of drugs in solution, to include the case of both a granulation and a nondisintegrating dosage form moving along the GI tract to a point where absorption no longer occurs. They also considered the case where the competing parallel reaction was zero order and introduced the concept of a lag time occurring prior to the onset of either parallel reaction. These authors (2) concluded that the nature of the rate constant obtained with a parallel first-order reaction was dependent upon the lag time. They also reported that in the case of a parallel zero-order reaction, although the computer-generated data showed curvature, when plotted according to the Wagner–Nelson (3) or Loo–Riegelman (4) method, the normal experimental error encountered in real situations could mask this. As a result, one would tend to accept the curves as linear and employ the slope to obtain an absorption rate constant.

The cases of parallel first-order and zero-order competitive processes with various lag times have been considered, and a mathematical interpretation is presented for the nature of the curves obtained both by the method of feathering and by the Wagner–Nelson (3) procedure. In the case of the parallel first-order loss of drug to extravascular compartment, it is concluded that these methods yield plots which tend to be curved until the onset of the lag time, at which time they become linear and are all parallel. In the case of a parallel zero-order process, one encounters curves that could be interpreted as linear, with the apparent linear relationships being a function of the lag time. In addition, a method was developed which in some cases allows an investigator to determine the correct absorption rate constant with concomitant recognition of the nature of the parallel process.

All of this work has been limited to the one-compartment open model with first-order absorption. However, parallel considerations for more complex models are possible in a manner similar to that presented in this report.

EXPERIMENTAL

In this analysis, the simple one-compartment open model is represented as shown in Scheme I, where k_1 and k_2 are the absorption

$$\underset{\text{absorption compartment}}{A} \xrightarrow{k_1} \underset{\text{plasma compartment}}{B} \xrightarrow{k_2} \underset{\text{elimination compartment}}{C}$$

Scheme I

and elimination rate constants, respectively. Two variations on this scheme were considered. In Case 1, drug in Compartment A is simultaneously being removed to an extravascular compartment by a first-order rate process with a rate constant of k_3. In Case 2, drug is being removed from Compartment A *via* a zero-order rate process with a rate constant of k_0. These are shown in Scheme II.

Case 1

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$
$$\downarrow k_3$$
$$D$$

Case 2

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$
$$\downarrow k_0$$
$$D$$

Scheme II

All calculations were performed on a programmable desk calculator[1]. The rate constants employed were those suggested by Perrier and Gibaldi (2) ($k_1 = 0.693$, $k_2 = 0.0693$, $k_3 = 0.5$, and $k_0 = 25$)[2]. Lag times were varied from 0 to 3 hr. In most cases only the final forms of the equations employed are presented[3].

[1] Wang model 700.

[2] k_1, k_2, and k_3 are first-order rate constants with dimensions of reciprocal hours; k_0 is a zero-order rate constant with dimensions of units per hour.

[3] Interested parties may obtain the derivations by communication with the authors.

RESULTS AND DISCUSSION

Case 1—It may be shown that the relationship governing the time course of drug in the body in the absence and presence of a lag time is defined by Eqs. 1 and 2, respectively:

$$C_p = \frac{k_1 A_0}{(K - k_2)V}[\exp(-k_2 t) - \exp(-Kt)] \quad \text{(Eq. 1)}$$

$$C_p = \frac{k_1 A_0 \exp(-k_1 t1)}{(K - k_2)V}\{\exp[-k_2(t - t1)] - \exp[-K(t - t1)]\} + \frac{B_{t1}}{V}\{\exp[-k_2(t - t1)]\} \quad \text{(Eq. 2)}$$

where k_1 and k_2 are the absorption and elimination rate constants, respectively; k_3 is the parallel nonabsorption first-order rate constant; t is time; $t1$ is lag time; C_p is the plasma concentration; A_0 is the amount of drug in the dosage form; B_{t1} is the amount of drug in Compartment B at lag time $t1$; K is the sum of the two parallel first-order rate constants ($k_1 + k_3$); and V is the volume of distribution. The similarity between Eq. 1 and that for the one-compartment open model with first-order absorption and no parallel reaction (Eq. 6) is obvious when one substitutes 0 for k_3 in Eq. 1. Equation 2 is applicable only from the onset of the lag time.

In the treatment of experimentally obtained data, one plots log C_p as a function of time and determines k_2 from the log-linear phase. The absorption rate constant is then evaluated by either the method of feathering or the Wagner–Nelson procedure. Under conditions of nonparallel reactions occurring, both methods yield essentially the same results. The type of data obtained from these techniques when one does encounter parallel competing reactions, both with and without lag times, was examined.

Feathering Method (Method of Residuals)—Where there is no lag time, one would employ Eq. 1. It is, therefore, obvious that after onset of the log-linear phase, C_p would be expressed in terms of Eq. 3:

$$C_p = \left[\frac{k_1 A_0}{(K - k_2)V}\right]\exp(-k_2 t) \quad \text{(Eq. 3)}$$

Thus, ΔC_p, which represents the difference in C_p between Eqs. 1 and 3 at any given time, would be expressed as shown in Eq. 4:

$$\Delta C_p = \left[\frac{k_1 A_0}{(K - k_2)V}\right]\exp(-Kt) \quad \text{(Eq. 4)}$$

It is then apparent that Eq. 4 represents a log-linear relationship which, when plotted, has a slope equal to K. This is implicit in what was stated by Notari *et al.* (1) and Perrier and Gibaldi (2).

In the case where there is a finite lag time, $t1$, C_p in the post-absorptive phase comes from Eq. 2 and is shown as Eq. 5:

$$C_p = \left[\frac{k_1 A_0 \exp(-k_1 t1)}{(K - k_2)V} + \frac{B_{t1}}{V}\right]\exp[-k_2(t - t1)] \quad \text{(Eq. 5)}$$

However, when t is less than $t1$, C_p is defined in terms of the classical one-compartment open model with first-order absorption as shown in Eq. 6:

$$C_p = \frac{k_1 A_0}{(k_1 - k_2)V}[\exp(-k_2 t) - \exp(-k_1 t)] \quad \text{(Eq. 6)}$$

Therefore, ΔC_p prior to the onset of the lag time is represented mathematically by Eq. 7, where M and N are constants. It is readily seen that Eq. 7 is not a log-linear relationship:

$$\Delta C_p = M\exp(-k_2 t) + \exp(-k_1 t) \quad \text{(Eq. 7)}$$

$$M = \frac{k_1 A_2 \exp(k_2 - k_1)t1}{(K - k_2)V} + \frac{B_{t1}\exp(k_2 t1)}{V} - N \quad \text{(Eq. 7a)}$$

$$N = \frac{k_1 A_0}{(k_1 - k_2)V} \quad \text{(Eq. 7b)}$$

In the range where t is between $t1$ and the onset of the log-linear phase, C_p is as defined in Eq. 2 and ΔC_p is defined by Eq. 8:

$$\Delta C_p = \left[\frac{k_1 A_0 \exp(k_2 t1)}{(K - k_2)V}\right]\exp(-Kt) \quad \text{(Eq. 8)}$$

It is again obvious that a plot of log ΔC_p *versus* t, according to Eq. 8, will be linear with a slope from which K may be obtained.

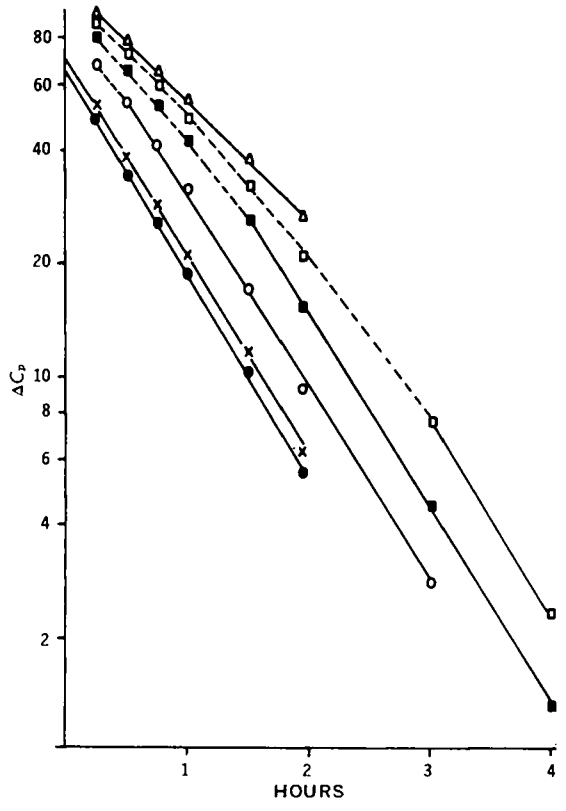

Figure 1—*Plot of* ΔC_p versus *time for data where competing first-order process is operative, calculated according to the method of residuals. Key:* ●, *no lag;* ×, *0.5-hr. lag;* ○, *1-hr. lag;* ■, *2-hr. lag;* □, *3-hr. lag; and* △, *no competitive process (control).*

From this discussion, therefore, it is apparent that when a lag time occurs prior to the onset of a parallel first-order reaction, the feathering technique results in a line that is initially curved followed by a straight portion from which the apparent absorption rate constant (K) is obtained. This value, while not the true absorption rate constant, would be the same whether or not there was a lag time occurring before onset of the competing process. Data of this type are shown in Fig. 1, employing the rate constant suggested by Perrier and Gibaldi (2).

Wagner–Nelson Technique—In the Wagner–Nelson (3) method, one first determines the fraction of drug absorbed, and the absorption rate constant is evaluated from a plot of log fraction unabsorbed as a function of time. The fraction absorbed is determined by dividing the amount of drug absorbed at any time period (D/V) by the total amount of drug absorbed (D_∞/V). The fraction unabsorbed is then expressed by the relationship ($1 - D/D_\infty$).

It may be shown that the total amount of drug absorbed is represented by a sum of the drug absorbed up to the lag time *via* the equation for a one-compartment open model with first-order absorption (Eq. 6), plus the drug absorbed from the onset of the lag time until the onset of the log-linear phase. This is expressed by Eq. 9:

$$D_\infty = D_{t1} + \left(\frac{k_1}{K}\right)A_{t1} = A_0\left[1 - \frac{k_3}{K}\exp(-k_1 t1)\right] \quad \text{(Eq. 9)}$$

where D_{t1} represents the amount of drug absorbed up to the lag time and $[(k_1/K)A_{t1}]$ represents the amount of drug absorbed from the lag time until absorption ceases. The term A_{t1} represents the amount of drug in Compartment A at the onset of the lag time.

Correspondingly, the amount of drug absorbed at any time after the lag time is represented by Eq. 10 where the constants are as designated previously:

$$D = A_0\left\{\left[1 - \frac{k_3}{K}\exp(-k_1 t1)\right] - \left[\frac{k_1}{K}\exp(k_2 t1)\right]\exp(-Kt)\right\} \quad \text{(Eq. 10)}$$

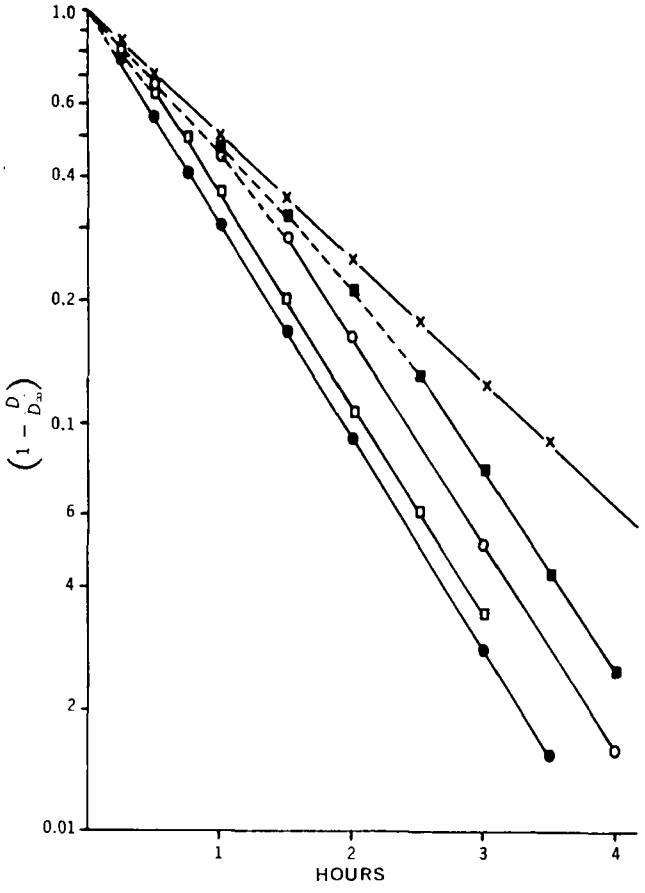

Figure 2—*Plot of Wagner-Nelson calculations* versus *time for data where competing first-order process is operative. Key:* ×, *control (no competition);* ●, *0.5-hr. lag;* □, *1-hr. lag;* ○, *2-hr. lag; and* ■, *3-hr. lag.*

Therefore, if there is no lag time, $D_{t1} = 0$ and the expression $(1 - D/D_\infty)$ may be represented as seen in Eq. 11:

$$(1 - D/D_\infty) = \exp(-Kt) \qquad \text{(Eq. 11)}$$

Equation 11 represents a log-linear relationship from which K may be determined, again in agreement with both Notari *et al.* (1) and Perrier and Gibaldi (2).

Where there is a lag time occurring prior to $t = t1$, the expression $(1 - D/D_\infty)$ is represented by Eq. 12 and is not a log-linear relationship:

$$(1 - D/D_\infty) = \frac{K\exp(-k_1t) - k_3\exp(-k_1t1)}{k_3\exp(-k_1t1) - K} \qquad \text{(Eq. 12)}$$

Between the onset of the lag time and completion of absorption, the expression $(1 - D/D_\infty)$ is represented by Eq. 13 and would be log-linear with the slope related to K:

$$(1 - D/D_\infty) = \left[\frac{k_1\exp(k_3t1)}{K - k_3\exp(-k_1t1)}\right]\exp(-Kt) \qquad \text{(Eq. 13)}$$

This discussion indicates that a Wagner-Nelson (3) plot will be comparable to one obtained by the feathering technique in that the plot will be curved prior to the lag time. After the onset of the lag time and independent of its magnitude, one obtains a straight line from which the identical, apparent first-order absorption rate constant (K) is obtained. Plots of this type are shown in Fig. 2, again employing Perrier and Gibaldi's rate constants. On initial inspection, the results appear to be different from those reported by Perrier and Gibaldi in their Fig. 1. However, if one considers the fact that they limited their results to $(1 - D/D_\infty)$ values of greater than 0.1, in some cases the true log-linear phase was not attained. In addition, for the purpose of emphasis, they intentionally fit all of their data linearly. This masked the cases where there were parallel log-linear relationships. Therefore, Fig. 2 in this publication and Fig. 1 of Perrier and Gibaldi are, in fact, the same.

Parallel Zero-Order Reaction—The relationships between plasma concentration and time resulting from the model designated as Case 2 are somewhat more complex than with Case 1 and are shown by Eq. 14 for the case where $t1 = 0$ and by Eq. 15 when there is a finite lag time:

$$C_p = \left[\frac{k_0}{k_2V} + \frac{k_1A_0 + k_0}{V(k_1 - k_2)}\right]\exp(-k_2t) - \left[\frac{k_1A_0 + k_0}{V(k_1 - k_2)}\right]\exp(-k_1t) - \frac{k_0}{k_2V} \qquad \text{(Eq. 14)}$$

$$C_p = \left[\frac{k_0}{k_2V} + \frac{k_1A_0\exp(-k_1t1) + k_0}{V(k_1 - k_2)}\right]\exp[-k_2(t - t1)] - \left[\frac{k_1A_0\exp(-k_1t1) + k_0}{V(k_1 - k_2)}\right]\exp[-k_1(t - t1)] - \frac{k_0}{Vk_2} + \frac{B_{t1}}{V}\exp[-k_2(t - t1)] \qquad \text{(Eq. 15)}$$

In these expressions, the constants are all as previously designated. Equations 14 and 15 may be expressed in a number of ways for which an equivalency is not immediately apparent. Moreover, Eq. 15 applies only after onset of the lag time.

Upon first examination of Eqs. 14 and 15, there appears to be an error in the fact that when time is equal to infinity C_p does not go to zero but becomes a finite negative value, as indicated by the constant (k_0/k_2V) present in both equations. Upon considering the situation, however, one recognizes that Eqs. 14 and 15 only apply up to a certain critical time, t_c, at which point there remains no drug in Compartment A. From this point on, the plasma concentration is defined as shown in Eq. 16 where B_c is equal to the concentration in Compartment B at t_c:

$$C_p = \frac{B_c}{V}\exp(-k_2t) \qquad \text{(Eq. 16)}$$

The term t_c is shown in Eq. 17:

$$t_c = \frac{1}{k_1}\ln\left(\frac{k_0}{k_1A_0 + k_0}\right) \qquad \text{(Eq. 17)}$$

B_c may be determined using the value for t_c and Eq. 14 or 15.

Feathering Technique—It is apparent that if one employs the feathering technique in the case of a parallel zero-order reaction with no lag time, the differences between Eqs. 14 and 16 at various times do not result in a log-linear relationship. Thus, a plot of log ΔC_p as a function of time would be curved. Correspondingly, when a lag time does occur, prior to its onset the difference between the equation for the one-compartment open model (Eq. 6) and Eq. 16 would also result in a ΔC_p-time relationship which is not log-linear. After t reaches $t1$, the ΔC_p values will be comparable to those in the case where there is no lag time. Thus, the data obtained by the feathering technique would be expected to give results that do not indicate the true absorption rate constant, in spite of the fact that in one exponential term there is a k_1 and not a pseudoconstant. However, as indicated by Perrier and Gibaldi (2), the normal error encountered in this type of data could be such as to make it appear to be log-linear. Such plots are shown in Fig. 3, and we agree with Perrier and Gibaldi that the data could be drawn linear, especially with values resulting from *in vivo* studies. They might also be considered to be curved initially followed by linearity. It should be mentioned, however, that there could exist values of k_1, k_2, and k_0 of such a magnitude as to result in an obviously curved relationship.

Wagner-Nelson Method—It may be demonstrated that the expression $(1 - D/D_\infty)$ is represented by rather complex functions both in the presence and absence of a finite lag time (Eqs. 18 and 19, respectively):

$$(1 - D/D_\infty) = \frac{M' - N'[1 - \exp(k_1t)] + k_0t}{M} \qquad \text{(Eq. 18)}$$

$$M' = A_0 + \frac{k_0}{k_1}\left(\ln\frac{k_0}{k_1A_0 + k_0}\right) \qquad \text{(Eq. 18}a\text{)}$$

$$N' = \frac{k_1A_0 + k_0}{k_1} \qquad \text{(Eq. 18}b\text{)}$$

$$(1 - D/D_\infty) = \frac{M^* - N^* \{1 - \exp[-k_1(t - t1)]\} + k_0(t - t1)}{M'} \quad \text{(Eq. 19)}$$

$$M^* = A_{t1} + \frac{k_0}{k_1}\left(\ln \frac{k_0}{k_1 A_{t1} + k_0}\right) \quad \text{(Eq. 19a)}$$

$$N^* = \frac{k_1 A_{t1} + k_0}{k_1} \quad \text{(Eq. 19b)}$$

It is apparent from an examination of both of these relationships that a Wagner–Nelson plot in the event of Case 2 would not result in a straight line. Once again, however, as proposed by Perrier and Gibaldi and as seen in Fig. 4, the data obtained could appear to be either log-linear or initially curved followed by an apparent log-linear relationship.

Evaluating True Absorption Rate Constant and Correct Model—Based on what has been stated to this point, if one obtains plasma level data resulting from a one-compartment open model with first-order absorption and treats them *via* either a feathering or the Wagner–Nelson method, various plots may result. If one obtains what appears to be an initial curvature followed by an apparent linear portion, it may be assumed that after a finite lag time the drug is also being lost from the absorption compartment *via* either a parallel first-order or zero-order process. However, if the lag time is less than 30 min., it probably would not be detected nor be sufficiently distinguishable from a lag time that is due to a dosage form effect such as the opening of a gelatin capsule or the removal of a coating from a sugar- or film-coated tablet. However, assuming that there is a lag time prior to the onset of the parallel secondary process, the true absorption rate constant may be determined by treatment of the data obtained prior to the onset of the lag time. A suggested technique is as follows.

If one considers what is occurring prior to the onset of the lag time, it is obvious that during this period the total amount of drug in the body may be represented by Eq. 20, where A_0 represents the amount of drug in the dosage form and k_1 is the true first-order absorption rate constant:

$$D = A_0[1 - \exp(-k_1 t)] \quad \text{(Eq. 20)}$$

Correspondingly, the D/V obtained from the Wagner–Nelson method is represented by Eq. 21:

$$\frac{D}{V} = \frac{A_0}{V}[1 - \exp(-k_1 t)] \quad \text{(Eq. 21)}$$

Thus, if one were to select two values of D/V at two different time intervals prior to onset of the lag time, where $t_1 = n$ and $t_2 = 2n$, the corresponding expressions for D/V could be shown as Eqs. 22 and 23:

$$\frac{D}{V}(2n) = \frac{A_0}{V}[1 - \exp(-2nk_1)] \quad \text{(Eq. 22)}$$

$$\frac{D}{V}(n) = \frac{A_0}{V}[1 - \exp(-nk_1)] \quad \text{(Eq. 23)}$$

Dividing Eq. 22 by Eq. 23, one obtains Eq. 24, which may be modified to give Eq. 25:

$$\frac{D_{2n}}{D_n} = \frac{[1 - \exp(-2nk_1)]}{[1 - \exp(-nk_1)]} = \frac{[1 + \exp(-nk_1)][1 - \exp(-nk_1)]}{[1 - \exp(-nk_1)]} \quad \text{(Eq. 24)}$$

$$\left(\frac{D_{2n}}{D_n} - 1\right) = \exp(-nk_1) \quad \text{(Eq. 25)}$$

It is apparent from Eq. 25 that if one plots the log of the fraction $\{[D/V(2n)/D/V(n)] - 1\}$ as a function of n, a straight line will result with a slope equal to $-k_1/2.303$. Another characteristic of data plotted *via* Eq. 25 is that the line resulting from such a plot will intercept the y axis at 1 (on semilog paper) when $n = 0$. When time is equal to or greater than $t1$, the relationship is no longer linear if the parallel reaction is zero order. If the parallel reaction is first order, after the onset of the lag time one obtains a second straight line with a slope equal to $-K/2.303$. Thus, using the n–$2n$ technique (Eq. 25), one is able to differentiate between Case 1 and Case 2 when there is a finite lag time. Plots of this type are shown in Figs. 5 and 6.

In addition to the situation described, if one obtains plasma level data resulting from the one-compartment open model with first-order absorption and treats them *via* either feathering or the Wagner–Nelson method, an apparent log-linear relationship through all data points may indicate one of the following three possibilities:

1. There is complete availability of the drug with no side reactions occurring, and the slope of the log-linear plot is related to the true absorption rate constant.

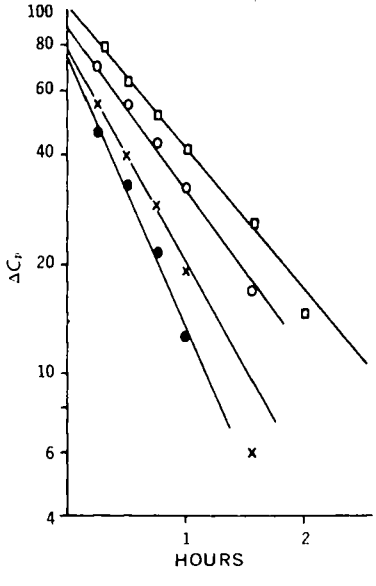

Figure 3 *Plot of* ΔC_p versus *time for data where competing zero-order process is operative, calculated according to the method of residuals* (k_0 = *25 units/hr.*). *Key:* ●, *0.5-hr. lag;* ×, *1.0-hr. lag;* ○, *2.0-hr. lag; and* □, *3.0-hr. lag.*

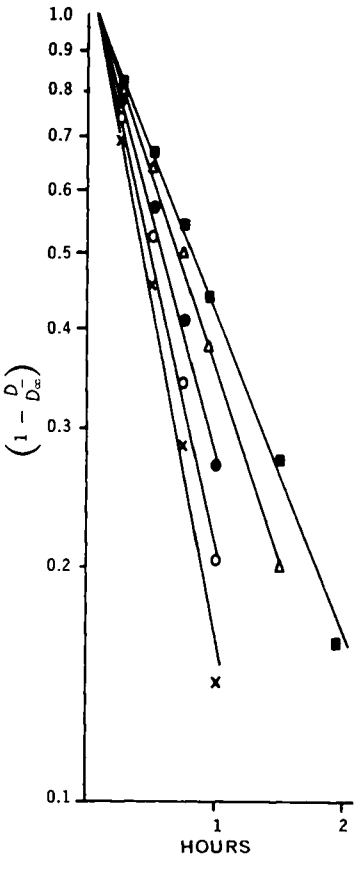

Figure 4—*Plot of Wagner–Nelson calculations* versus *time for data where competing zero-order process is operative* (k_0 = *25 units/hr.*). *Key:* ×, *no lag;* ○, *0.5-hr. lag;* ●, *1-hr. lag;* △, *2-hr. lag; and* ■, *3-hr. lag.*

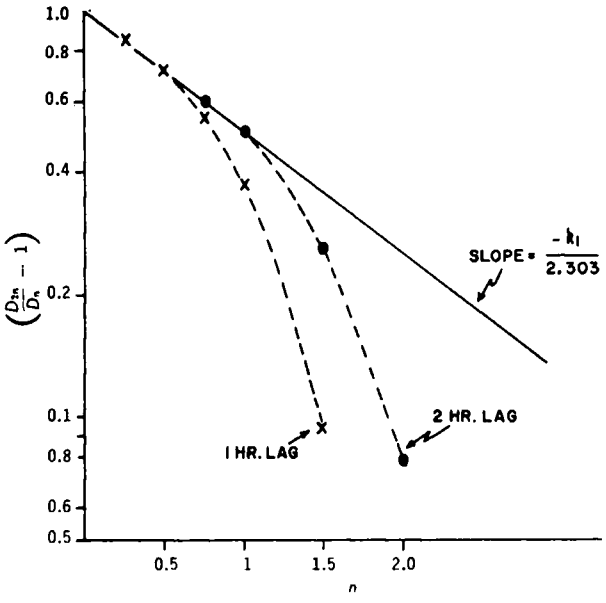

Figure 5—*Plot of data calculated according to* n–2n *method (see text for explanation)* versus *time for a competitive zero-order process* (k_0 = *25 units/hr.*). *Key:* ×, *1-hr. lag; and* ●, *2-hr. lag.*

2. In addition to absorption, there is a parallel first-order reaction occurring simultaneously with no lag time and the slope of the line represents the sum of the first-order rate constants for both the absorption and the competing process.

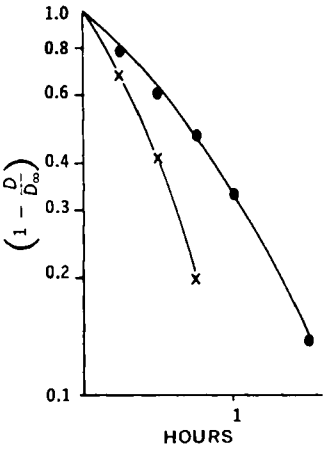

Figure 7—*Plot of Wagner–Nelson calculations* versus *time for an all-or-none competitive phenomenon. Key:* ×, *50% drug available; and* ●, *75% drug available.*

3. There is a parallel zero-order reaction process occurring, either with or without a lag time, but the data are such a magnitude as to appear linear. The apparent first-order absorption rate constant obtained is a complex function of the true rate constant and zero-rate constant.

Applying the *n–2n* technique for determining the true first-order absorption rate constant will result in linear relationships in both possibilities 1 and 2, with the resulting slope being identical to that obtained *via* the Wagner–Nelson or feathering method. Therefore, this procedure cannot differentiate between possibilities 1 and 2, and one does not get a measure of the true first-order absorption rate constants in the case of possibility 2. The plot, however, in the case of possibility 3 demonstrates a marked degree of curvature if there is no lag time. If there is a finite lag time, the data up to this time are linear, passing through $y = 1$ (on semilog paper) at $n = 0$.

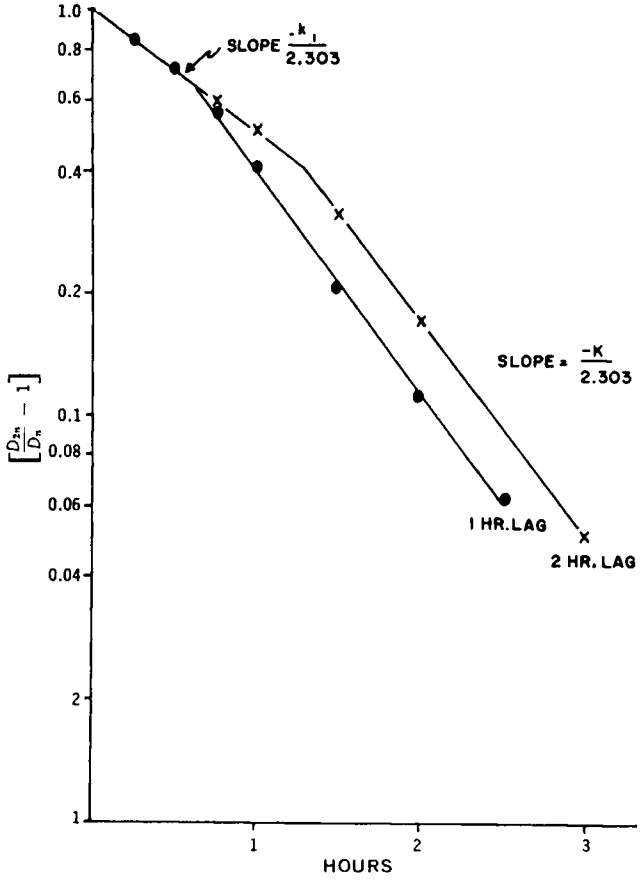

Figure 6—*Plot of data calculated according to* n–2n *method* versus *time for a competitive first-order process* (k_1 = *0.5*). *Key:* ●, *1-hr. lag; and* ×, *2-hr. lag.*

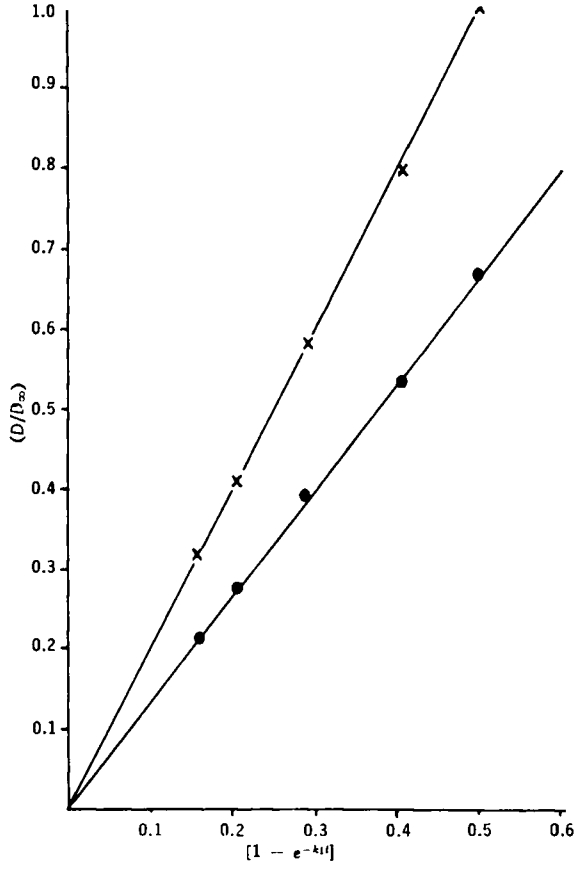

Figure 8—*Plot for determining availability (see text for explanation) for all-or-none phenomenon. Key:* ×, *50% drug available; and* ●, *75% drug available.*

In addition, $t1$ is approximately twice the last n value to fall on the line. Such results allow one to differentiate between this case and the other two (Fig. 5).

This discussion has indicated that the n–$2n$ method may be used to distinguish between parallel zero-order and parallel first-order reactions which may be occurring with no lag time and parallel zero-order and parallel first-order reactions which may be occurring with finite lag times. However, it is not able to distinguish between the parallel first-order reaction with no lag time and the case of no parallel reaction occurring. In addition, one is unable to make an evaluation of the true first-order absorption rate constant in the case of a parallel first-order reaction with no lag time.

Notari *et al.* (1) have indicated a technique for determining the true first-order absorption rate constant. This is done by multiplying K by the fraction of the drug absorbed. However, data other than merely plasma levels (*e.g.*, urinary excretion) would be required to estimate the fraction of drug absorbed. Unfortunately, in many instances, one obtains only plasma level data. The n–$2n$ technique for determining the true first-order absorption rate constant, although not requiring any additional measurements, does necessitate the occurrence of a finite lag time. In addition, if one does have a finite lag time with a parallel first-order process and determines the true absorption rate constant, the fraction of drug available after onset of the lag time may be determined from a ratio of (k_1/K). Correspondingly, the true fraction available (f) is defined by Eq. 26:

$$f = 1 - \frac{k_3}{K} \exp(-k_1 t1) \qquad \text{(Eq. 26)}$$

$$k_3 = K - k_1 \qquad \text{(Eq. 26}a\text{)}$$

In such a case, one is able to evaluate the availability employing *only* plasma level measurements.

"All or None" Phenomena—The previous discussion omitted consideration of the "all or none" phenomena proposed by Perrier and Gibaldi (2). This refers to the case of a nondisintegrating dosage form moving through the GI tract where absorption is occurring and suddenly reaching an area where absorption ceases. Treatment of these data *via* the Wagner–Nelson method results in a non-log-linear relationship. This is because of the considerations in Eqs. 27–30, where f is the fraction of drug absorbed and the other constants are as previously defined:

$$\frac{D}{V} = \frac{A_0}{V}[1 - \exp(-k_1 t)] \qquad \text{(Eq. 27)}$$

$$\frac{D_\infty}{V} = f\left(\frac{A_0}{V}\right) \qquad \text{(Eq. 28)}$$

$$\frac{D}{D_\infty} = \frac{[1 - \exp(-k_1 t)]}{f} \qquad \text{(Eq. 29)}$$

$$[1 - D/D_\infty] = \frac{f - 1 + \exp(-k_1 t)}{f} \qquad \text{(Eq. 30)}$$

It may be seen from Eq. 30 that the expression $(1 - D/D_\infty)$ is not a log-linear relationship when f is less than 1. Plots of this type are shown in Fig. 7 for f values of 0.5 and 0.75. However, if one employs the n–$2n$ technique, the true first-order absorption rate constant would be obtained in these cases. In addition, once k_1 has been evaluated, from Eq. 29 it is seen that from a plot of D/D_∞ against $(1 - e^{-k_1 t})$ the fraction absorbed may be determined as the reciprocal of the slope (Fig. 8). Therefore, employing Eqs. 25 and 29, one may test for the existence of the all-or-none phenomena.

In conclusion, as indicated by Perrier and Gibaldi, the occurrence of incomplete availability will in most cases result in an incorrect measure of the true absorption rate constant. The one exception to their generalization is the case of a poorly designed formulation which would only release a certain fraction of its drug, even if it remained at an absorption site for an infinite length of time. In this instance, the value obtained for the absorption rate constant will be the correct one.

Because the data in this report were computer generated rather than experimentally determined, one could suggest that *in vivo* results would not allow the detection of some of the anomalies reported here. However, on occasion these authors have encountered curvature of a log $(1 - D/D_\infty)$ or ΔC_p plot, and an awareness of the concepts proposed by Notari *et al.* (1) or Perrier and Gibaldi (2) would have allowed for an alternative data treatment. In addition, this report proposes an alternative technique for treating data generated by the Wagner–Nelson (3) or Loo–Riegleman (4) techniques which could allow detection of the fraction of drug absorbed in some of the models proposed by Perrier and Gibaldi.

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* Present address: Ortho Pharmaceutical Corp., Raritan, NJ 08869

▲ To whom inquiries should be directed.