Effect of Parallel First-Order Drug Loss from Site of Administration on Calculated Values for Absorption Rate Constants

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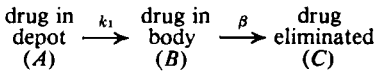
Abstract □ Methods commonly employed to calculate absorption rate constants from the time course for drug in the blood are shown to yield "apparent" values, k, when the drug at the site of administration is simultaneously lost to an extravascular compartment(s). The value for k obtained by either Wagner–Nelson calculations for a drug distributed according to a one-compartment model or Loo–Riegelman calculations for a drug described by a two-compartment model is shown to be the sum of all individual rate constants for simultaneous first-order loss of drug from the absorption site. The parallel rate processes leading to this situation may be chemical or biological degradation of the drug at the absorption site, transfer to an extravascular compartment, or any other first-order process that decreases the concentration of drug in the depot as a function of time simultaneously with the absorption process. The true rate constant for absorption in such a case can be calculated by determining the fraction of the dose actually absorbed, f, provided that all of the initial dose can be accounted for by the simultaneous rate processes. The absorption constant, k_1, is then calculated from the equation $k_1 = fk$.

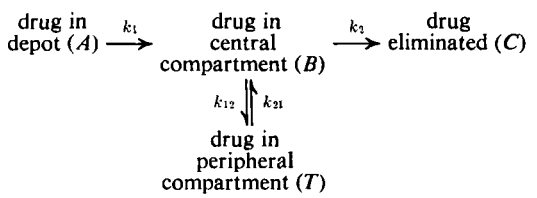
Keyphrases □ Absorption rate constants—effect of parallel first-order drug loss from site of action on calculated values □ Drug loss, parallel first order—effect on calculated values for absorption rate constants

The determination of absorption rate constants from blood level data is a common problem when biopharmaceutics and pharmacokinetics are applied to dosage form evaluation or design. Wagner and Nelson (1) developed a method for calculating the absorption rate constant for transfer from an extravascular depot into the body for a drug whose distribution can be described by a one-compartment model. For the case where absorption is first order, this may be illustrated by Scheme I, where k_1 is the first-order constant for absorption from



Scheme I

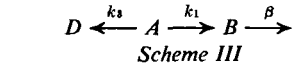
the depot into the body, and β is the first-order rate constant representing the sum of elimination by all routes. Similarly, Loo and Riegelman (2) reported a method for calculating the absorption rate constant, k_1, for the case where the drug is distributed according to a two-compartment model. This is illustrated in Scheme II,



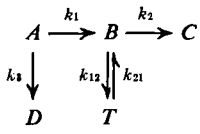
Scheme II

where k_{12} and k_{21} are the first-order rate constants for distribution between the central and peripheral compartments, and k_2 is the first-order constant for total elimination from the central compartment. The values for these constants are calculated from data following a rapid intravenous injection, and the results are used in calculating the absorption constant, k_1, following an oral dose of the same drug.

Both of the methods work well when appropriately applied to the proper cases, as defined in Schemes I and II. But a question arises as to the physical meaning of the calculated value for k_1 when a parallel first-order process takes place at the absorption site. This may be illustrated as shown in Scheme III for the one-compartment model and in Scheme IV for the two-compartment model. This report demonstrates that the application of Wagner–Nelson (1) calculations based on Scheme III or Loo–Riegelman (2) calculations applied to Scheme IV results in an "apparent" first-order rate constant which is the sum of the true absorption rate constant, k_1, and the rate constant for parallel loss of drug from the depot, k_3.



Scheme III



Scheme IV

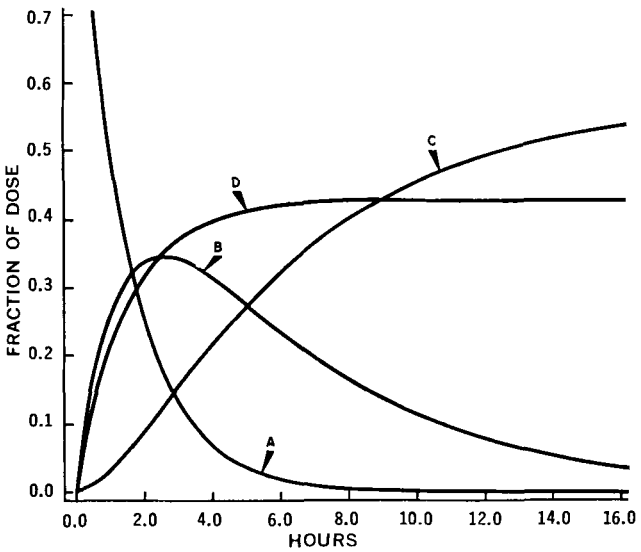


Figure 1—*Typical analog computer simulation of the time course for fraction of drug in each compartment in Scheme III, where* A = *absorption site,* B = *body,* C = *elimination,* D = *process competing with absorption,* $k_1 = 0.4$, $\beta = 0.2$, *and* $k_3 = 0.3$ ($hr.^{-1}$).

An example of this potential problem would be simultaneous first-order hydrolysis and absorption of a drug in solution in the stomach, intestines, or muscle when the sum of hydrolysis and absorption represents all of the original drug in solution as illustrated in Schemes III and IV. The loss of drug to additional compartments by non-first-order rate processes (such as excretion of undissolved drug) is not included in these schemes and is, therefore, not described by the following kinetic expressions. The simplest case (simultaneous first-order rate processes competing for drug at the depot) is presented here to illustrate that the calculated value for the absorption rate constant can be influenced by loss of drug to nonabsorption processes. Such processes may be chemical degradation, biotransformation by enzymes or intestinal bacteria, or transfer to a compartment other than the blood. If both absorption and parallel loss are first order and these represent the only processes for loss of A from the depot, then the "apparent" first-order absorption rate constant may be corrected to obtain the true value for k_1, as shown in the *Discussion* section.

EXPERIMENTAL

Parallel Loss from Depot in One-Compartment Model—Scheme III represents the simultaneous transfer of drug from the depot, A, into the body, B, and into the compartment for competing drug loss, D, for a drug obeying a one-compartment model. Compartment C represents the sum of all elimination routes from the body. This compartmental scheme was programmed on an analog computer[1], and the rate constants were assigned values. Curves similar to those illustrated in Fig. 1 were generated for each set of rate constants chosen, and simulated blood level data were analyzed using the Wagner–Nelson (1) equation.

Parallel Loss from Depot in Two-Compartment Model—Scheme IV represents the simultaneous transfer of a two-compartment model drug from the depot, A, into the central compartment, B, and also into compartment D which represents an alternate route of drug loss from the depot. The peripheral compartment (tissues) is represented by T, and total drug loss by all routes is represented by C. This compartmental scheme was programmed on an analog computer[1], and the output was analyzed by a digital computer using a program based on the steps outlined for the Loo–Riegelman (2) method as described by Notari (3). The data generated by the analog computer for each set of rate constants chosen were similar to those illustrated in Fig. 2.

RESULTS

Parallel Loss from Depot in One-Compartment Model—Curves generated by the anlog computer for the fraction of dose in the plasma as a function of time in a one-compartment model (Scheme III) were analyzed using the Wagner–Nelson (1) equation:

$$(A/Vd)_{t_n} = P_{t_n} + \beta \int_{t_0}^{t_n} P\,dt \qquad \text{(Eq. 1)}$$

where $(A/Vd)_{t_n}$ represents the total amount absorbed, A, at time t_n, expressed in units of concentration in terms of the volume of distribution, Vd; P is the plasma concentration; and β is the rate constant for elimination from the body[2]. An introduction to the mechanics for applying this equation is given in *Reference 3*.

Typical results are illustrated in Table I, which represents the data shown in Fig. 1. A plot of ln [100% − % (A/V)] *versus* t for the case described in Scheme I would have a slope of $-k_1$. However, the k from the plot for the data illustrated in Table I is 0.7, which is seen to be the sum of k_1 and k_3 or, in this case, 0.4 plus 0.3. Thus, the application of Wagner–Nelson calculations to blood level data in a system described by Scheme III will yield an apparent constant, k, which is the sum of the constants for the parallel rate processes.

Table I—Application of Wagner–Nelson Calculations[a] to:

$$D \xleftarrow{k_3} A \xrightarrow{k_1} B \xrightarrow{\beta} C$$

where $k_1 = 0.4$, $\beta = 0.2$, and $k_3 = 0.3$ (hr.$^{-1}$)[b]

t_n, hr.	P_{t_n}, mcg./ml.	$\beta \int_{t_0}^{t_n} P\,dt$	$(A/Vd)_{t_n}$	%(A/Vd)	100% − % (A/Vd)
0.5	1.10	0.055	1.16	29.7	70.3
1.0	1.78	0.199	1.98	50.8	49.2
1.5	2.17	0.396	2.57	65.9	34.1
2.0	2.35	0.622	2.97	76.1	23.9
3.0	2.37	1.095	3.46	88.8	11.2
4.0	2.15	1.55	3.70	94.8	5.2
5.0	1.85	1.95	3.80	97.5	2.5
7.0	1.30	2.58	3.88	99.5	0.5
9.0	0.88	3.01	3.89	100	0

[a] See Eq. 1. [b] See Fig. 1.

Parallel Loss from Depot in Two-Compartment Model—Analog computer curves representing the central compartment in Scheme IV were analyzed by digital computer using the Loo–Riegelman (2) equations:

$$(A/Vp)_{t_n} = P_{t_n} + k_2 \int_{t_0}^{t_n} P\,dt + T_{t_n} \qquad \text{(Eq. 2)}$$

where $(A/Vp)_{t_n}$ represents the total amount absorbed, A, at time t_n, expressed in terms of the plasma volume, Vp; P represents the drug concentration in the plasma; and the tissue concentration, T, is defined:

$$T_{t_n} = T_{t_{n-1}} e^{-k_{21}\Delta t} + (k_{12}/k_{21})P_{t_{n-1}}(1 - e^{-k_{21}\Delta t}) + k_{12}\Delta P\,\Delta t/2 \qquad \text{(Eq. 3)}$$

A typical example is shown in Fig. 2, where $k_1 = 0.6$, $k_2 = 0.2$' $k_{12} = 0.4$, $k_{21} = 0.2$, and $k_3 = 0.3$ (in hr.$^{-1}$); Table II lists the values obtained when Eq. 2 was applied to the blood level data. In this particular example, a first-order plot of the data found in the last column results in a calculated apparent first-order rate constant of 0.9 (hr.$^{-1}$), which is the sum of the true absorption constant, $k_1 = 0.6$, and the rate constant for alternate drug loss from the depot, $k_3 = 0.3$. This example illustrates the fact that the application of Eq. 2 to a drug whose kinetics are described by Scheme IV results in an apparent rate constant, k, which is the sum of k_1 and k_3.

DISCUSSION

The simultaneous first-order loss of drug from the site of administration in either Scheme III or IV may be represented by:

$$D \xleftarrow{k_3} A \xrightarrow{k_1} B$$

Scheme V

where A is the depot, B is the plasma, and D is the competing first-order rate process for loss of drug from the depot. It can easily be shown (3) that:

$$A_t = ae^{-kt} \qquad \text{(Eq. 4)}$$

where A_t is the amount of drug in compartment A at time t; a is the dose of drug at time zero; and k, the apparent first-order rate constant for loss from the depot, may be defined as:

$$k = k_1 + k_3 \qquad \text{(Eq. 5)}$$

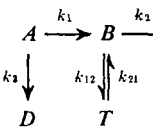
Furthermore, a first-order plot of data for any one of the compartments, A, B, or D, will also yield the same rate constant, k, or, in other words, the sum of the two individual rate constants, k_1 plus k_3. The individual rate constants can easily be determined from the relationships:

$$kB_\infty/a = k_1 \qquad \text{(Eq. 6)}$$

[1] EAI model TR 20.

[2] For a discussion of the differences between the constants k_2 and β and the one- and two-compartment models, see Section III, B and C, in Chapter 3 of *Reference 3*.

Table II—Application of Loo–Riegelman Calculations[a] to:



where $k_1 = 0.6$, $k_2 = 0.2$, $k_3 = 0.3$, $k_{12} = 0.4$, and $k_{21} = 0.2$ (hr.$^{-1}$)[b]

t_n, hr.	P_{t_n}, mcg./ml.	$k_2\int_{t_0}^{t_n} P\,dt$	T_{t_n}	$(A/Vp)_{t_n}$	%(A/Vp)	100% − %(A/Vp)
0.25	1.60	0.040	0.080	1.72	18.6	81.4
0.50	2.83	0.151	0.294	3.27	35.4	64.6
0.75	3.57	0.311	0.592	4.47	48.3	51.7
1.00	4.00	0.500	0.933	5.43	58.8	41.2
1.50	4.20	0.910	1.626	6.74	72.9	27.1
2.00	4.08	1.324	2.258	7.66	82.8	17.2
3.00	3.30	2.062	3.172	8.53	92.3	7.7
4.00	2.60	2.652	3.654	8.91	96.4	3.6
5.00	2.10	3.122	3.834	9.06	98.0	2.0
6.00	1.79	3.511	3.838	9.14	98.8	1.2
7.00	1.59	3.849	3.751	9.19	99.5	0.7
8.00	1.44	4.152	3.618	9.21	99.7	0.3
9.00	1.35	4.431	3.466	9.25	100	0.0

[a] See Eq. 2. [b] See Fig. 2.

$$kD_\infty/a = k_3 \qquad \text{(Eq. 7)}$$

or:

$$B/D = k_1/k_3 \qquad \text{(Eq. 8)}$$

which also were derived elsewhere (3).

In Scheme V, the true first-order rate constant for absorption, k_1, may be calculated from any one of the relationships shown in Eqs. 6–8. Thus, the apparent first-order rate constant for absorption from an extravascular site into the central compartment can be corrected for parallel loss by taking into account the total amount of drug absorbed from the site. The percent absorbed can be determined by comparing the area under the plasma level *versus* time curve following extravascular administration to the area following intravenous administration. The percent absorbed also can be calculated from the data obtained in the Wagner–Nelson calculations by multiplying the maximum value for (A/Vd) by the value for Vd (Table I). In the case of a two-compartment model, the Loo–Riegelman calculations may be used by multiplying the maximum value for (A/Vp) by the value for Vp (Table II). It should be emphasized that the percent values given in the last columns of Tables I and II are *not* the percent of the dose unabsorbed. They are, instead, the percent of *absorbable drug* remaining as a function of time since these numbers are calculated by assigning the total amount of drug absorbed (expressed in concentration terms) a value of 100%. When Scheme V represents the loss of drug from the depot and the total amount of absorbed drug is determined, the true rate constant for absorption, k_1, can be calculated by modifying Eq. 6 to give:

$$k_1 = fk \qquad \text{(Eq. 9)}$$

where f is the fraction of the dose absorbed, and k is the apparent rate constant obtained by the Wagner–Nelson or Loo–Riegelman calculations.

Although Scheme V represents two competing processes, Eq. 9 is also applicable to any case where drug is lost from the depot by more than two simultaneous first-order processes. If drug is lost from the depot by n different first-order rate processes, the "apparent" first-order constant, k, calculated from data representing any one of the compartments in this system is defined as:

$$k = \sum_{i=1}^{n} k_i \qquad \text{(Eq. 10)}$$

where n is the total number of competing rate processes, and k_i is the rate constant for the loss of drug from A to X_i. In the case of absorption of a drug with either a one- or two-compartment open model, one of the parallel processes, X_i, will represent transfer from the depot to the blood and the rate constant for that process may be called the absorption rate constant. The apparent rate constant calculated either by the Wagner–Nelson (1) or Loo–Riegelman (2) method is thus defined by Eq. 10. It is quite obvious that no problem exists when the constant k is calculated for the case $i = 1$, since k would then be equal to k_1 as illustrated in Schemes I and II. However, the calculated value for k can be quite misleading when $i > 1$, and the first-order rate constants for the competing first-order processes are, therefore, included in the calculated value for the absorption rate constant.

The significance of this potential problem is readily apparent. False impressions of rapid absorption could result from rapidly hydrolyzable analogs or dosage forms. The compound with the fastest apparent absorption rate constant in a series may be the most susceptible to biotransformation. The total amount of drug absorbed from the depot should be determined for an accurate interpretation of the calculated rate constants for absorption. If a drug is well absorbed from the depot, the calculated absorption rate constant may be considered to be a good estimate. If, however, the drug is poorly absorbed, the reason for the incomplete absorption must be determined before one can assign a physical meaning to the calculated value of the apparent absorption rate constant. In the case where two or more simultaneous first-order rate processes are involved, Eq. 9 can be used to calculate the value for k_1. The difference between the observed k and the value for k_1 would then represent the sum of the first-order rate constants for all other routes. As an example of the potential significance, suppose an investigator were to find that a drug derivative had a calculated absorption rate constant twice that of the original drug but that only 50% of the dose of the new analog was absorbed due to first-order hydrolysis in the depot whereas the original drug was completely absorbed. This would mean that the true absorption constant, k_1, was not affected at all by the chemical modification but that the drug was simply destroyed more rapidly at the absorption site.

This problem is not unique to oral dosage forms. Doluisio *et al.* (4) showed that intramuscular injections of sodium dicloxacillin and sodium ampicillin solutions were only 75–78% absorbed. They suggested that the drug may have undergone chemical or enzymatic decomposition at the injection site. If 22–25% of the drug placed into the muscle is indeed undergoing some simultaneous first-order rate process, the apparent absorption rate constants can be partitioned into two components. For example, the absorption rate constant for an ampicillin solution given intramuscularly was calculated to be 0.89 (hr.$^{-1}$) using the Loo–Riegelman method (4). Since the fraction absorbed was found to be 0.77, one can calculate k_1 from Eq. 9 as:

$$k_1 = (0.77)(0.89) = 0.69\ (\text{hr.}^{-1}) \qquad \text{(Eq. 11)}$$

and the difference, or 0.89 − 0.69 = 0.20 (hr.$^{-1}$), is, therefore, the

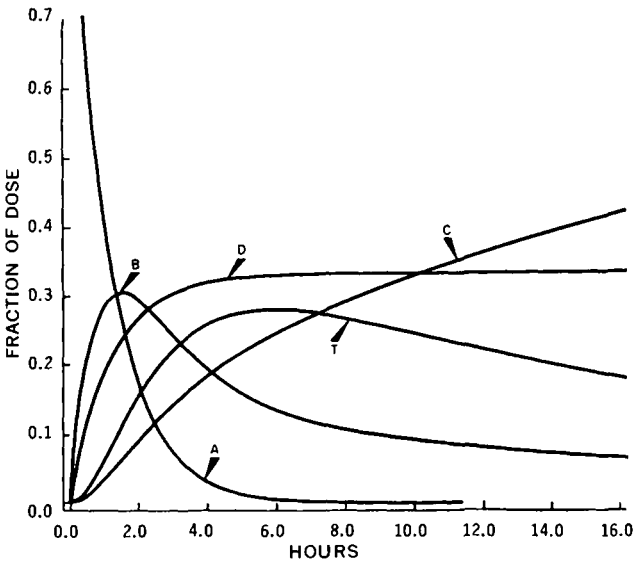


Figure 2—*Typical analog computer simulation of the time course for fraction of drug in each compartment in Scheme IV, where* A = *absorption site*, B = *central compartment*, C = *elimination*, D = *process competing with absorption*, T = *peripheral compartment*, k_1 = *0.6*, k_2 = *0.2*, k_3 = *0.3*, k_{12} = *0.4, and* k_{21} = *0.2* (*hr.*$^{-1}$).

sum of the rate constants for parallel first-order loss from the depot, a loss which amounts to 23% of the dose.

It would thus appear that the fraction of dose absorbed should be routinely calculated in studies employing the Wagner–Nelson (1) or Loo–Riegelman (2) method to determine whether or not additional data might be needed to assign a physical meaning to the calculated value for the absorption rate constant.

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Effects of Protein Binding of Drugs on Areas under Plasma Concentration–Time Curves

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Abstract □ By using a conservation-of-mass treatment, it can be shown that the area under a free drug concentration–time curve is determined by the rate constant of elimination of free drug, regardless of the extent of protein binding. In the absence of information on the free drug elimination constant, the area under the free drug curve can be calculated from the limiting value of the apparent total drug elimination constant and the binding parameters. The effect of competitive binding inhibitors depends strongly on the pharmacokinetics of the inhibitor; and, if the inhibitor is eliminated much more rapidly than drug, it is without effect on the area under the free drug curve.

Keyphrases □ Protein binding—effects on area under plasma concentration–time curve, conservation-of-mass treatment, equations □ Plasma concentration–time curves—effects of protein binding of drugs on area under curve, pharmacokinetics of inhibitor, equations

In the course of recent investigations into the quantitative aspects of nonlinear plasma protein binding effects on pharmacokinetics (1), some interesting relationships between binding parameters and the areas under plasma concentration–time curves emerged. First, if the elimination rate constant for free drug is known, the standard relationship yields the area under the free drug concentration curve, regardless of the extent of the binding. Second, the effect of competitive inhibition of binding on the area under a concentration–time curve depends strongly on the pharmacokinetics of the inhibitor and, in some cases, inhibition of binding may have no effect on this parameter.

THEORETICAL

The notations are identical to those used in a previous paper (1): C_f = concentration of free drug; C_b = concentration of bound drug; C_t = total concentration of drug, *i.e.*, $C_b + C_f$; P = concentration of protein–drug binding sites; and K_d = dissociation constant of the drug–protein complex.

If V_1 is the volume of the plasma compartment, then, regardless of the number of compartments in the system, the amount of drug eliminated from the plasma in the time interval, dt, is given by:

$$dA_{out} = V_1 k_{app} C_t \, dt \qquad \text{(Eq. 1)}$$

where k_{app} is an apparent constant of elimination. In systems that include binding of drugs to plasma proteins, k_{app} is not constant but is a function of time.

The total amount of drug eliminated is then:

$$A_{out} = V_1 \int_0^\infty k_{app} C_t \, dt \qquad \text{(Eq. 2)}$$

By applying the conservation-of-mass treatment of Wagner (2) and letting D equal the total amount of drug absorbed or injected:

$$\frac{D}{V_1} = \int_0^\infty k_{app} C_t \, dt \qquad \text{(Eq. 3)}$$

However, k_{app} is simply the elimination rate constant for free drug multiplied by the fraction of drug that is free:

$$k_{app} = k_2 \frac{C_f}{C_t} \qquad \text{(Eq. 4)}$$

where k_2 is the free drug elimination rate constant. Substituting in Eq. 3:

$$\frac{D}{V_1 k_2} = \int_0^\infty C_f \, dt \qquad \text{(Eq. 5)}$$

Thus, if the elimination rate constant for free drug is used, the standard expression (2) for the area under the concentration–time curve always relates to free drug, regardless of the amount of drug bound.

However, it is not always necessary to know k_2. If the concentration–time curve is extended to sufficiently low concentrations, the right-hand side of the binding relationship:

$$C_b = \frac{PC_f}{K_d + C_f} \qquad \text{(Eq. 6)}$$

reduces approximately to PC_f/K_d, and C_t/C_f becomes constant:

$$\frac{C_t}{C_f} = \frac{C_b + C_f}{C_f} = 1 + \frac{P}{K_d} \qquad \text{(Eq. 7)}$$

The value of k_{app} then becomes constant at sufficiently long times;