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Report

An Area Function Method for Estimating the Apparent Absorption Rate Constant

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A new method for calculation of the apparent absorption rate constant of a drug has been derived based on the relationship between the plasma concentrations after an oral dose and the area intervals under both the oral and the intravenous plasma concentration–time curves. The method is a noncompartmental technique evolved from the convolution integral and does not use any theoretical approximation. It has been evaluated and compared with nonlinear regression analysis using NONLIN84 and moment analysis using both errorless and errant data. The approach is as adequate as nonlinear regression analysis under a variety of conditions but offers ease and simplicity in handling experimental data.

KEY WORDS: apparent first-order absorption rate constant; convolution integral; nonlinear regression analysis; moment analysis; noncompartmental analysis.

INTRODUCTION

In biopharmaceutical studies it is often important to assess drug absorption quantitatively. Many methods for estimating the apparent first-order absorption rate constant (k_a) have been reported (1–8). These methods can be categorized into either compartmental or noncompartmental analyses. Obviously, each method has its own strength and limitations. Recently, many of these methods were evaluated and compared under the same simulation conditions. In 1984, using data obtained from computer simulations, Chan and Gibaldi (9) evaluated the Wagner–Nelson method, the Loo–Riegelman method, and moment analysis for their ability to estimate k_a accurately under a variety of conditions. Later, the Loo–Riegelman method and moment analysis were also compared with nonlinear regression analysis using NONLIN (10,4). Although the simulations were not exhaustive, they were sufficient to demonstrate clearly some of the strengths and/or the limitations. These analyses also indicated that nonlinear regression analysis and moment analysis generally gave more accurate estimates of a purely first-order k_a than either the Wagner–Nelson method or the Loo–Riegelman method.

This report presents a new noncompartmental method which is based on the relationship between oral plasma concentrations and area intervals obtained from intravenous and oral plasma concentration–time curves.

THEORETICAL

For a linear mammillary system the concentration–time curve after oral administration of drug, $C_{po}(t)$ can be obtained by the convolution integral:

$$C_{po}(t) = \int_0^t C_{iv}(\tau)g(t-\tau)d\tau = \int_0^t C_{iv}(t-\tau)g(\tau)d\tau = C_{iv}(t) * G(t) \quad \text{(1a, b, c)}$$

where $C_{iv}(\tau)$ is the concentration–time function following i.v. administration of drug and $G(\tau)$ is the transfer function describing the absorption process.

The Laplace transform of Eq. (1) yields

$$C_{po}(s) = C_{iv}(s) \times G(s) \quad (2)$$

or

$$G(s) = \frac{C_{po}(s)}{C_{iv}(s)} \quad (3)$$

Benet (11) has defined these $C(s)$ values as follows:

$$C_{po}(s) = (In_s^{po}) \cdot (d_{s,1})/V_1 \quad (4)$$

$$C_{iv}(s) = (In_s^{iv}) \cdot (d_{s,1})/V_1 \quad (5)$$

where In_s is the Laplace transform of the input function, $d_{s,1}$ is the Laplace transform of the disposition function for the central compartment, and V_1 is the volume of the central compartment. Equations (4) and (5) can be substituted into Eq. (3) to yield the following relationship:

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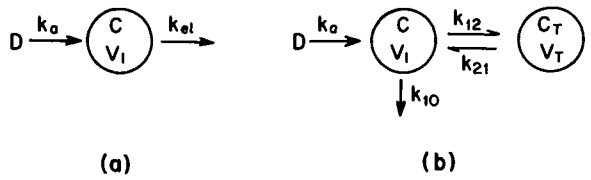

Fig. 1. (a) One-compartment model for drug concentration (C), volume of distribution (V_1), and rate constants for absorption (k_a) and elimination (k_{el}). (b) Two-compartment model depicting drug concentrations in the central (C) and tissue compartments (C_T), volumes of distribution (V_1, V_T), the rate constant for absorption (k_a), and distribution and elimination constants (k_{12}, k_{21}, k_{10}).

$$G(s) = \frac{C_{po}(s)}{C_{iv}(s)} = \frac{In_s^{po}}{In_s^{iv}} \quad (6a, b)$$

For an intravenous bolus dose (D),

$$In_s^{iv} = D \quad (7)$$

For first-order absorption,

$$In_s^{po} = F \cdot D \cdot k_a/(s + k_a) \quad (8)$$

where F is the bioavailability of the drug. Substituting Eqs. (7) and (8) into Eq. (6) results in Eqs. (9) and (10).

$$\frac{C_{po}(s)}{C_{iv}(s)} = \frac{F \cdot k_a}{(s + k_a)} \quad (9)$$

or

$$(s + k_a) \cdot C_{po}(s) = F \cdot k_a \cdot C_{iv}(s) \quad (10)$$

Since $C_{po}(t)$ at time zero is zero, Eq. (10) can be written as follows:

$$sC_{po}(s) - C_{po}(0) = (F \cdot k_a) \cdot C_{iv}(s) - k_a \cdot C_{po}(s) \quad (11)$$

Performing anti-Laplace transformation of Eq. (11) yields the first derivative:

$$\frac{dC_{po}(t)}{dt} = F \cdot k_a \cdot C_{iv}(t) - k_a \cdot C_{po}(t) \quad (12)$$

Multiplying both sides by dt yields

$$dC_{po}(t) = [F \cdot k_a \cdot C_{iv}(t) - k_a \cdot C_{po}(t)]dt \quad (13)$$

Integrating both sides of Eq. (13) from time t_1 to time t_2 yields

$$\int_{t_1}^{t_2} dC_{po}(t) = F \cdot k_a \cdot \int_{t_1}^{t_2} C_{iv}(t)dt - k_a \cdot \int_{t_1}^{t_2} C_{po}(t)dt \quad (14)$$

or

$$C_{po}(t_2) - C_{po}(t_1) = F \cdot k_a \cdot \int_{t_1}^{t_2} C_{iv}(t)dt - k_a \cdot \int_{t_1}^{t_2} C_{po}(t)dt \quad (15)$$

or

$$k_a = \frac{C_{po}(t_2) - C_{po}(t_1)}{F \cdot \int_{t_1}^{t_2} C_{iv}(t)dt - \int_{t_1}^{t_2} C_{po}(t)dt} \quad (16)$$

when $t_1 = 0$, $C_{po}(t_1) = 0$ and Eq. (16) yields

$$k_a = \frac{C_{po}(t_2)}{F \cdot \int_0^{t_2} C_{iv}(t)dt - \int_0^{t_2} C_{po}(t)dt} = \frac{C_{po}(t_2)}{F \cdot AUC_{iv}^{0 \to t_2} - AUC_{po}^{0 \to t_2}} \quad (17a, b)$$

or

$$k_a = C_{po}(t_2)/AUCF(t_2) \quad (17c)$$

where $AUCF(t_2)$ denotes the area function.

$$AUCF(t_2) = F \cdot AUC_{iv}^{0 \to t_2} - AUC_{po}^{0 \to t_2} \quad (18)$$

Therefore, the apparent first-order absorption rate constant can be obtained from either Eq. (16) or Eq. (17) where F is generated from

$$F = AUC_{po}/AUC_{iv} \quad (19)$$

Similarly, for first-order absorption with concurrent first-order decomposition in the gut (k_d), the following equation can also be derived:

$$k_a + k_d = \frac{C_{po}(t_2)}{F \cdot AUC_{iv}^{0 \to t_2} - AUC_{po}^{0 \to t_2}} = \frac{C_{po}(t_2)}{AUCF(t_2)} \quad (20a, b)$$

Thus, the sum of $k_a + k_d$ can be calculated according to Eq. (20).

METHODS

Three sets of intravenous and oral concentrations at 0, 0.1, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, and 24 hr for a hypothetical drug following a one-compartment model (Fig. 1) were simulated by assigning D = 260 mg, F = 0.60, V_1 = 32 liters, k_{el} = 0.12 hr^{-1}, and k_a values ranging from 0.090 to 1.20 hr^{-1} to the following equations:

$$C_{iv}(t) = D \cdot e^{-k_{el} \cdot t}/V_1 \quad (21)$$

$$C_{po}(t) = F \cdot D \cdot (e^{-k_{el} \cdot t} - e^{-k_a \cdot t})/V_1 \cdot (k_a - k_{el}) \quad (22)$$

where k_{el} is the first-order elimination rate constant from the central compartment. For each set of data 10 additional errant data sets were generated by introducing a normally distributed random error with a relative standard deviation (RSD) of 10% into all of the data points.

Similarly, for a hypothetical drug obeying a two-compartment model (Fig. 1), 4 sets of errorless data and 40 sets of errant data at time 0, 0.08, 0.2, 0.4, 0.7, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, and 72 hr were generated by the following equations with D = 2000 mg, V_1 = 7.52 liters, k_{12} = 0.46 hr^{-1}, k_{21} = 1.23 hr^{-1}, k_{10} = 0.18 hr^{-1}, F = 1, and k_a values in the range of 0.07–1.85 hr^{-1}:

$$C_{iv}(t) = \frac{D \cdot (\lambda_1 - k_{21}) \cdot e^{-\lambda_1 \cdot t}}{V_1(\lambda_1 - \lambda_2)} - \frac{D \cdot (\lambda_2 - k_{21}) \cdot e^{-\lambda_2 \cdot t}}{V_1(\lambda_1 - \lambda_2)} \quad (23)$$

$$C_{po}(t) = \frac{F \cdot D \cdot k_a}{V_1}\left[\frac{(k_{21} - k_a) \cdot e^{-k_a \cdot t}}{(\lambda_1 - k_a)(\lambda_2 - k_a)} + \frac{(k_{21} - \lambda_1) \cdot e^{-\lambda_1 \cdot t}}{(\lambda_2 - \lambda_1)(k_a - \lambda_1)} + \frac{(k_{21} - \lambda_2) \cdot e^{-\lambda_2 \cdot t}}{(\lambda_1 - \lambda_2)(k_a - \lambda_2)}\right] \quad (24)$$

Table I. Calculation of Absorption Rate Constants for a One-Compartment Model by the Proposed Method, by Nonlinear Regression, and by the Moment Method

Data set	Input value (hr^{-1}) k_{el}	k_a	Data	Calculated k_a (hr^{-1}) This method	Nonlinear regression	Moment method
1	0.12	0.090	Errorless	0.088 ± 0.0005[a]	0.090	0.090
			Errant[b]	0.086 ± 0.006	0.088 ± 0.005	0.089 ± 0.005
2	0.12	0.11	Errorless	0.11 ± 0.0004	0.11	0.11
			Errant	0.11 ± 0.008	0.11 ± 0.007	0.11 ± 0.005
3	0.12	1.20	Errorless	1.20 ± 0.001	1.20	1.21
			Errant	1.19 ± 0.21	1.15 ± 0.08	1.68 ± 1.80

[a] Mean ± SD; data points from time zero to time t_{max} and Eq. (17) were used to calculate k_a.
[b] Mean ± SD; $N = 10$.

where k_{21} is the exit rate constant from the peripheral compartment, λ_1 and λ_2 are the macroconstants describing the drug disposition, and $\lambda_1 > \lambda_2$.

The data sets were then evaluated by the proposed method, by moment analysis, and by linear regression analysis based on the simultaneous fitting of intravenous and oral data to appropriate equations using NONLIN84 (12). The LAGRAN computer program (13) was used to calculate values of $AUC_{0\to t_2}$, area under the first moment curve (AUMC), and mean residence time (MRT).

RESULTS

The results of the simulation study on a hypothetical drug, which exhibits one-compartment model characteristics, are summarized in Table I. When $k_a < k_{el}$ or $k_a \cong k_{el}$, the proposed method, the nonlinear regression analysis, and the moment method were adequate when applied to errorless as well as errant data sets. When $k_a > k_{el}$ and applied to errorless data sets, all these methods performed satisfactorily. However, when applied to errant data sets, the moment method yielded values for k_a which were less accurate than those estimated by the proposed method and the nonlinear regression analysis (Table I). Therefore, under a variety of $k_a : k_{el}$ conditions, both the proposed method and nonlinear regression analysis were adequate; when $k_a > k_{el}$, the moment method did not perform as well.

These methods were also tested for a hypothetical drug following a two-compartment model. As shown in Table II, when applied to errorless data sets, the proposed method gave accurate estimates of k_a. Both the moment method and nonlinear regression analysis also yielded correct estimates for k_a (Table II). In cases where $k_a < \lambda_1$ all these methods performed satisfactorily when errant data were used. However, when $k_a > \lambda_1$, estimates of k_a by the moment method were inaccurate. In contrast, both the proposed method and nonlinear regression analysis remained adequate in this case. The poor estimation of k_a values by the moment method when $k_a > \lambda_1$ has also been reported by Patel *et al.* (10). As shown previously (10) in this situation, estimates of k_a by the moment method can be improved by sampling more frequently in the absorption phase. The same applies to the present method and any other methods which utilize AUC for k_a estimation.

According to Eq. (17), when the values of the numerator and/or denominator in Eq. (17) approach zero, estimates of k_a are very susceptible to round-off error and error due to inaccurate approximation of areas. In addition, this approach works best when data obtained in the absorption phase are used. Thus, we suggest the use of only data obtained in the absorption phase and that results be expressed as the mean ± SD of several individual k_a values.

DISCUSSION

A method has been derived and evaluated for the determination of a first-order absorption rate constant. The pro-

Table II. Calculation of Absorption Rate Constants for a Two-Compartment Model by the Proposed Method, by Nonlinear Regression, and by the Moment Method

Data set	Input value (hr^{-1}) λ_1	λ_2	k_a	Data	Calculated k_a This method	Nonlinear regression	Moment method
1	1.74	0.13	0.070	Errorless	0.069 ± 0.0001[a]	0.070	0.070
				Errant[b]	0.068 ± 0.004	0.071 ± 0.002	0.072 ± 0.004
2	1.74	0.13	0.12	Errorless	0.12 ± 0	0.12	0.12
				Errant	0.12 ± 0.01	0.12 ± 0.01	0.12 ± 0.005
3	1.74	0.13	0.40	Errorless	0.40 ± 0.0005	0.40	0.41
				Errant	0.40 ± 0.03	0.39 ± 0.02	0.38 ± 0.005
4	1.74	0.13	1.85	Errorless	1.85 ± 0.0004	1.85	1.84
				Errant	1.79 ± 0.27	1.78 ± 0.11	2.91 ± 3.68

[a] Mean ± SD; data points from time zero to time t_{max} and Eq. (17) were used to calculate k_a.
[b] Mean ± SD; $N = 10$.

cedure evolves from the convolution integral and requires both intravenous and oral plasma concentration–time data. It allows estimation of k_a values provided that values of $C_{po}(t)$ and AUCF(t) can be accurately determined.

Although the proposed method was developed based on a linear mammillary system, like the Loo–Riegelman method (14), it is also valid for linear systems in which drug is eliminated from either peripheral compartment(s) alone or from both the central and the peripheral compartments.

As shown in Fig. 2, when F is equal to unity, the area function obtained at time t_2 [AUCF(t_2)] corresponds to the area between the intravenous and oral plasma concentration–time curves and the time 0 and t_2 ordinates. According to Eq. (17), the ratio of $C_{po}(t_2)$ and AUCF(t_2) provides the value of k_a. It should be noted that when $t_2 = \infty$, Eq. (17) yields an indeterminate result as AUCF(∞) = 0. In a situation when a lag time exists (t_{lag}), Eq. (17) can also be employed to estimate k_a by simply using $t_2 = t - t_{lag}$, where t is the sampling time.

Since information on absorption kinetics is useful for establishing correlations between *in vivo* drug absorption and *in vitro* dissolution rate to assist in making predictions regarding drug absorption from new dosage forms, it is of interest to characterize the drug absorption process and calculate the absorption rate constant. However, assessment of the absorption rate constant is often difficult because of the complexity of gastrointestinal physiology. Moreover, the absorption rate constant estimated may not accurately describe conditions when the absorption and disposition processes of a drug are indistinguishable. The well-recognized problems of vanishing exponential terms and "flip-flop" phenomena (15,16) encountered in k_a calculations are typical examples. Therefore, an adequate and reliable technique to characterize the absorption process of a drug is still highly desirable. The present method may potentially satisfy this need. As shown above, it is comparable in accuracy to nonlinear regression analysis. However, in contrast to the latter method, the proposed method does not require the assumption of any specific pharmacokinetic models or presume any knowledge of the disposition of a drug. Thus, it is a "noncompartmental" approach. It is also more accurate than moment analysis. In addition, the calculations are simple and the method is easy to execute.

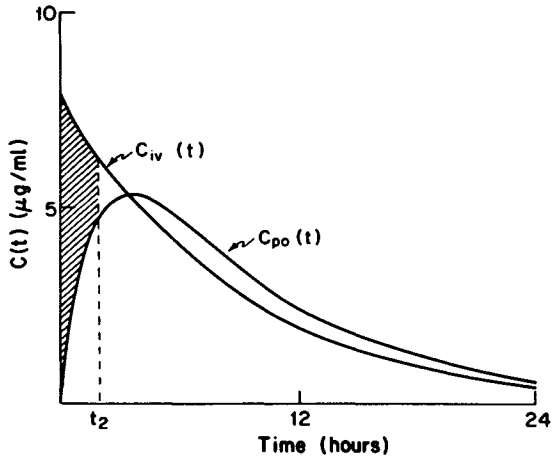

Fig. 2. Illustration of AUCF(t_2) using simulated concentration–time profiles for the one-compartment model. The shaded area corresponds to AUCF(t_2).

Despite these advantages, like moment analysis and nonlinear regression, the proposed method assumes no intrasubject variability in the kinetics of drug distribution and elimination between the intravenous and the oral studies. It is also limited to the assumption of first-order absorption and calculation of the apparent k_a [see Eq. (20)]. Moreover, since the proposed method assumes that the kinetics of drug disposition are linear, it is not applicable to systems with nonlinear disposition process (e.g., Michaelis–Menten elimination).

In conclusion, this paper has shown that a derivation technique evolving from the convolution integral could be applied to first-order drug absorption. Further application of a similar area function method to estimate the apparent zero-order absorption rate constant will be addressed in a subsequent report.

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