Graphical Approach for Determining Whether Absorption and Elimination Rate Constants are Equal in the One-Compartment Open Model with First-Order Processes

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Received May 14, 1984, from the *Department of Pharmacy, Athens University, Athens 10680, Greece.* Accepted for publication February 5, 1985.

Abstract □ An equation was developed which enables blood level data to be utilized for determining whether or not the first-order absorption and elimination rate constants are equal in the one-compartment open model. This equation was tested using simulated data with excellent results.

The only available simple method for determining whether absorption (k_a) and elimination (k_e) rate constants are equal in the one-compartment model with first-order processes was reported by Bialer.[1] This method uses Eq. 1 as the criterion for the equality or inequality of rate constants:

$$C_{max}t_{max} = \frac{(AUC)_0^\infty}{e} \quad (1)$$

where C_{max} is peak drug concentration, t_{max} is the time of peak drug concentration, $(AUC)_0^\infty$ is area under the blood level curve between times 0 and infinity, and e is the base of the natural logarithm. However, this method has been characterized by Chan and Miller[2] as impractical since the accuracy of the determination or even the knowledge of the peak blood level C_{max} is, in most cases, doubtful. Moreover, the sensitivity of the above criterion has been found to be low.[3]

Recently, nonlinear regression analysis was found[2] to be a suitable way for the determination of the equivalence of rate constants. It was proven that the 1974 version of NONLIN is capable of revealing the real common value of rate constants (for the cases where $k_a = k_e$). The last method is entirely satisfactory if suitable computer programs and services are available.

The objective of this study was to develop a method which does not require either computer assistance or knowledge of specific parameters, namely C_{max} and t_{max}. In this report one equation is derived which, when solved graphically, would reveal the equivalence or nonequivalence of rate constants. In addition, when the equality of rate constants is justified, the graphical solution can also provide the real value of the unique rate constant.

Theoretical Section

The drug concentrations in blood for the linear one-compartment open model with unequal and equal absorption and elimination rate constants are described by eqs. 2 and 3, respectively:[4,5]

$$C = \frac{FDk_a}{Vd(k_a - k_e)}(e^{-k_e t} - e^{-k_a t}) \quad (2)$$

$$C = \frac{FD}{Vd}kt \cdot e^{-kt} \quad (3)$$

where C is drug concentration at time t, F is fraction of dose D absorbed, Vd is the apparent volume of distribution of drug, and k is either the absorption or elimination rate constant. Equations 2 and 3 show the normal behavior of such a biexponential function: the concentration is zero at time zero, rises to a maximum (C_{max}), and thereafter declines. Thus, a given drug concentration, C^*, lower than C_{max} will be reached on both upward and downward limbs of the curve, at times t_1 and t_2, respectively. It is obvious that the difference $t_2 - t_1$ is the maintenance time Δt of blood level C^*. Generalizing these definitions, the times of the data points on the absorptive phase will be symbolized with $(t_1)_i$, while $(t_2)_i$ will refer to the corresponding times on the downward limb of the curve for the same blood levels, defined as C_i^*. Analogous with the above, maintenance times of the blood levels C_i^* will be denoted as $(\Delta t)_i$.

Equal Rate Constants ($k_a = k_e$)—In this case, eq. 3 which describes the blood–drug concentration can be separately expressed for a given concentration of drug C^* in terms of times t_1 and t_2:

$$C^* = \frac{FD}{Vd}kt_1 \cdot e^{-kt_1} \quad (4)$$

$$C^* = \frac{FD}{Vd}kt_2 \cdot e^{-kt_2} \quad (5)$$

Subtracting eq. 4 from eq. 5, rearranging, and taking logarithms, eq. 6 can be obtained:

$$t_2 - t_1 = \Delta t = \frac{1}{k} \cdot \ln\left(\frac{t_2}{t_1}\right) \quad (6)$$

As can be seen from eq. 6, a plot of maintenance times $(\Delta t)_i$ for the various blood levels C_i^* versus $\ln [(t_2)_i/(t_1)_i]$ gives a straight line which intercepts the origin of the axes and has a slope equal to the reciprocal of the unique rate constant k (Fig. 1).

Unequal Rate Constants ($k_a \neq k_e$)—In cases of nonequivalence of rate constants, eq. 2 is applicable. Based on this equation the blood level C^* can be separately expressed in terms of t_1 and t_2 as above. Subtracting the resulting equations:

$$e^{-k_e t_1} - e^{-k_a t_1} = e^{-k_e t_2} - e^{-k_a t_2} \quad (7)$$

Substituting $t_1 = t_2 - \Delta t$ to the one exponential in the left-hand side of eq. 7, rearranging, taking logarithms, and subsequent solution for Δt will result in the following:

$$\Delta t = \frac{1}{k_e} \cdot \ln [e^{-k_e t_2}(e^{-k_a t_1} + e^{-k_e t_2} - e^{-k_a t_2})] \quad (8)$$

The last equation, in contrast with eq. 6, shows a nonlinear relationship between $(\Delta t)_i$ and $\ln [(t_2)_i/(t_1)_i]$. However, at some

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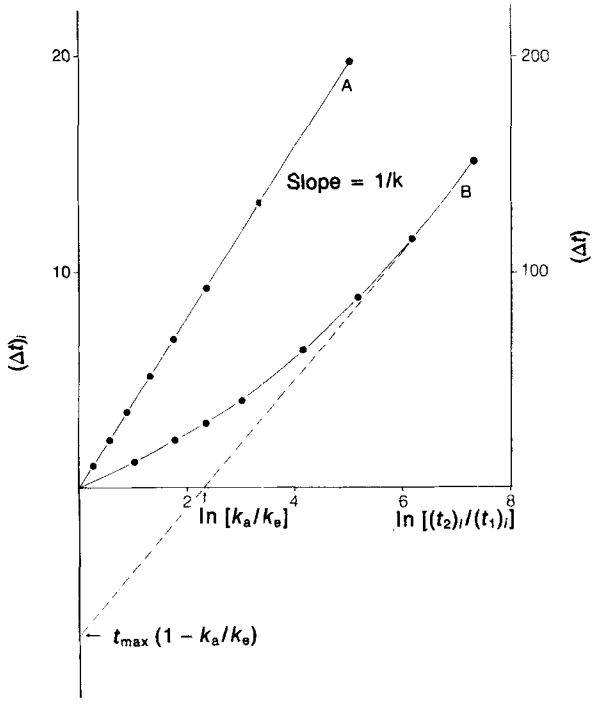

Figure 1—*Plots of* $(\Delta t)_i$ *versus ln* $[(t_2)_i/(t_1)_i]$ based on simulated data derived from eqs. 2 and 3 assuming FD/Vd = *50 units. Key (equation, curve,* k_a, k_e, *ordinate): 3, A, 0.25, 0.25, left-hand; 2, B, 0.25, 0.025, right-hand; 2, B, 0.025, 0.25, right-hand. The upper two data points, used for the back-extrapolation in curve B, have values of* $(t_2)_i$ *equal to 4.2 and 5.5 times the half-life.*

time t_2, it is plausible to state that the inequality:

$$\exp(-k_a t_1) \gg \exp(-k_e t_2) \gg \exp(-k_a t_2) \quad (9)$$

starts to hold assuming $k_a > k_e$. The right-hand side of eq. 9 is the conventional assumption quoted when the method of residuals is used. The validity of the left-hand side of eq. 9 becomes operative when $t_2/t_1 \gg k_a/k_e$. Under these conditions it can be easily seen that eq. 8 is reduced to the following expression:

$$\Delta t = \frac{1}{k_e} \cdot \ln (e^{k_e t_2} \cdot e^{-k_a t_1}) \quad (10)$$

or:

$$\Delta t = t_2 - \frac{k_a}{k_e} t_1 \quad (11)$$

which is valid for all the values of t_2 satisfying eq. 9 and shows that Δt is principally determined from the value of t_2. Hence, the plot of $(\Delta t)_i$ versus ln $[(t_2)_i/(t_1)_i]$ will progressively become linear (Fig. 1). According to eq. 11, back-extrapolation of the linear region of the plot $(\Delta t)_i$ against ln $[(t_2)_i/(t_1)_i]$ will give for $(\Delta t)_i = 0$:

$$\frac{(t_2)_i}{(t_1)_i} = \frac{k_a}{k_e} \quad (12)$$

or the intercept of the ln $[(t_2)_i/(t_1)_i]$ axis equals ln (k_a/k_e). Similarly, the intercept of the back-extrapolated line with the $(\Delta t)_i$ axis can be easily derived from eq. 11. It is apparent that when ln $[(t_2)_i/(t_1)_i] = 0$, then $t_1 = t_2 = t_{max}$; thus, eq. 11 can be written as:

$$(\Delta t)_i = t_{max} - \frac{k_a}{k_e} t_{max} \quad (13)$$

which leads to:

$$\text{intercept on the } (\Delta t)_i \text{ axis} = t_{max}\left(1 - \frac{k_a}{k_e}\right) \quad (14)$$

It is rather apparent that in the flip-flop case (where $k_e > k_a$) the plot of $(\Delta t)_i$ versus ln $[(t_2)_i/(t_1)_i]$ is also curvilinear, while k_a replaces k_e and vice versa in the terms of the intercepts of Fig. 1.

It should be noted, however, that Fig. 1 shows that the distinction of (in)equality of rate constants is based on the highest $(\Delta t)_i$ estimates available. Therefore, the proper use of this method presupposes an accurate determination of drug concentrations at the commencement of the absorptive phase and at the termination of the postabsorptive phase. Since the drug concentrations are low in these regions, a sensitive and accurate method of analysis combined with a sampling protocol focusing on the phases mentioned above will enable the efficient application of the method.

Discussion

To illustrate the use of the proposed method the following examples were considered. Equation 3 was employed to simulate plasma drug concentrations at times 0.25, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20 h, assuming $FD/Vd = 10$ and $k = 0.33$. Twelve additional sets of readings were also generated by adding normally distributed random error with an RSD of ±5%. Error-free data and data that were also contaminated to the above order were generated by using eq. 2 with $FD/Vd = 10$ and $k_e = 0.33$ while the value of k_a ranged from 0.396 to 0.594, i.e., $1.2 \leq (k_a/k_e) \leq 1.8$. In all cases, linearity was assumed between zero and the first measurement at 0.25 h. This enabled the calculation of the $(t_1)_i$ values, needed to apply eq. 6, for each of the $(t_2)_i$ values corresponding to the times of the data points at the terminal phase. Subsequently, the data were analyzed according to eq. 6. To test the sensitivity of the method, the simulated data were evaluated in various ways (Tables I–III).

It is seen from Table I that for the error-free blood level data, the proposed method clearly reveals the (in)equality[6] of rate constants in accordance with the values assigned to the ratio k_a/k_e in both data sets tested. The analysis of data set B, in cases where $k_a \neq k_e$, supports the nonequivalence of rate constants more explicitly. This is in agreement with eq. 9 and Fig. 1 which both show that the later the samples have been collected, the more efficient the application of the method.

The results of the method, as applied to data with error, are presented in Table II. As can be seen, there is no considerable distinction between the two sets of data in relation to the analytical capability of the method. Its sensitivity in terms of the k_a/k_e value lies at 1.8 under the conditions of the experi-

Table I—Estimates of Intercepts Using Eq. 6 with Two Sets of Simulated Error-Free Data Derived from Eqs. 2 and 3

Data Set[a]	k_a/k_e	Intercept[b]
A	1.0	0.0000 (0.0000)
B	1.0	0.0000 (0.0000)
A	1.2	−0.1057 (0.0111)
B	1.2	−0.1363 (0.0175)
A	1.4	−0.3750 (0.0147)
B	1.4	−0.4769 (0.0207)
A	1.6	−0.7379 (0.0403)
B	1.6	−0.9204 (0.0371)
A	1.8	−1.1355 (0.0476)
B	1.8	−1.3875 (0.0319)

[a] Data set A: plasma concentrations at 0.25, 12, 13, 14, 15, 16, 17, and 18 h. Data set B: plasma concentrations at 0.25, 14, 15, 16, 17, 18, 19, and 20 h. [b] Standard deviation in parentheses.

Table II—Estimates of Intercepts Using Eq. 6 with Two Sets of Eight Simulated Data Points with ±5% Random Error Derived from Eqs. 2 and 3

Data Set[a]	k_a/k_e	Mean Intercept[b]	Equality Identified[c]
A	1.0	−0.0528 (0.2935)	8
B	1.0	−0.0572 (0.3324)	8
A	1.2	−0.0101 (0.4146)	8
B	1.2	−0.0352 (0.4716)	9
A	1.4	−0.2806 (0.3720)	6
B	1.4	−0.3676 (0.4250)	5
A	1.6	−0.6328 (0.3716)	2
B	1.6	−0.7940 (0.4270)	2
A	1.8	−1.1303 (0.3383)	0
B	1.8	−1.3792 (0.3901)	0

[a] See Table I for the sampling design of each set. Twelve data subsets with ±5% random error were analyzed for sets A and B. [b] Average of intercepts and SDs (in parentheses) found for each subset. [c] The number of cases conforming to the criterion of equality.

mental error and the sampling design studied. However, a more satisfactory discrimination between equivalence and nonequivalence of rate constants would be possible if more data points were used at the terminal phase. To substantiate this argument, in Table III are listed the results obtained when two more data points for each set were incorporated into the analysis based on eq. 6. An inspection of the results quoted in Table II and III indicates that the utilization of a greater number of data points enhanced the analytical power of the method remarkably by reducing the standard error of the intercept.

In view of the foregoing results, it is advisable to collect two samples at the commencement of the absorptive phase, as suggested by Bialer et al.[7] and to frequently collect sampling between 5 and 10 half-lives of the drug for an adequate testing of eq. 6. Such a sampling protocol will impose several data points to satisfy eq. 9 (if unequal rate constants are met), and the discrimination of (in)equality of rate constants will become accordingly feasible. In addition, the early data points of the absorption phase will clarify if lag-time corrections are necessary when performing the calculations. Undoubtedly, most of the studies are not specifically designed to test the equivalence of rate constants and, therefore, data which are used in the proposed method are not usually collected. The commonly applied data, however, can be used for a rough estimation of the half-life of the drug. Thus, a decision about the sampling design of the terminal phase, which is indispensable for testing eq. 6, can be reached ad hoc during the process of the experiment.

Table III—Estimates of Intercepts Using Eq. 6 with Two Sets of Ten Simulated Data Points with ±5% Random Error Derived from Eqs. 2 and 3

Data Set[a]	k_a/k_e	Mean Intercept[b]	Equality Identified[c]
C	1.0	0.0266 (0.1800)	8
D	1.0	0.0306 (0.2054)	7
C	1.2	0.0482 (0.2356)	5
D	1.2	0.0476 (0.2692)	5
C	1.4	−0.2761 (0.2592)	5
D	1.4	−0.3699 (0.2982)	4
C	1.6	−0.6090 (0.2324)	0
D	1.6	−0.7792 (0.2688)	0
C	1.8	−1.0387 (0.2336)	0
D	1.8	−1.2984 (0.2710)	0

[a] Data set C: plasma concentrations at 0.25, 10, 11, 12, 13, 14, 15, 16, 17, and 18 h. Data set D: plasma concentrations at 0.25, 12, 13, 14, 15, 16, 17, 18, 19, and 20 h. Twelve data subsets with ±5% random error were analyzed for sets C and D. [b] Average of intercepts and SD (in parentheses) found for each subset. [c] The number of cases conforming to the criterion of equality.

Table IV—Comparison of Real and Estimated Values Obtained by Eq. 15 Using the Data of Chan and Miller[a]

	FD/Vd	k	R^2	$s_{y\cdot x}$[b]
Real values	10.00	0.500	—	—
Data with only rounding error	9.99 (1.00)	0.499 (0.002)	0.999	0.004
Data with 5% noise	10.15 (1.02)	0.504 (0.022)	0.999	0.046

[a] Ref. 2; SD of the parameter estimates in parentheses. [b] SEM of the estimate.

The data in Tables I–III indicate that the method presented is valid. Furthermore, since this method and the method relying on eq. 1 are utilizing different data, they can be employed as complementary to one another.

As can be deduced from the aforementioned, in the case of equal rate constants the value of the constant term $(FD)/Vd$ of eq. 3 cannot be determined from the plot of $(\Delta t)_i$ versus ln $[(t_2)_i/(t_1)_i]$. Nevertheless, once the equality of rate constants is justified, the complete analysis of the system with equal rate constants can be determined by:

$$\ln (C/t) = \ln [(FDk)/Vd] - kt \qquad (15)$$

This equation is derived from eq. 3 after rearrangement and logarithmic transformation. It shows that a plot of ln (C/t) versus t gives a straight line with a slope equal to $-k$ and an intercept equal to ln $[(FDk)/Vd]$. Equation 15 was used to analyze the data given in Table I of the paper by Chan and Miller.[2] By applying linear regression analysis, in accordance with eq. 15, the results listed in Table IV were obtained. As it can be seen from Table IV, the values of R^2 and $s_{y\cdot x}$ as well as the small standard deviation of the parameter estimates show clear proof of the goodness of fit of data to eq. 15.

In conclusion, the described method based on eq. 6 appears to be a unique solution to the problem of whether absorption and elimination rate constants are equal in the one-compartment open model with first-order processes when computer facilities are unavailable or the knowledge of C_{max} and t_{max} is doubtful. Moreover, the utilization of eq. 15 offers a reliable graphical method of analysis of the one-compartment model with equal first-order processes.

References and Notes

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