On the Assessment of the Relative Magnitude of Rate Constants in the Linear Open One-Compartment Model

To the Editor:

The proper analysis of a linear one-compartment model with comparable values of rate constants is of particular importance for the evaluation of slow-release products. However, the graphical methods of analysis[1,2] for this model give biased estimates of the rate constants when comparable values are encountered. Under these conditions, even the application of the nonlinear regression technique,[3] which requires appropriate guess values for the estimation of the rate constants, becomes questionable. On this account, two methods[4,5] have been proposed to ascertain the (in)equality of rate constants.

This study was undertaken to show that the (in)equality criteria[4,5] of rate constants are, in essence, special cases of explicit functions that relate the pharmacokinetic parameters involved with the ratio of rate constants. With simulated data, it is shown that these criteria are not capable of revealing the (in)equivalence of rate constants.

The one-compartment first-order absorption model in pharmacokinetics is described by the following general equation[2]:

$$C = [FDk_a/V(k_a - k)]\,[\exp(-kt) - \exp(-k_a t)] \quad (1)$$

In eq 1, C is the concentration of drug in plasma at time t; F is the fraction of dose (D) that is absorbed; V is the apparent volume of distribution; and k_a and k are the absorption and elimination rate constants, respectively. When k_a and k are equal ($k_a = k = k'$), the equation describing the concentration in plasma for the linear one-compartment model is given by eq 2[6]:

$$C = (FDk't/V)\exp(-k't) \quad (2)$$

Bialer's criterion[4] (eq 3) represents the original reported method for assessing the equivalence of k_a and k:

$$(C_{max}t_{max})/(AUC)_0^\infty = 1/e \quad (3)$$

In eq 3, C_{max} is the peak drug concentration, t_{max} is the time at which C_{max} is reached, $(AUC)_0^\infty$ is the area under the curve of drug level in blood versus t between times zero and infinity, and e is the base of the natural logarithm.

For the general case $k_a \neq k$, the parameters C_{max}, t_{max}, and $(AUC)_0^\infty$ can be expressed as functions of k_a, k, and FD/V.[2] Combination of these functions results in the following equation:

$$C_{max}t_{max}/(AUC)_0^\infty = [\phi^{1/(1-\phi)} \ln \phi]/(\phi - 1) \quad (4)$$

In eq 4, $\phi = k_a/k$. The parameters of Bialer's criterion (eq 3) are related to the ratio of rate constants (k_a/k) with eq 4. In addition, eq 3 can be considered as a special case of eq 4, which relates the basic pharmacokinetic parameters C_{max}, t_{max}, and $(AUC)_0^\infty$ with the ratio of rate constants. In fact, $1/e$ is the limit of eq 4 when $\phi = 1$ and the maximum of the plot of $(C_{max}t_{max})/(AUC)_0^\infty$ versus k_a/k (Figure 1). In theory, the master curve presented in Figure 1 can be used to derive two estimates for the k_a/k ratio based on the values of C_{max}, t_{max}, and $(AUC)_0^\infty$ calculated with the trapezoidal rule from the experimental data. The two estimates for the ratio of rate constants are reciprocal numbers that correspond to the usual ($k_a > k$) and the flip-flop[2] ($k_a < k$) kinetics, and their origin is associated with the local identifiability problem.[7]

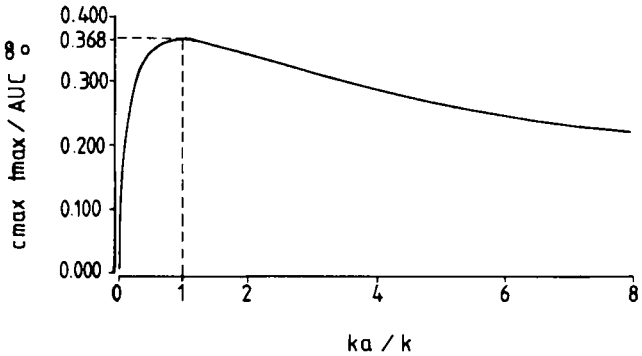

Figure 1—Effect of increasing the k_a/k on $C_{max}t_{max}/(AUC)_0^\infty$. The criterion of the equivalence of rate constants is schematically depicted with the dashed line.

Simulated data including only rounding error were used so that the capability of eq 3 in discerning the equivalency of rate constants could be studied. Concentrations of drug in plasma expected at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, and 24.0 h were simulated from eq 1, with $FD/V = 15.0$, $k = 0.200$, and k_a ranging from 0.200 to 0.600 (i.e., $1.000 \leq k_a/k \leq 3.000$). Additional data sets of readings were also generated from eq 2, with $FD/V = 15.0$ and k' values ranging from 0.200 to 0.300. The generated higher concentration value was assigned to C_{max}, with the corresponding time representing t_{max}, and areas were calculated with the trapezoidal rule. The results of the simulation study (Table I) were

Table I—Calculated Values for $C_{max}t_{max}/(AUC)_0^\infty$ from Errorless Data Generated from Eqs 1 and 2

Real Value of k_a/k	t_{max}		$C_{max}t_{max}/(AUC)_0^{\infty\,a,b}$	
	Real	Experimental[a]	Estimate 1	Estimate 2
1.100[c]	4.77	5.00 (5)	0.381 (4)[f]	0.365 (1)
1.250[c]	4.46	4.00 (10)	0.319 (13)	0.308 (16)
1.500[c]	4.05	4.00 (1)	0.344 (4)	0.335 (7)
1.750[c]	3.73	4.00 (7)	0.364 (3)	0.357 (1)
2.000[c]	3.47	3.00 (14)	0.285 (18)	0.281 (19)
2.500[c]	3.05	3.00 (2)	0.313 (6)	0.309 (7)
3.000[c]	2.75	3.00 (9)	0.332 (5)	0.328 (3)
1.000[d,e]	5.00	5.00 (0)	0.369 (0.3)[f]	0.349 (5)
1.000[d,g]	4.44	4.00 (10)	0.321 (13)	0.311 (15)
1.000[d,h]	4.00	4.00 (0)	0.352 (4)	0.346 (6)
1.000[d,i]	3.64	4.00 (10)	0.382 (4)[f]	0.378 (3)[f]
1.000[d,j]	3.33	3.00 (10)	0.311 (15)	0.309 (16)

[a] Numbers in parentheses are percent error. [b] For estimate 1, $(AUC)_0^\infty$ was calculated up to the last experimental concentration ($t = 24$); for estimate 2, the portion of the curve $(AUC)_{24}^* = C_{24}/k$ was taken into consideration [C_{24} is the last experimental concentration and k is the terminal slope (two points) of the ln C versus t plot]. [c] $k_a \neq k$; values for k_a ranged from 0.220 to 0.600; k was always 0.200. [d] $k_a = k = k'$. [e] $k' = 0.200$. [f] Values higher than the theoretical maximum of 0.368. [g] $k' = 0.225$. [h] $k' = 0.250$. [i] $k' = 0.275$. [j] $k' = 0.300$.

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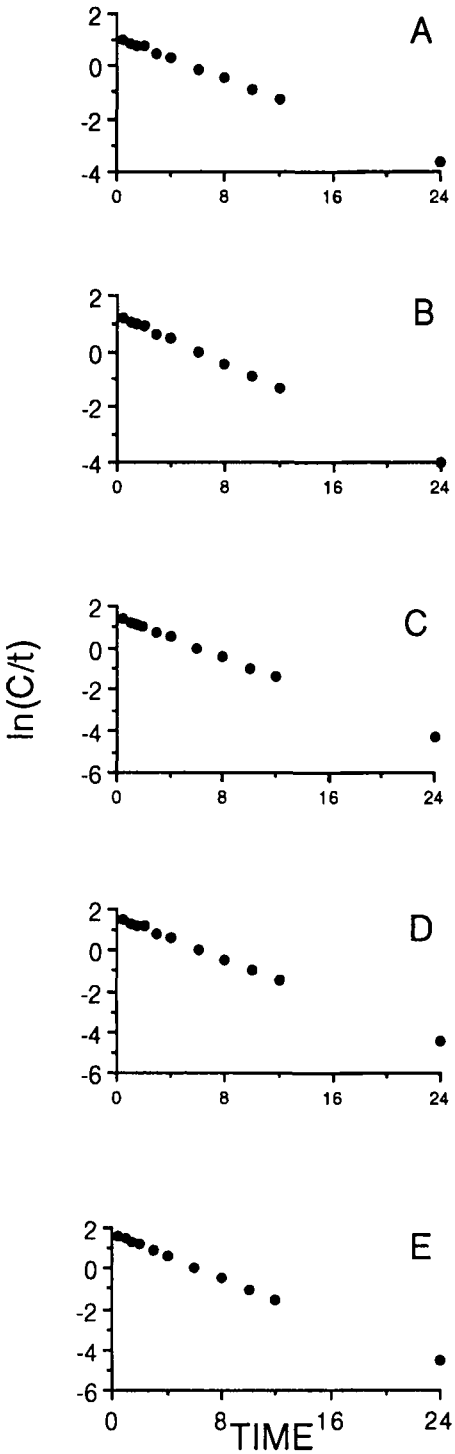

Figure 2—Plot of ln (C/t) versus t from errant data (RSD, ±5%) generated from eqs 1 and 2, with FD/V = 15.0 and k = 0.200. Key: (**A**) k_a = 0.200; (**B**) k_a = 0.250; (**C**) k_a = 0.300; (**D**) k_a = 0.350; (**E**) k_a = 0.400.

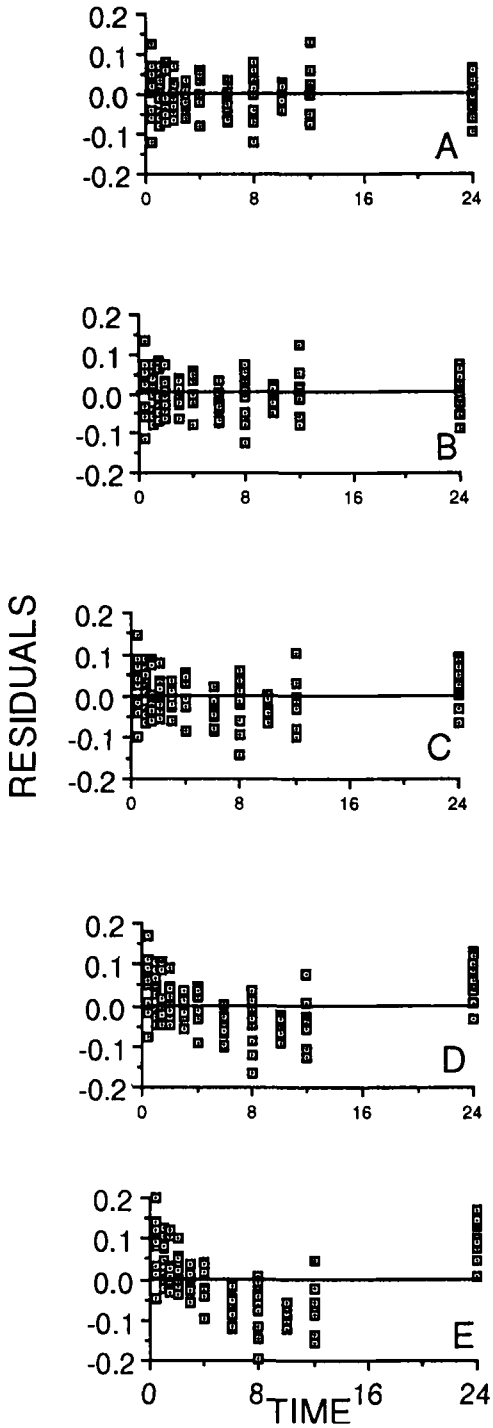

Figure 3—Residual plots for 10 sets of errant data (RSD, ±5%) generated from eqs 1 and 2, with FD/V = 15.0 and k = 0.200, and analyzed with eq 5. Key as in caption for Figure 2.

evaluated in light of the graph shown in Figure 1. Calculation of the parameter $C_{max}t_{max}/(AUC)_0^\infty$ is prone to error whether the experimental t_{max} values (and, therefore, C_{max} values) are close or not to the true values. In addition, the results (rows 8 and 10 of Table I) show that this calculation is very susceptible to round-off error and error due to inaccurate approximation of areas. A value for $C_{max}t_{max}/(AUC)_0^\infty$ higher than the theoretical maximum of 0.368 (Table I) indicates the closeness of rate constants under the experimental conditions simulated. Overall, the data (Table I) show that the values for $C_{max}t_{max}/(AUC)_0^\infty$ lie in the vicinity of 0.368, regardless of the simulated data analyzed (i.e., data generated either from eq 1 or 2, with unequal or equal rate constants, respectively). This observation is inherently linked with the "flat maximum" corresponding to k_a/k = 1.0 of the curve in Figure 1. Therefore, the discerning ability of eq 3 for testing the (in)equivalence of rate constants will be even lower in real practice where experimental error is also encountered. Although this conclusion is not in accordance with a recent report,[5] previously reported concerns[3,8] on the usefulness of eq 3 as a criterion of (in)equivalence of rate constants agree with our observations.

Another equation for the assessment of (in)equality of rate constants has been recently proposed by Zhi[5]:

$$\ln C/t = [\ln(FDk'/V)] - k't \quad (5)$$

According to eq 5, the linearity of the plot of ln (C/t) versus t identifies the closeness of k_a and k. However, it has been shown[9] that when k_a = k, eq 1 can be approximated by eq 6:

$$C = (FDk_a/V)\, t \exp[-t(k_a + k)/2] \quad (6)$$

Equation 6 can be written in the linearized form shown in eq 7:

$$\ln C/t = \ln FDk_a/V - [(k_a + k)/2]t \quad (7)$$

Obviously, for $k_a \simeq k$, eq 7 collapses to eq 5; therefore, eq 5 can be considered as a special case of the more general eq 7.

The inadequacy of the ln (C/t) versus t plot for discriminating whether k_a and k are equal under experimental conditions is shown in Figure 2 with errant data with normally distributed error with a relative standard deviation (RSD) of ± 5%. The nonlinear character of the plot for the data with $1 < k_a/k \leq 2$ cannot be detected by visual inspection. To evaluate further the analytical power of eq 5 in discerning the relative magnitude of k_a and k, a simulative study was undertaken. For each ϕ value, 10 sets of errant data with an RSD of ±5% were generated from eqs 1 and 2 by assigning FD/V = 15.0 and k = 0.200 and using the same random sequence for all ϕ values. The simulated data were analyzed with eq 5, and the residual plots[10] obtained are shown in Figure 3. At this low level of experimental error, the residual plot (Figure 3) could be useful for the identification of nonlinearity only when $k_a/k > 1.75$. Therefore, it can be concluded that, under real conditions of experimental error, neither the ln (C/t) versus t plot nor the corresponding residual plot can be used as a tool for the (in)equality of rate constants. Rather, an apparently linear ln (C/t) versus t plot should be considered only as an indicator of the similarity in the magnitude of rate constants. It is advisable, therefore, to apply a proper analysis[9] for the initial estimates of k_a and k when values of the same size for k_a and k are justified.

References and Notes

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CORRECTIONS AND ADDITIONS

Enhancement of Percutaneous Absorption by Laurocapram. Ogiso, Taro; Iwaki, Masahiro; Bechako, Kazuko; Tsutsumi, Yoko. *J. Pharm. Sci.* **1992**, *81*, 762–767.

On page 762, column 2, paragraph 3, the last sentence should read: "The concentrations of these lipids in the incubation medium were not determined...."