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METHOD OF RESIDUALS: ESTIMATION OF ABSORPTION AND ELIMINATION RATE CONSTANTS HAVING COMPARABLE VALUES

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ABSTRACT

An equation was developed to be used with the method of residuals for the analysis of the linear one-compartment open model. This equation can provide information about the magnitude of the ratio of rate constants, without assuming that the terminal phase reflects solely either an elimination or an absorption process, as must be done for the graphical techniques. It also enhanced the analytical power of the method of residuals in that it gave better estimates of the absorption rate constant when the latter and the elimination rate constant have comparable magnitudes.

KEY WORDS One-compartment open model Method of residuals Estimation Absorption rate constant

INTRODUCTION

Several methods have been developed for the estimation of the parameters of the linear one-comparment open model. The method of residuals[1–3] and the Wagner-Nelson method[4] are very useful in this respect and are widely applied. Both techniques, though, are based on the assumption that the terminal phase reflects solely either an elimination or an absorption process. However, in some cases sampling is not conducted for a time long enough to warrant this assumption. Besides, if the rate constants of absorption and elimination are of comparable magnitude, absorption occurs essentially throughout the whole time and the assumption is, in practice, then not justified. Consequently, under such circumstances the methods are not appropriate for analysis of this system and will fail to provide valid estimates of the model's parameters.[5]

Another alternative for the estimation of the parameters in this model is to use various computer-based non-linear regression techniques. Although these methods make no assumption about the terminal phase, they may fail to converge if the starting points of the iterative algorithms are poor estimates of the true rate constants.[6] Since the initial estimates utilized are usually derived

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from the Wagner-Nelson method and the method of residuals, this study was undertaken to:

1. justify the validity of the terminal phase assumption postulated in these methods, and
2. provide a better estimate for the absorption rate constant when this assumption is violated.

THEORETICAL SECTION

The one-compartment, first-order absorption model in pharmacokinetics is described by the general equation:

$$C_p = \frac{FD}{V_d} \frac{k_a}{k_a - k_e} (e^{-k_e t} - e^{-k_a t}) \tag{1}$$

where C_p corresponds to the plasma drug concentration at time t, F is the fraction of dose absorbed, D is the dose, V_d is the apparent volume of distribution, and k_a and k_e are the absorption and elimination rate constants, respectively.

Expanding the exponential terms in equation 1 to the first two powers, i.e.

$$C_p = \frac{FD}{V_d} \frac{k_a}{k_a - k_e} \left[1 - k_e t + \frac{1}{2}(k_e t)^2 - 1 + k_a t - \frac{1}{2}(k_a t)^2 \right]$$

then gives

$$C_p = \frac{FD}{V_d} k_a t \left(1 - \frac{k_a + k_e}{2} t\right) \tag{2}$$

The expression in the parenthesis of the last equation is a one-term Taylor series expansion of

$$\exp \left[- (k_a + k_e)\, t/2 \right] .$$

Accordingly, equation 2 may be written as

$$C_p = \frac{FD}{V_d} k_a t \cdot e^{-\frac{k_a + k_e}{2} t} \tag{3}$$

The reliability with which equation 3 approximates equation 1 is dependent upon the absolute and relative values of rate constants k_a and k_e as well as upon time t. Evidently though, when k_a approaches k_e, i.e. $k_a \doteq k_e = k$

regardless of the time, t, equation 3 simplifies to the equation,

$$C_p = \frac{FD}{V_d} kt.e^{-kt} \tag{4}$$

which does in fact represent the true equation for the model.[7] It can be anticipated therefore than when $k_a \neq ke$ and t is low, equation 3 will adequately describe data adhering to the model of equation 1 provided that the magnitudes of the rate constants are comparable. This is illustrated in Figure 1 where error-free concentration data generated from equations 1 and 3 for two values of the ratio k_a/k_e, namely 1·2 and 3·0, are compared. As can be seen the absorption phase data almost coincide, irrespective of the value of the ratio k_a/k_e, while differences become patent, particularly for the higher ratios of k_a/k_e, during the postabsorptive and elimination phase. An overall view of the applicability of equations 1 and 3 is presented in Table 1 for various absolute and relative values of k_a and k_e. An arbitrary 5 per cent difference in the values of the simulated concentrations for the two equations was utilized to ascertain the time limits for reliable use of equation 3 in place of equation 1. As can be seen, the lower the absolute and relative values of the rate constants the longer the period of time for which equation 3 is applicable. However, by comparing the time limits for its use with the t_{max} values calculated from equation 1 quoted in Table 1, it can be concluded that equation 3 can be applied in practice. Moreoever, if rough estimates of t_{max} and k_e can be obtained from a concentration-time plot, Table 1 can be used to check whether equation 3 is applicable or not.

Equation 5 can be obtained from equation 3 in a manner similar to that used elsewhere,[8]

$$\ln\left(\frac{t_x C_p^y}{t_y C_p^x}\right) = \frac{k_a + k_e}{2} \Delta t \tag{5}$$

where (C_p^x, t_x) and (C_p^y, t_y) are any two data points conforming to the restrictions of Table 1 and Δt the time interval t_x to t_y. This equation reveals that a plot of $\ln(t_x C_p^y / t_y C_p^x)$ versus Δt utilizing data conforming to the restrictions of Table 1, would give a slope corresponding to the average of the non-equivalent k_a and k_e.

Focusing on the consideration of the elimination phase data, which are routinely described in the method of residuals, assuming $k_a > k_e$, equation 1 reduces to:

$$C_p = \frac{FD}{V_d} \frac{k_a}{k_a - k_e} . e^{-k_e t} \tag{6}$$

but an equation analogous to equation 5 cannot be derived.

When the principle of the concentration ratio method[8] for the utilization of

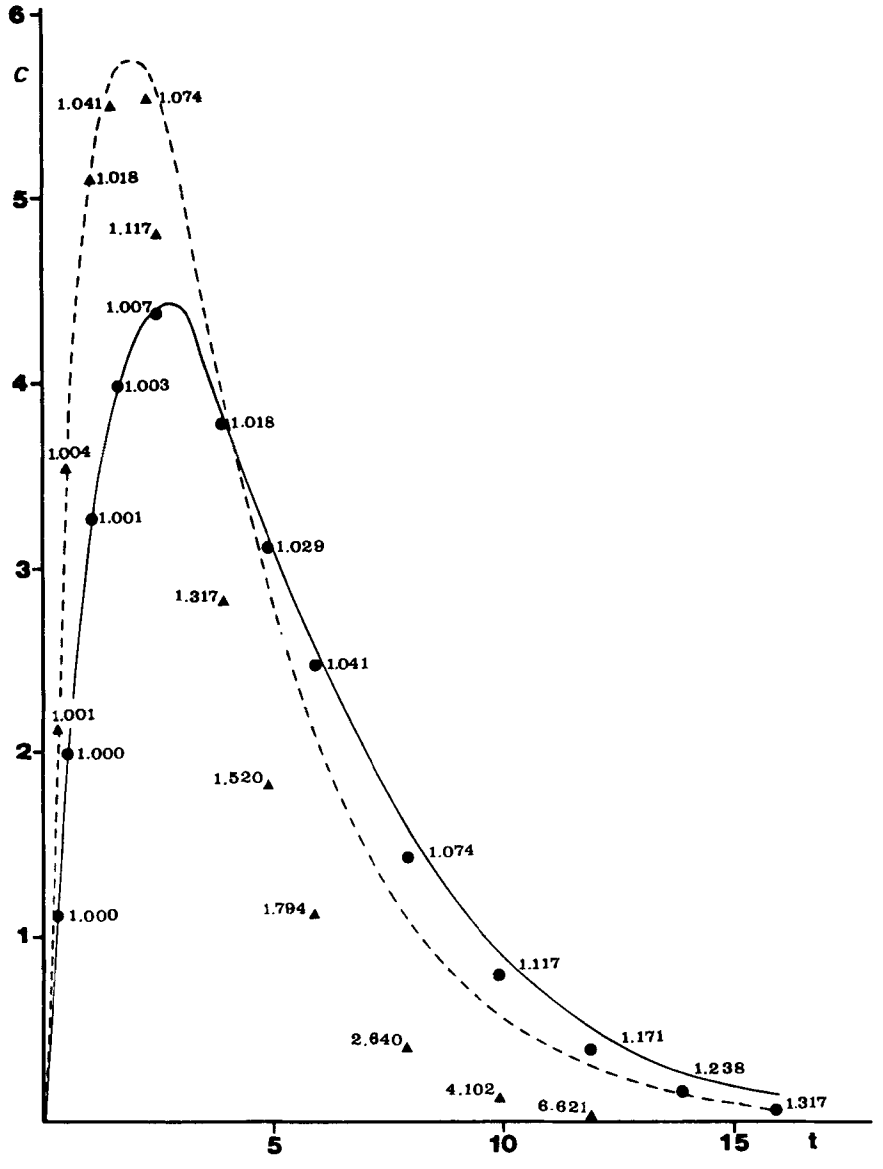

Figure 1. Concentration time plots of error free data generated from equation 1 with $FD/V_d=10$, $k_e=0{\cdot}330$, and $k_a=0{\cdot}396$ (continuous line) or $k_a=0{\cdot}990$ (broken line). Simulated error free data from equation 3 using the same values of the parameters are presented as circles ($k_e=0{\cdot}330$, $k_a=0{\cdot}396$) and triangles ($k_e=0{\cdot}330$, $k_a=0{\cdot}990$). The numbers beside the symbols represent the values of the ratio: (concentration generated from equation 1/concentration generated from equation 3), prevailing at the time corresponding to each symbol

Table 1. Time limits for the use of equation 3 instead of equation 1 for various values of absolute and relative values of rate constants

k_c*	k_a/k_c 1·1	1·5	2·0	2·5	3·0	3·5	4·0
	$t_{5\%}$†‡ − t_{max}†§						
0·05	108·7−19·1	21·7−16·2	10·9−13·9	7·2−12·2	5·4−11·0	4·3−10·0	3·6−9·2
0·075	72·5−12·7	14·5−10·8	7·2− 9·2	4·8− 8·1	3·6− 7·3	2·9− 6·7	2·4−6·2
0·10	54·4− 9·5	10·9− 8·1	5·4− 6·9	3·6− 6·1	2·7− 5·5	2·2− 5·0	1·8−4·6
0·125	43·5− 7·6	8·7− 6·5	4·3− 5·5	2·9− 4·9	2·2− 4·4	1·7− 4·0	1·4−3·7
0·15	36·2− 6·3	7·2− 5·4	3·6− 4·6	2·4− 4·1	1·8− 3·7	1·4− 3·3	1·2−3·1
0·175	31·1− 5·4	6·2− 4·6	3·1− 4·0	2·1− 3·5	1·5− 3·1	1·2− 2·9	1·0−2·6
0·20	27·2− 4·8	5·4− 4·0	2·7− 3·5	1·8− 3·0	1·4− 2·7	1·1− 2·5	0·9−2·3
0·25	21·7− 3·8	4·3− 3·2	2·2− 2·8	1·4− 2·4	1·1− 2·2	0·9− 2·0	0·7−1·8
0·30	18·1− 3·2	3·6− 2·7	1·8− 2·3	1·2− 2·0	0·9− 1·8	0·7− 1·7	0·6−1·5
0·35	15·5− 2·7	3·1− 2·3	1·5− 2·0	1·0− 1·7	0·8− 1·6	0·6− 1·4	0·5−1·3
Overall ratio $t_{5\%}/t_{max}$:	5·70	1·34	0·78	0·59	0·49	0·43	0·39

* Arbitrary units.
† Inverse units to those assigned to k_c.
‡ At this time the concentration ratio defined in the legend of Figure 1 equals 1·05, i.e. there is a 5 per cent difference between the concentrations generated from equations 1 and 3.
§ t_{max} from equation 1.

all possible combinations of the elimination phase data (C_p^x, t_x), (C_p^y, t_y) was applied to equation 6, the following equation resulted

$$\ln (C_p^y/C_p^x) = k_e (t_x - t_y) = k_e \Delta t \quad (7)$$

Equation 7 is different from equation 5 in that it does not involve the variable of time in the logarithmic factor. However, differences between equations 5 and 7 can be utilized to provide information about the magnitude of the ratio k_a/k_e. It is conceivable that when $k_a = k_e = k$, the fundamental equation 8 of the concentration ratio method,[8]

$$\ln \left(\frac{t_x C_p^y}{t_y C_p^x} \right) = k. \Delta t \quad (8)$$

prevails throughout the time course of the drug in the body. Therefore, linear regression analysis of $\ln(t_x C_p^y/t_y C_p^x)$ versus Δt utilizing separately data from the two extreme phases, i.e. absorptive and elimination, will theoretically result in identical regression lines. On the other hand, it can be anticipated by inspection of equations 5 and 7, that when $k_a \neq k_e$ an analysis of such segmented data would reveal statistically significant differences between the regression lines.

RESULTS AND DISCUSSION

To provide an adequate test for the method developed herein, a BASIC language program has been written for the microcomputer to generate data and do the calculations utilizing the appropriate combinations of pairs of data required for the solution of equations. For comparative purposes the method of residuals was also incorporated into the program.

Plasma drug concentrations expected at times 0·25, 0·5, 1·0, 1·5, 2·0, 8·0, 10·0, 12·0, 14·0, 16·0, and 18·0 were simulated for equation 4 with $FD/V_d = 10$ and $k = 0{\cdot}33$, including rounding error. Twelve additional datum sets of readings were also generated by adding normally distributed error with an RSD of ± 5 per cent. Error free data and data which were also contaminated to the above order were generated by using equation 1 with $FD/V_d = 10$, $k_e = 0{\cdot}33$, and k_a ranging from 0·396 to 0·990 i.e.

$$1{\cdot}2 \leqslant k_a/k_e \leqslant 3{\cdot}0$$

The usefulness of equation 5 for estimating the average of rate constants utilizing the first data points is shown in Table 2; fairly good estimates were obtained in the examples considered. As expected, the estimates approximated most closely to the real values when data points fulfilling the restrictions of Table 1 were employed, i.e. when $k_a/k_e \leqslant 2{\cdot}2$. Slight bias was noted at higher k_a/k_e ratios ($k_a/k_e \geqslant 2{\cdot}4$). Table 2 also demonstrates that the

Table 2. Comparison of real and estimated values obtained by equation 5 with data* derived from equation 1

Real value of k_a/k_c	Real value of $(k_a+k_c)/2$	Estimated slope† (CV)‡	Per cent error
0·330/0·330 = 1·0§	0·330	0·345 (7·18)	4·54
0·396/0·330 = 1·2	0·363	0·376 (10·40)	3·58
0·462/0·330 = 1·4	0·396	0·397 (11·64)	0·25
0·528/0·330 = 1·6	0·429	0·428 (5·49)	−0·23
0·594/0·330 = 1·8	0·462	0·464 (8·53)	0·43
0·660/0·330 = 2·0	0·495	0·482 (8·11)	−2·63
0·726/0·330 = 2·2	0·528	0·497 (7·85)	−5·87
0·792/0·330 = 2·4	0·561	0·555 (8·85)	−1·25
0·858/0·330 = 2·6	0·594	0·558 (7·46)	−6·06
0·924/0·330 = 2·8	0·627	0·576 (8·33)	−8·13
0·990/0·330 = 3·0	0·660	0·614 (7·21)	−6·97

* Only data with ± 5 per cent error was used.
† Average of 12 datum sets utilizing equation 5 with the first five data points.
‡ Coefficient of variation.
§ Data derived from equation 4 with ± 5 per cent random error.

Table 3. The performance of the inequality criterion as related to the mean slopes estimates derived from equation 5 with simulated concentration data* based on equations 1 and 4 with $FD/V_d=10$ and various values of the ratio k_a/k_c

k_a/k_c†	Mean‡ $(slope)_i$	Mean§ $(slope)_{ii}$	Inequality‖ identified
1·0	0·345 (0·042)	0·328 (0·013)	2
1·2	0·376 (0·047)	0·357 (0·015)	1
1·4	0·397 (0·044)	0·382 (0·019)	4
1·6	0·428 (0·036)	0·386 (0·017)	5
1·8	0·464 (0·035)	0·394 (0·017)	8
2·0	0·482 (0·038)	0·391 (0·021)	9
2·2	0·497 (0·050)	0·390 (0·017)	10
2·4	0·555 (0·043)	0·396 (0·017)	12
2·6	0·558 (0·036)	0·396 (0·019)	12
2·8	0·576 (0·044)	0·392 (0·016)	12
3·0	0·614 (0·042)	0·399 (0·017)	12

* Only data with ± 5 per cent random error were used.
† For each ratio of k_a/k_c twelve datum sets were analysed.
‡ Average of slope and SD (in parentheses) found for each set utilizing the first five data points.
§ Average of slope and (SD) in parentheses found for each set utilizing the last four data points.
‖ Inequality was identified when $(slope)_i \pm SD$ did not overlap $(slope)_{ii} \pm SD$. The number of cases conforming to this criterion is reported.

use of inappropriate data results in underestimation of the average of rate constants. This observation is illustrated in Figure 1.

Table 3 contrasts the results listed in Table 2 with those derived from the same type of analysis but utilizing the last four data points. When the magnitude and distribution of error, the number of data points and their location in time space are as specified in the present example, the method is capable of elucidating whether or not the ratio of rate constants k_a/k_c is bigger or smaller than 2·4.

The information obtained from the analysis of data as shown in Table 3 can be useful in several situations. Thus, a pretreatment of data confirming that the inequality criterion for rate constants is met will justify the application of graphical techniques, rather than assuming *a priori* that there is an acceptable difference. Conversely, when the analysis does not clearly prove the inequality of rate constants, non-linear regression analysis has to be preferred to avoid biased estimates of the rate constants.[5] In the latter case, equation 5 can be more satisfactory than the residuals method for the determination of the initial estimates required for iterations until convergence criteria are met.

The results for two data sets presented in Table 4 demonstrates that equation 5 outperforms the conventional residuals method in that it furnishes estimates of k_a which are closer to the real values in cases where the ratio k_a/k_c varies from 1·0 to 2·2. This superiority may be because the estimation of k_a by the method of residuals is based on back-extrapolation of the linearized

Table 4. Comparison of real and estimated values of the absorption rate constant by the method of residuals and equation 5 for various values of the ratio k_a/k_e

Real values of the ratio k_a/k_e	Data set	Estimated k_e†-PE‡	Estimated k_a†-PE‡	
			Method of residuals	Equation 5
0·330/0·330 = 1·0	A	0·242 (0·009) – 26·67	0·507 (0·024) – 53·64	0·458 (0·067) – 38·79
	B	0·261 (0·010) – 26·44	0·465 (0·021) – 40·91	0·430 (0·054) – 30·30
0·396/0·330 = 1·2	A	0·271 (0·010) – 17·88	0·538 (0·041) – 26·39	0·471 (0·080) – 18·94
	B	0·289 (0·010) – 12·42	0·499 (0·035) – 26·01	0·463 (0·075) – 16·92
0·462/0·330 = 1·4	A	0·289 (0·011) – 12·42	0·591 (0·036) – 27·92	0·490 (0·103) – 6·06
	B	0·314 (0·014) – 4·85	0·526 (0·042) – 13·85	0·479 (0·090) – 3·68
0·528/0·330 = 1·6	A	0·301 (0·013) – 8·79	0·652 (0·055) – 23·48	0·530 (0·110) – 0·38
	B	0·318 (0·014) – 3·64	0·580 (0·044) – 9·85	0·538 (0·052) – 1·89
0·594/0·330 = 1·8	A	0·313 (0·018) – 5·15	0·699 (0·108) – 17·68	0·601 (0·044) – 1·18
	B	0·327 (0·010) – 0·91	0·610 (0·043) – 2·69	0·601 (0·081) – 1·18
0·660/0·330 = 2·0	A	0·324 (0·009) – 1·82	0·703 (0·043) – 6·51	0·640 (0·059) – 3·03
	B	0·323 (0·010) – 2·12	0·723 (0·085) – 9·54	0·640 (0·078) – 3·03
0·726/0·330 = 2·2	A	0·328 (0·011) – 0·61	0·761 (0·074) – 4·82	0·701 (0·073) – 3·44
	B	0·323 (0·013) – 2·12	0·820 (0·144) – 12·94	0·672 (0·079) – 7·02

* Data set A: plasma concentrations at 0·25, 0·5, 1·0, 1·5, 2·0, 8, 10, 12, and 14. Data set B: plasma concentrations at 0·25, 0·5, 1·0, 1·5, 2·0, 12, 14, 16, and 18. Twelve data subsets with ± 5 per cent random error were analysed for sets A and B.
† Average of estimates and SD (in parentheses) found for each subset.
‡ Per cent error.

elimination phase followed by linear regression analysis of the absorption phase residuals. Estimation of k_a by such a procedure results in a considerable magnification of the error deriving from the initial poor estimates of k_e, when the values of k_a and k_e are comparable (Table 4, data set B). This propagation of error is even greater when the blood sampling is not continued for long enough to allow a proper estimate of k_e (Table 4, data set A). In contrast, equation 5 achieves an independent determination of the average of rate constants and ultimately provides better estimates of k_a than those obtained from the method of residuals in spite of the fact that both methods utilize the same value of k_e.

In the light of the results of this study, it appears that the use of equation 5 enhances the analytical capacity of the conventional residuals method in two ways. First, it provides an insight into the magnitude of the ratio of rate constants and (in)validates the assumption for the terminal phase. Secondly, it appears to give more accurate estimates of the absorption rate constant than the method of residuals when the magnitudes of k_a and k_e are similar.

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