BIOPHARMACEUTICS & DRUG DISPOSITION, VOL. 8, 387–394 (1987)

SHORT COMMUNICATION

IMPROVEMENT WITHOUT COMPUTER ASSISTANCE OF THE GRAPHICALLY ESTIMATED PARAMETERS OF THE LINEAR ONE-COMPARTMENT OPEN MODEL

PANAYOTIS E. MACHERAS

Department of Pharmacy, University of Athens, Athens 10680, Greece.

KEY WORDS One-compartment model Pharmacokinetic parameters Estimation

INTRODUCTION

In a one-compartment open model with first-order absorption and elimination the plasma drug concentration (C_{b_1}) is defined generally by equation (1),

$$(C_{b_1}) = \frac{FDk_a}{V_d(k_a - k)} (e^{-kt} - e^{-k_a t}) \quad (1)$$

in which t is time, k_a and k are absorption and elimination rate constants, respectively, F is the fraction of dose D absorbed, and V_d is the apparent volume of distribution of the drug. Techniques used to obtain values for the parameters which make up equation (1), include manual methods and computer-based non-linear regression calculations[1–5] using least-squares and maximum likelihood criteria. The manual methods, known as the method of residuals[6] and the Wagner–Nelson method,[7] are used mainly to provide initial estimates for the parameters of the model. These are then further utilized as the starting points for the iterative algorithms of the non-linear estimation. This procedure is entirely satisfactory if suitable computer programs and services are available.

The inherent drawback of all graphical techniques is that they do not provide a unique set of parameter estimates; they are subject to the bias of the investigator. This bias can be removed by using an appropriate algorithm on a computer. The accuracy of the estimates and the rate of convergence depend on the goodness of fit of the model to the observed data and the nature of those data, e.g. the number of minima and the contour. In some

0142–2782/87/040387–08 $05.00

Received 5 May 1986
Revised 28 August 1986

cases, however, programs for non-linear regression analysis may fail to yield convergence when the graphical estimates are poor.[8] Moreover, improvement of the estimates becomes impossible when either computer facilities or the special pharmacokinetic modelling program needed is unavailable.

It would therefore be of value to establish an alternate method which, without computer assistance, gives more accurate estimates of the parameters than those obtained by the graphical techniques.

THEORETICAL SECTION

Recently, it was found[9] that a method based on equation (2),

$$(C_{b_2}) = \frac{FD}{V_d}\, k_a t \cdot e^{-\frac{k_a + k}{2} \cdot t} \tag{2}$$

is superior to the conventional method of residuals when applied to the analysis of the linear one-compartment model in cases where the rate constants have comparable values.

This equation can be written in a linearized form:

$$\ln [(C_{b_2})/t] = \ln (FDk_a/V_d) - \frac{k_a + k}{2}\, t \tag{3}$$

which shows that a plot of $\ln [(C_{b_2})/t]$ versus time gives a straight line with an intercept equal to $\ln (FDk_a/V_d)$ and a slope of $-(k_a + k)/2$.

By dividing equation (1) by equation (2) and rearranging the following equation is obtained:

$$\frac{(C_{b_1})}{(C_{b_2})} = \frac{e^{\frac{k_a - k}{2} t} - e^{-\frac{k_a - k}{2} t}}{(k_a - k)\, t}$$

or, more simply:

$$\frac{(C_{b_1})}{(C_{b_2})} = \frac{e^{Wt} - e^{-Wt}}{2Wt} \tag{4}$$

where $W = (k_a - k)/2$. This step eliminates FD/V_d from the equations and yields equation (4) which is monoparametric. In fact, for a given time, t, $(C_{b_1})/(C_{b_2})$ is solely determined by W, i.e. half the difference between the rate constants. Accordingly, equation (4) can be employed to give the corresponding (C_{b_2}) values for all experimental (C_{b_1}, t) data points, provided that W is known or postulated.

The steps for estimating the parameters of the model, using equations (1), (3), and (4), are as follows:

1. Apply a graphical method to determine initial estimates for the model's parameters. Calculate the sum of the squared deviations, SS, by the following equation where $(C_{b_1})_i$ is the observed concentration, $(\widehat{C_{b_1}})_i$ is the calculated drug concentration, and n is the total number of data points:

$$SS = \sum_{i=1}^{n} [(C_{b_1})_i - (\widehat{C_{b_1}})_i]^2$$

Calculate the value of W from the graphical estimates of k_a and k.
2. From a concentration-time plot of the experimental data along with the generated data based on the parameter estimates obtained in step 1, evaluate visually the goodness of fit as well as the overestimation or underestimation of W. Compute (C_{b_2}) values for all $[(C_{b_1}), t]$ data points from equation (4) using values of W in the neighbourhood of the initial estimate.
3. Using equations (3) and (4), calculate $[(C_{b_2}), t]$ values and determine sets of estimates for the parameters of the model, i.e. FD/V_d, k_a and k.
4. Compute the (C_{b_1}) values from equation (1) for each set of the model parameter estimates obtained in step 3. Calculate the sum of the squared deviations, SS, between the observed concentrations and the concentrations predicted by the model for each set of parameter estimates. Select the set of parameter estimates which yield the lowest value of SS.

The model described assumes that drug absorption commences at $t = 0$ but it is sometimes desirable to incorporate a lag time (t_0) to allow for delay in the onset of the process. The model now becomes,

$$(C_{b_1}) = \frac{FDk_a}{V_d(k_a - k)} [e^{-k(t-t_0)} - e^{-k_a(t-t_0)}] \tag{5}$$

Applying the method,[9] used to derive equation (2) from equation (1), to equation (5), gives:

$$(C_{b_2}) = \frac{FD}{V_d} k_a(t - t_0) \cdot e^{-\frac{k_a + k}{2}(t - t_0)}$$

which can be written in a linearized form

$$\ln [(C_{b_2})/(t-t_0)] = \ln (FDk_a/V_d) - \frac{k_a + k}{2}(t-t_0) \tag{6}$$

The concentration ratio equation can be obtained in an analogous manner, i.e.

$$\frac{(C_{b_1})}{(C_{b_2})} = \frac{e^{W(t-t_0)} - e^{-W(t-t_0)}}{2W(t-t_0)} \tag{7}$$

Equations (6) and (7) should be utilized whenever lag-time corrections are necessary. Early data points of the absorption phase can provide an estimate for t_0.

RESULTS AND DISCUSSION

An Example. Simulated data were utilized to illustrate the application of the method. One set of data with 5 per cent random noise was generated using equation (1) with $FD/V_d = 10$, $k_a = 0{\cdot}495$ and $k = 0{\cdot}330$ (Table 1).

Application of the graphical method of residuals, using the three last points of the terminal phase to estimate k, yielded the values for FD/V_d, k_a, k, W, and SS listed in Table 2. The data generated from equation (1), using these estimates along with the simulated data of Table 1, are presented in Figure 1. From Figure 1, it is clear that the magnitude of the difference between rate constants, i.e. $W = (k_a - k)/2$, is overestimated by the method of residuals. This means that a lower value of W, than the estimate 0·1845 (Table 2, encircled), would fit the data more closely.

To test this argument and obtain a set of parameter estimates capable of giving a better fit, six values close to the graphically-determined value were assigned to W (Table 2). The data were analysed as described in the Theoretical Section and the results obtained are also listed in Table 2. As anticipated, the higher value for W, 0·230, gave worse estimates than the method of residuals, demonstrated by the high value of SS (Table 2). A general view of the influence of varying W on the goodness of fit is shown in Figure 2 by the plot of SS versus W. As can be seen, the lower value of SS obtained corresponds to the value of 0·080 for W which also gives the lower per cent errors for the parameter estimates (Table 2).

Table 1. Simulated concentration data using equation (1)

Time	Concentration with rounding error	Concentration with 5% noise
0·25	1·12	1·13
0·5	2·01	2·02
1·0	3·28	3·25
2·0	4·36	4·29
3·0	4·35	4·35
4·0	3·87	4·12
5·0	3·24	3·14
6·0	2·60	2·44
8·0	1·57	1·56
10·0	0·89	0·90
12·0	0·49	0·50

Table 2. Comparison of real and estimated values obtained by the method of residuals and this method by varying the value of W*

	FD/V_d	k_a	k	$W = \frac{k_a - k}{2}$	SS
Real values	10	0·495	0·330	0·0825	–
Method of residuals	8·64	0·653	0·284	0·1845	0·2312
	(13·6)	(31·9)	(13·9)		
This method assigning:					
W = 0·230	7·66	0·716	0·256	–	0·3960
	(23·4)	(44·6)	(22·4)		
W = 0·130	9·05	0·560	0·300	–	0·1276
	(9·5)	(13·1)	(9·1)		
W = 0·080	10·03	0·492	0·332	–	0·1029
	(0·3)	(0·6)	(0·6)		
W = 0·050	10·70	0·454	0·354	–	0·1049
	(7·0)	(8·3)	(7·3)		
W = 0·025	11·39	0·426	0·376	–	0·1086
	(13·9)	(13·9)	(13·9)		
W = 0·010	11·81	0·410	0·390	–	0·1100
	(18·1)	(17·2)	(18·2)		

* Per cent error of the parameter estimates in parentheses.

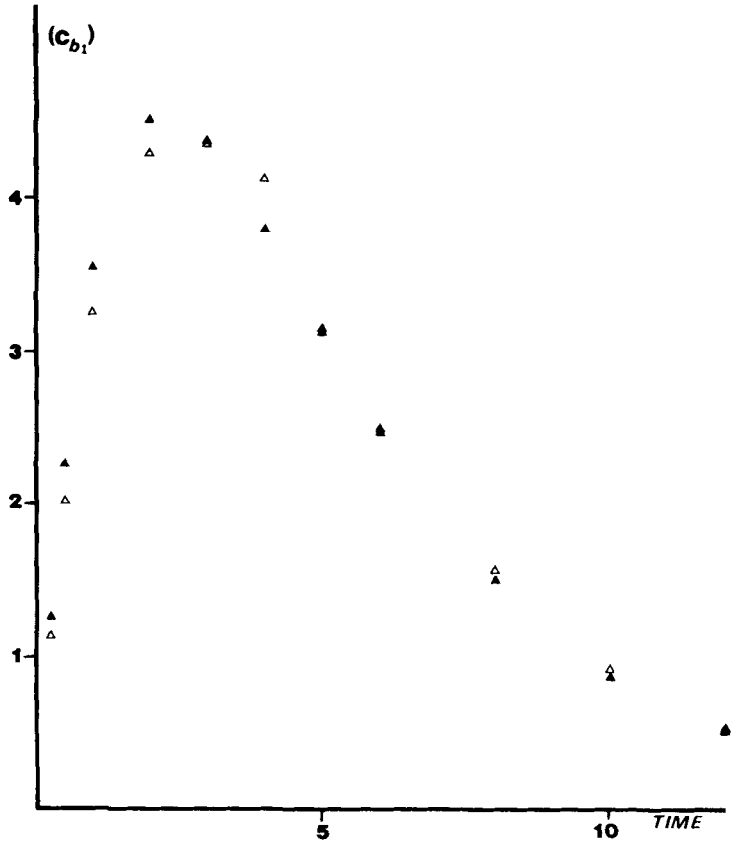

Figure 1. Experimental data (△), and data generated from equation 1 (▲) using the parameter estimates obtained by the method of residuals

The example considered indicates that the key step for the improvement of the parameter estimates relies on the appropriate choice of the initial estimates for W. Undoubtedly, a concentration–time plot of the experimental data along with the generated data based on the graphical estimates, would be of great value. This sort of graph is critical in deciding whether higher or lower values than the graphically estimated W should be utilized. When conclusive information from the plot cannot be drawn, it is advisable to allocate both higher and lower values to W and treat the data as shown in Figure 2. Thus, a parabola will be delineated and the choice of the appropriate value(s) for W will be facilitated. In the example, the low theoretical value of W used, i.e. 0·0825, produced a long, gently sloping valley at the left-hand side of the SS versus W plot. In cases, however, where a high value for W was assumed, the curves of the SS versus W plot were parabolas with sharp minima.

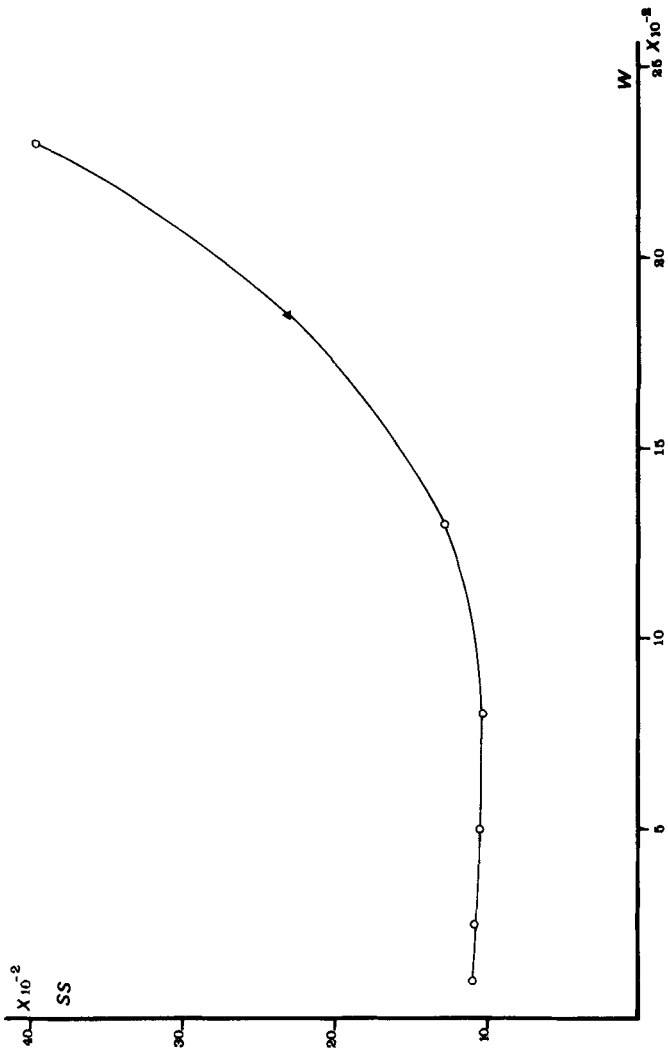

Figure 2. The impact of varying W on the SS value. The triangle represents results obtained by the method of residuals

The method described here appears to be the best approach to improving upon the graphically-determined estimates of the parameters of equation (1) when computer facilities are unavailable. Although essentially new, the method can be handled computationally by repeated calculations of a simple and universally available linear least-squares routine supplemented by a few additional calculations, as illustrated in the example. The method does not provide 'the best fit', as computer programs do; however, remarkable improvement of the estimates can be achieved. The determination of the importance of this method of parameter estimation in pharmacokinetics will require further experimentation, which it is hoped, this report will facilitate.

REFERENCES

1. Y. Bard, *Nonlinear Parameter Estimation*, Academic Press, New York, 1974, chap. 4.
2. A. J. Sedman and J. G. Wagner, *AUTOAN: A Decision-Making Pharmacokinetic Computer Program*, Publication Distribution Service, Ann Arbor, MI, 1974.
3. C. M. Metzler, G. L. Elfring and A. J. McEwen, *Biometrics*, **30**, 562 (1974).
4. C. C. Peck and B. B. Barrett, *J. Pharmacokinet. Biopharm.*, **7**, 537 (1979).
5. D. P. Thornhill and E. J. Schwerzel, *J. Pharm. Sci.*, **74**, 545 (1985).
6. M. Gibaldi and D. Perrier, *Pharmacokinetics*, Marcel Dekker, New York, 1982, p. 433.
7. J. G. Wagner and E. Nelson, *J. Pharm. Sci.*, **53**, 1392 (1964).
8. K. T. Muir and S. Riegelman, *J. Pharmacokinet. Biopharm.*, **7**, 685 (1979).
9. P. Macheras, *Biopharm. Drug Disposit.*, **8**, 47 (1987).
10. S. Niazi, *Textbook of Biopharmaceutics and Clinical Pharmacokinetics*, Appleton-Century-Crofts, New York, 1979, p. 157.