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Quick method for the calculation of the absorption rate constant of the linear one-compartment model using all available blood level data

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Several methods have been developed for the determination of the absorption rate constant since the latter is widely used as a measure of the rate of drug bioavailability. The classical method of residuals (Gibaldi and Perrier, 1975; Ritschel, 1976) along with the graphically solved equations given by Pidgeon and Pitlick (1977) and Barzegar-Jalali (1982a, b and c) constitute the graphical procedures for the estimation of the absorption rate constant.

However, these methods require either frequent sampling during the absorption phase or knowledge of the peak blood level. Moreover, not all graphical techniques do use all available data points, but a limited, appropriately chosen, number of them. Thus, from the statistical point of view, the validity of such a selection is in most cases weak.

In this communication a method is proposed which overcomes the difficulty of many samples at the absorptive phase and the uncertainty of the peak blood level while it is uitilizing all the data points available. Details for the derivation of the equations used in this method are as follows.

For a drug whose kinetics can be described by the linear one-compartment model, the drug concentration in the blood C is given by Eqn. 1 (Gibaldi and Perrier, 1975):

$$C = \frac{k_a FD}{V(k_a - K)}\left[e^{-Kt} - e^{-k_a t}\right] \quad (1)$$

in which t is time, k_a and K are first-order absorption and elimination rate constants, respectively, F is the fraction of dose D absorbed, and V is the apparent volume of distribution of the drug.

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It is also known (Gibaldi and Perrier, 1975) that the linear post-absorptive phase of the blood vs time for the model is described by Eqn. 2,

$$\ln C = \ln\left[\frac{k_a FD}{(k_a - K)V}\right] - Kt \tag{2}$$

The values of $k_a FD/(k_a - K)V$ and K are calculated from the intercept and the slope, respectively, of the line of best fit describing the post-absorptive phase, Eqns. 3 and 4:

$$\text{intercept} = \ln\frac{k_a FD}{(k_a - K)V} \tag{3}$$

$$\text{slope} = -K \tag{4}$$

Eqn. 3 can be rearranged to

$$\frac{k_a FD}{(k_a - K)V} = e^{(\text{intercept})} = Q \tag{5}$$

Thus, Eqn. 1 may be written as:

$$C = Q[e^{-Kt} - e^{-k_a t}] \tag{6}$$

Solving Eqn. 6 for k_a will result in the following equation:

$$k_a = -\frac{1}{t} \cdot \ln\left[e^{-Kt} - \frac{C}{Q}\right] \tag{7}$$

Eqn. 7 can be solved to give the value of k_a for each C_i, t_i data point since the values of K and Q can be obtained from Eqns. 4 and 5, respectively, i.e.

$$k_a = -\frac{1}{t_i}\ln\left[e^{-Kt_i} - \frac{C_i}{Q}\right] \tag{8}$$

The mean or the median of all calculated k_a values provides the best estimate of k_a. If a normal distribution of error is encountered, the use of mean would be favourable. Conversely, when the assumption of equal variance for all experimental data is not applicable, i.e. when outliers are present, the selection of median should be preferred. In the latter case, the use of median minimizes the effect of outliers on the parameter estimate (Endrenyi and Tang, 1980; Koup, 1981).

Although the calculation of k_a from Eqn. 8 requires minimum computation, it can be further simplified. Expressing k_a in terms of K, i.e.

$$k_a = nK \tag{9}$$

Substituting k_a from Eqn. 9 into Eqn. 8 and solving the resulting equation for n will give Eqn. 10.

$$n = -\frac{1}{Kt_i} \cdot \ln\left[e^{-Kt_i} - \frac{C_i}{Q}\right] \tag{10}$$

This equation was used to construct the curves presented in Fig. 1. Based on Fig. 1, the value of n can be estimated from values of the dimensionless quantities Kt_i and C_i/Q. Subsequently the value of k_a can be calculated from Eqn. 9.

Another point which requires mentioning is that Eqns. 8 and 10 are valid as long as

$$e^{-Kt_i} > \frac{C_i}{Q} \tag{11}$$

or

$$t_i < -\frac{1}{K} \cdot \ln\frac{C_i}{Q} \tag{12}$$

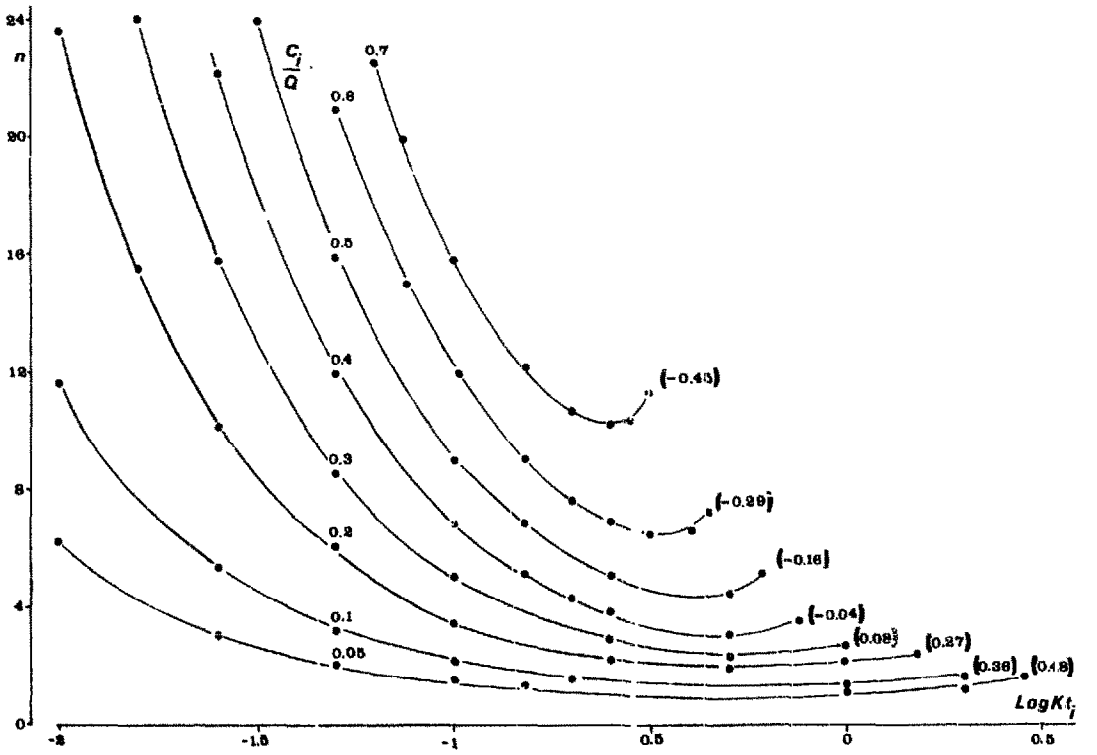

Fig. 1. Relationship between n and log Kt_i for different values of C_i/Q. The values in parentheses are the maxima of log Kt_i for each corresponding value of C_i/Q shown at the left-hand side, for which Eqn. 10 can be solved.

Accordingly, if for a certain C_i,t_i data point the inequality 11 is not satisfied, then Eqns. 8 and 10 cannot be solved. Apparently, a considerably higher value for C_i than that theoretically expected for a given set of data, K, Q and t_i, is the reason for the inapplicability of the inequality 11. Under these conditions this particular C_i,t_i data point is an outlier, but, it will be taken into account as giving a value for k_a higher than all others observed. If that is the case, the use of median is unequivocal. Caution should be exercised though with data points which belong to the terminal part of the elimination phase, since the inequality 11 is not true for any of these points. Here, however, the irrelevance of the inequality 11 is caused by the higher values of t_i than those imposed by the inequality 12.

The performance of the above method is shown in the following example. Concentrations expected at times 1, 2, 3, 4, 5, 8, 12, 24, 36 and 48 h were simulated for the equation

$$C = 40(e^{-0.06t} - e^{-0.6t}) \tag{13}$$

Error with a coefficient of variation of either 5 or 20% was assigned to the simulated concentrations such that 4 of the 9 observations were affected by the larger error. Three of the four outliers were randomly chosen among the concentrations observed between 5 and 48 h. In order to test the resistance of this method against outlying observations at the absorptive phase, either of the data points at times 1, 2 and 3 h were separately assumed to be affected by the larger error. Higher or lower values than those theoretically expected for each individual C_i were randomly assigned. The last 4 data points were used to construct the post-absorptive linear phase. The results of the absorption rate constant estimation using this method as well as the method of residuals are shown in Table 1. In this example, the developed method resulted in a definite value for $k_a = 0.58\ h^{-1}$ (3.3% error), regardless of which point was affected by the larger error. On the contrary, estimates of k_a were highly dependent on the particular point affected using the method of residuals. Although by neglect-

TABLE 1

VALUES OF ABSORPTION RATE CONSTANT CALCULATED USING THIS METHOD AND THE METHOD OF RESIDUALS. ACTUAL VALUE OF $k_a = 0.60\ h^{-1}$

Points affected with the larger error at the absorptive phase: (C_i,t_i) [a]	Absorption rate constant (h^{-1}) (% error)		
	This method [b]	Method of residuals	
		3 points used	2 points used [c]
(15.72,1)	0.58 (3.3)	0.65 (8.3)	0.57 (5.0)
(28.11,2)	0.58 (3.3)	0.61 (1.7)	0.61 (1.7)
(32.14,3)	0.58 (3.3)	0.99 (65.0)	0.65 (8.3)

[a] Values of all data points (C_i,t_i) used, except when assumptions of column 1 were operating: (14.93,1), (24.59,2), (28.14,3), (29.01,5), (29.31,8), (18.47,12), (11.37,24), (5.54,36), (2.13,48).

[b] Estimation of k_a was based on the median.

[c] The outlier was excluded.

ing the outlier in the regression analysis of the residuals better estimates were obtained, they were still dependent on the point affected by the larger error and basically inferior to that obtained by the method described.

In conclusion, the developed method behaves favourably in two important respects of pharmacokinetic analysis. First, the estimates obtained are quite resistant to the presence of outliers. Second, the method is capable of locating the outliers. The latter characteristic can facilitate other methods using regression analysis for the exclusion of outliers present. It is rather obvious that when outlying observations are non-existent this method and the method of residuals will give similar estimates.

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