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# Estimation of the absorption rate constant for a drug subject to non-linear elimination: comparison on non-linear regression and the $C_{max}$, $T_{max}$ approach

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## Summary

A method was developed for calculating the absorption rate constant ($k_a$) of drugs whose elimination involves a capacity-limited process. Pidgeon and Pitlick reported a method for calculating $k_a$ of drugs whose disposition obeys a first-order rate process. Their method obviates the need for large numbers of samples in the absorption phase and is less influenced by errors in data points prior to the maximum plasma concentration where the rate of change of concentration is rapid and error is likely. In the present study, a method for calculating the absorption rate constant of drugs whose elimination involves a capacity-limited process was designed based on Pidgeon and Pitlick's method, and the method was tested on theoretical data. On the comparison of $k_a$ obtained by nonlinear least-squares analysis with that obtained by the present method, the overall correlation for the fits obtained by non-linear least-squares analysis was superior. On the other hand, on the theoretical data (without error), the present method gave less percentage error in calculated $k_a$, and a good correlation was obtained for the fits. Consequently, for the calculation of $k_a$ of drugs whose elimination involves Michaelis-Menten metabolism, the present method is convenient when relatively few sample points are available in the absorption phase.

## 1. Introduction

Classical linear pharmacokinetics is based on the assumption that the drug elimination from the body obeys first-order kinetics. However, Wagner (1973) suggested that this assumption was not strictly valid even after administration of low doses. We (Hiura et al., 1984) reported that the disposition of hexobarbital in dogs could be approximated by a simple one-compartment model with Michaelis-Menten metabolism. Martis and Levy (1973) reported a method for calculating the absorption rate constant ($k_a$) of drugs whose elimination from a one-compartment model occurred by one or more apparent first-order processes in parallel with one capacity-limited elimination process. On the other hand, Pidgeon and Pitlick (1977, 1980) reported a unique method for the calculation of $k_a$ in the linear one-compartment model, in which $k_a$ is derived based on the maximum plasma concentration ($C_{max}$), the area under the blood concentration–time curve

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from the time of $C_{max}$ to infinity ($\infty$), and the elimination rate constant ($k_{el}$). The method obviates the need for large numbers of data points in the absorptive phase, and is less influenced by errors in data points prior to $C_{max}$, where the rate of change of concentration is rapid and error is likely. We (Kaneniwa et al., 1985) calculated $k_a$ of six barbiturates in rabbits by the Pidgeon and Pitlick method (Pidgeon and Pitlick, 1977, 1980) and the calculated $k_a$ values gave good agreement between the observed and calculated plasma concentrations.

No method has been reported for calculating $k_a$ of drugs whose elimination involves a capacity-limited process, except for the report of Martis and Levy (1973). In the present study, a method for calculating the absorption rate constant of drugs whose elimination involves a capacity-limited process was designed based on the Pidgeon and Pitlick's method (Pidgeon and Pitlick, 1977, 1980) by assuming a one-compartment model with first-order absorption, with no lag phase, and a single elimination pathway that is capacity-limited. The method was tested on theoretical data and $k_a$ of hexobarbital in dogs was also considered in the present study.

## Theoretical

If the disposition of a drug can be approximated by a simple one-compartment model with Michaelis-Menten metabolism, the rate of change of the amount of drug in the body ($A_b$) at any time t is given by:

$$\frac{dA_b}{dt} = k_a \cdot D_g - \frac{V_m \cdot V_d \cdot A_b}{K_m \cdot V_d + A_b} \qquad (1)$$

which is similar to Eqn. 1 of the paper by Pidgeon and Pitlick (1977), and where $D_g$ is the amount of drug in the gastrointestinal tract, $V_m$ and $K_m$ are the Michaelis-Menten parameters, and $V_d$ is the distribution volume. The model which can describe the limitation of present method is shown in Fig. 1. The amount of drug absorbed (i.e. the amount reaching the general circulation) up to time t ($A_{abs}$) is given by:

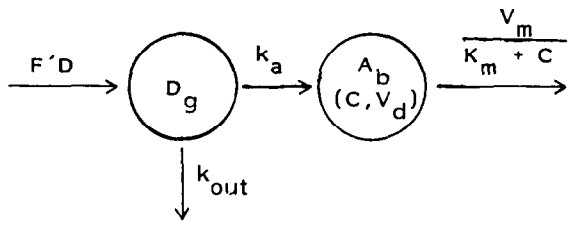


Fig. 1. The model which can describe the limitations of the present model. The rate constant $k_{out}$ is the sum of all rate constants which describe processes other than absorption accounting for loss of drug from the absorption site. The definitions of other rate constants are shown in text.

$$A_{abs} = F(F' \cdot D - D_g) \qquad (2)$$

which is similar to Eqn. 2 of the paper by Pidgeon and Pitlick (1977), and where F is the fraction of the dose (D) that is absorbed and F′ is the fraction of the dose that is available after passage through the liver. The amount of drug eliminated up to time T ($A_{el}$) is given by:

$$A_{el_T} = FF'D \frac{\int_0^T \frac{V_m \cdot C}{K_m + C} dt}{\int_0^\infty \frac{V_m C}{K_m + C} dt} \qquad (3)$$

which is also similar to Eqn. 3 of the paper by Pidgeon and Pitlick (1977). The amount of drug in the body at any time T is given by Eqn. 2 minus Eqn. 3

$$A_{b_T} = F \cdot F' \cdot D - F \cdot D \cdot g_T - F \cdot F' \cdot D \times \frac{\int_0^T \frac{V_m \cdot C}{K_m + C} dt}{\int_0^\infty \frac{V_m \cdot C}{K_m + C} dt} \qquad (4)$$

At the time of maximum plasma concentration ($T_{max}$), the rate of change of the amount of drug in the body is zero, and by rearranging of Eqn. 1:

$$k_a \cdot D_{gT_{max}} = \frac{V_m \cdot V_d \cdot A_{bT_{max}}}{K_m \cdot V_d + A_{bT_{max}}} \qquad (5)$$

Substituting Eqn. 4 into Eqn. 5 and solving for $D_g$:

$$D_{gT_{max}} = \frac{V_m}{K_m + C_{max}} F \cdot F' \cdot D \times \left( 1 - \frac{\int_0^T \frac{V_m \cdot C}{K_m + C} dt}{\int_0^\infty \frac{V_m \cdot C}{K_m + C} dt} \right) \times \left( k_a + \frac{F \cdot V_m}{K_m + C_{max}} \right)^{-1} \quad (6)$$

Eqn. 5 may be rearranged to:

$$k_a \cdot D_{gT_{max}} = \frac{V_m}{K_m + C_{max}} V_d \cdot C_{max} \quad (7)$$

Substituting Eqn. 6 into the left hand side of Eqn. 7 and rearranging it, we obtain Eqn. 8:

$$C_{max} = \frac{k_a}{k_a + \frac{F \cdot V_m}{K_m + C_{max}}} \left( \frac{F \cdot F' \cdot D}{V_d} \right) \times \left( 1 - \frac{\int_0^{T_{max}} \frac{V_m \cdot C}{K_m + C} dt}{\int_0^\infty \frac{V_m \cdot C}{K_m + C} dt} \right) \quad (8)$$

Now

$$\int_0^\infty \frac{V_m \cdot C}{K_m + C} dt = \frac{F \cdot F' \cdot D}{V_d}$$

and

$$\int_0^\infty \frac{V_m \cdot C}{K_m + C} dt - \int_0^{T_{max}} \frac{V_m \cdot C}{K_m + C} dt = \int_{T_{max}}^\infty \frac{V_m \cdot C}{K_m + C} dt$$

Substituting these relations into Eqn. 8 and solving for $k_a/F$, we have:

$$\frac{k_a}{F} = \frac{\frac{V_m}{K_m + C_{max}}}{\int_{T_{max}}^\infty \frac{V_m \cdot C}{K_m + C} dt / C_{max} - 1} \quad (9)$$

The left hand side of Eqn. 9, $k_a/F = K_a$, represents the overall rate constant for all processes that occur during absorption which cause a decrease in the amount of drug in the gastrointestinal tract. Substitution of $k_a/K_a$ for F in Eqn. 9 gives:

$$K_a = \frac{\frac{V_m}{K_m + C_{max}}}{\int_{T_{max}}^\infty \frac{V_m \cdot C}{K_m + C} dt / C_{max} - 1} \quad (10)$$

On the other hand, if $F = 1$ is assumed, an equation equivalent to Eqn. 10 can be derivated in different form. At $T_{max}$:

$$k_a D_{gT_{max}} = k_a \cdot D\, e^{-k_a T_{max}} = \frac{V_m \cdot V_d \cdot C_{max}}{K_m + C_{max}} \quad (7')$$

and

$$k_a = \frac{\frac{V_m}{K_m + C_{max}}}{\frac{D}{V_d \cdot C_{max}}} \cdot e^{k_a T_{max}} \quad (11)$$

Eqn. 11 may be rearranged to:

$$f(k_a) = \frac{\frac{V_m}{K_m + C_{max}}}{\frac{D}{V_d \cdot C_{max}}} e^{k_a T_{max}} - k_a \quad (11')$$

Eqn. 11' can be solved by Newton-Raphson method (Melzak, 1973).

## Materials and Methods

### *Materials*

Hexobarbital was obtained commercially

(Teikoku Kagaku Sangyo Co., Osaka) and was used without further purification. All other reagents were commercial products of special grade.

*Analytical method*

The concentrations of hexobarbital in the plasma were determined by gas chromatography with a hydrogen flame ionization detector, as described in a previous report (Kaneniwa et al., 1979).

*Animal experiment*

Adult male mongrel dogs weighing 10 kg were used, and the weight of the dogs was held constant by controlling food intake throughout the experimental period. Two dogs were used repeatedly at one-week intervals to test various doses. After being fasted for 24 h, with water available ad libitum, hexobarbital was administered orally in solution at various doses. Enzyme induction by hexobarbital was not detected under this dosage schedule. Blood was withdrawn at predetermined intervals from the foreleg vein, and plasma was separated. The drug solution was prepared at a concentration of 10 mg/ml for oral administration. This was done by adding the drug and an equimolar amount of NaOH to water shortly before each experiment.

*Data analysis*

As the disposition of hexobarbital in dogs could be approximated by a simple one-compartment model with Michaelis-Menten metabolism (Hiura et al., 1984), the absorption rate constant was calculated by using Eqn. 10 or Eqn. 11. The values of $V_m$ and $K_m$ were obtained by i.v. administration in the same dog (Table 1). The relative error in $T_{max}$ can be calculated as follows:

$$\text{Relative error} = T_{max \cdot est}/T_{max \cdot obs} \tag{12}$$

where $T_{max \cdot est}$ and $T_{max \cdot obs}$ are estimated and observed $T_{max}$, respectively. Estimated $T_{max}$ can be calculated as follows with the use of $K_a$ obtained by Eqn. 10 or Eqn. 11:

$$T_{max \cdot est} = \ln\left(\frac{K_a}{\frac{V_m}{(K_m + C_{max})}}\right) \times \left(K_a - \frac{V_{max}}{K_m + C_{max}}\right)^{-1} \tag{13}$$

The absorption rate constant obtained by using Eqn. 10 or Eqn. 11 was multiplied by the relative error (Eqn. 12), and thus corrected for the error of determination of $T_{max}$.

In order to compare $k_a$ calculated by Eqn. 10 or Eqn. 11 with the result of non-linear regression analysis, plasma data were simultaneously fitted to Eqns. 14 and 15 with use of the non-linear least-squares program MULTI (RUNGE; Yamaoka and Nakagawa, 1983), in which the differential equations were solved by the Runge-Kutta-Gill method:

$$\frac{dC}{dt} = \frac{k_a \cdot D_g}{V_d} - \frac{V_m \cdot C}{K_m + C} \tag{14}$$

$$\frac{dD_g}{dt} = -k_a \cdot D_g \tag{15}$$

with initial conditions $C_0$ ($= D/V_d$) $= 0$ and $D_{g \cdot 0}$ (initial amount of drug in the gastrointestinal tract) $= F \cdot D$ at time (t) zero. Distribution volume was obtained by i.v. administration in the same dog. Because hexobarbital is completely absorbed from the gastrointestinal tract (Hiura et al., 1984),

TABLE 1

PHARMACOKINETIC PARAMETERS OF HEXOBARBITAL FOLLOWING INTRAVENOUS ADMINISTRATION IN DOGS [a]

| Dog | Dose (mg/kg) | $V_d$ (ml/kg) | $V_m$ (μg/ml/h) | $K_m$ (μg/ml) | F′ |
|---|---|---|---|---|---|
| A | 10 | 862 | 4.8 | 11.5 | 0.74 |
| | 20 | 816 | 4.9 | 11.8 | 0.82 |
| | 30 | 754 | 5.2 | 11.9 | 0.94 |
| | mean | 811 | 5.0 | 11.7 | 0.83 |
| | S.E. | 31 | 0.1 | 0.1 | 0.06 |
| B | 10 | 1111 | 10.5 | 10.7 | 0.62 |
| | 20 | 901 | 9.7 | 10.9 | 0.79 |
| | 30 | 737 | 9.3 | 10.4 | 0.80 |
| | mean | 916 | 9.8 | 10.7 | 0.74 |
| | S.E. | 108 | 0.4 | 0.1 | 0.06 |

[a] Data are from Hiura et al. (1984).

F equals unity in the present study and $K_a$ equals $k_a$. The fraction of the dose that is available after passage through the liver was taken from a previous report (Hiura et al., 1984), in which F′ was calculated as follows:

$$F' = \frac{\int_0^\infty \frac{V_m \cdot C}{K_m + C} dt}{C_0} \quad (16)$$

where $C_0$ is the zero-time plasma concentration of drug following intravenous administration. The overall correlation ($r^2$) for the fits was calculated from Eqn. 17:

$$r^2 = \left(\Sigma(\overline{obs} - obs_i)^2 - \Sigma(calc_i - obs_i)^2\right) / \Sigma(\overline{obs} - obs_i)^2 \quad (17)$$

where $\overline{obs}$ is the mean of observed plasma concentrations, $obs_i$ is the ith point of observed plasma concentrations, and $calc_i$ is the ith point of calculated plasma concentrations in solving the differential Eqns. 14 and 15 by the Runge-Kutta-Gill method.

## Results and Discussion

The fact that the disposition of hexobarbital involves a capacity-limited elimination process was already reported (Hiura et al., 1984). It is clear that the elimination of hexobarbital from plasma following oral administration is also capacity-limited. In all methods (i.e. Eqns. 10 and 11, and non-linear regression analysis), the calculated values were in good agreement with the observed values.

The pharmacokinetic parameters used in these methods to calculate $k_a$ are shown in Table 1; these parameters were obtained from the intravenous data. Because the Michaelis-Menten parameters were almost the same in each dog regardless of the dose, intra-subject variation may be negligible. However, inter-subject variation of $V_m$ may be significant, since $V_m$ of dog B was 2-fold larger than that of dog A. Detailed discussions of these parameters were presented in the previous report (Hiura et al., 1984).

Pidgeon and Pitlick (1980) tested their method to obtain $k_a$ on theoretical data with error introduced only in the absorption phase or throughout all concentrations, and compared the deviation of $k_a$ from theoretical values with that in the case of non-linear least-squares analysis. They suggested that there was no difference in percentage error of calculated $k_a$ between these methods, but in the case of data with large errors introduced only in the absorption phase, their method was more accurate than nonlinear least-squares analysis. A comparison of $k_a$ obtained by non-linear least-squares analysis with that obtained by present methods is shown in Table 2. Dog B has higher $k_a$ but lower F′ presumably because of its higher metabolizing capacity, while A has lower $k_a$ and greater F′. The overall correlation for the fits obtained by non-linear least-squares analysis was better than that obtained by present methods. The errors attendant on the estimation of $V_m$, $K_m$, and $C_{max}$ were complicated in the present study, in contrast with the case of Pidgeon and Pitlick, in which errors attendant on estimation of elimination rate constant did not influence the calculation of $k_a$ for a first-order rate process.

On the other hand, Pidgeon and Pitlick (1980) reported that the percentage error in the estimation of $k_a$ by their method or the non-linear least-squares method increased with increasing input $k_a$. As shown in Table 2, in the case of dog B at the dose of 30 mg/kg, we could not obtain $k_a$ from Eqn. 10 because in this case the denominator of Eqn. 10 is negative; this might be due to random error of observed $C_{max}$ or variation of the Michaelis-Menten constant depending on the route of administration. When observed $C_{max}$ of dog B at the dose of 30 mg/kg was reduced to the level which keeps the positive sign of denominator of Eqn. 10, calculated $k_a$ and $r^2$ were 6.844 and 0.988, respectively.

To ascertain the validity of Eqn. 10 or Eqn. 11, theoretical data (without error) generated from $k_a$ obtained by the non-linear least-squares analysis and the parameters shown in Table 1 were analyzed. As shown in Table 3, on the theoretical data without error, calculated $k_a$ obtained by Eqn.

TABLE 2

ESTIMATES OF $k_a$ DERIVED BY NON-LINEAR REGRESSION ANALYSIS (MULTI(RUNGE)), EQN. 10 [a] OR EQN. 11 [a]

| Dog | Dose (mg/kg) | $k_a$ ($h^{-1}$) | | | $r^2$ | | |
|---|---|---|---|---|---|---|---|
| | | RUNGE | Eqn. 10 | Eqn. 11 | RUNGE | Eqn. 10 | Eqn. 11 |
| A | 10 | 1.799 | 1.632 | 1.425 | 0.994 | 0.991 | 0.975 |
| | 20 | 2.831 | 2.280 | 1.734 | 0.998 | 0.990 | 0.950 |
| | 30 | 1.189 | 0.914 | 1.271 | 0.959 | 0.924 | 0.957 |
| | mean | 1.940 | 1.609 | 1.477 | 0.984 | 0.968 | 0.961 |
| | S.E. | 0.479 | 0.395 | 0.136 | 0.012 | 0.022 | 0.007 |
| B | 10 | 1.935 | 2.790 | 1.501 | 0.878 | 0.800 | 0.834 |
| | 20 | 1.918 | 2.803 | 2.078 | 0.968 | 0.919 | 0.965 |
| | 30 | 4.312 | | 2.676 | 0.994 | | 0.970 |
| | mean | 2.722 | 2.797 | 2.085 | 0.947 | 0.860 | 0.923 |
| | S.E. | 0.795 | | 0.339 | 0.035 | | 0.045 |

[a] The values represent the corrected $k_a$ obtained by multiplying the values of Eqns. 10 and 11 by Eqn. 12.

The sampling schedules of dog A were 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, and 9 h for 10 mg/kg, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 h for 20 mg/kg, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 14 h for 30 mg/kg.

The sampling schedules of dog B were 0.5, 1, 1.5, 2, 2.5, 3, and 3.5 h for 10 mg/kg, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, and 6 h for 20 mg/kg, and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 h for 30 mg/kg.

$T_{max \cdot obs}$ of dog A were 1.5 h for 10 mg/kg, 1.5 h for 20 mg/kg, and 2 h for 30 mg/kg.

$T_{max \cdot obs}$ of dog B were all 1 h at doses of 10, 20, and 30 mg/kg.

10 gave a smaller percentage error and good $r^2$. The percentage errors for $k_a$ of Eqn. 11 were slightly larger than that of Eqn. 10 and this may be attributed to the fact that Eqn. 11 is based on only $C_{max}$ and $T_{max}$ data, although Eqn. 10 reflects all the data points following $T_{max}$. From these results, it appears that Eqn. 10 is theoretically valid; the attendant minimum percentage error with the theoretical data may be associated with the calculation of areas

$$\left( \int_{T_{max}}^{\infty} \frac{V_m \cdot C}{K_m + C} dt \right)$$

TABLE 3

ESTIMATES OF $k_a$ DERIVED BY APPLYING EQN. 10 OR EQN. 11 TO THEORETICAL PLASMA CONCENTRATION DATA [a]

| Dog | Dose (mg/kg) | $k_a$ ($h^{-1}$) | | % error | | $r^2$ | |
|---|---|---|---|---|---|---|---|
| | | Eqn. 10 | Eqn. 11 | Eqn. 10 | Eqn. 11 | Eqn. 10 | Eqn. 11 |
| A | 10 | 1.711 | 1.428 | 4.89 | 20.62 | 0.999 | 0.982 |
| | 20 | 2.805 | 3.127 | 0.92 | 10.46 | 1.000 | 0.999 |
| | 30 | 1.188 | 1.289 | 0.08 | 8.41 | 1.000 | 0.997 |
| | mean | | | 1.96 | 13.16 | 1.000 | 0.993 |
| | S.E. | | | 1.48 | 3.78 | 0.000 | 0.005 |
| B | 10 | 1.786 | 1.599 | 7.70 | 17.36 | 0.996 | 0.975 |
| | 20 | 1.885 | 2.068 | 1.72 | 7.82 | 1.000 | 0.998 |
| | 30 | 4.520 | 1.663 | 4.82 | 61.43 | 1.000 | 0.873 |
| | mean | | | 4.75 | 28.87 | 0.999 | 0.949 |
| | S.E. | | | 1.73 | 16.51 | 0.001 | 0.038 |

[a] The values represent the corrected $k_a$ obtained by multiplying the values of Eqns. 10 and 11 by Eqn. 12.

The calculating intervals are all the same as shown in the footnote of Table 2.

by means of the linear trapezoidal rule.

Consequently, the present method is applicable for the estimation of $k_a$ of drugs whose elimination involves the Michaelis-Menten metabolism, and is convenient when few data points are available in the absorption phase. However, minimum data points are necessary to ascertain the lack of lag phase and first-order absorption. On the other hand, by deciding the reasonable $T_{max}$, reasonable $k_a$ can be obtained in the case of multiple $C_{max}$ and $T_{max}$. The value of $k_a$ obtained by Eqn. 10 is also useful as an initial value for the non-linear least-squares method and a more reliable value can be obtained by the non-linear least-squares method.

## References


Hiura, M., Kawashima, H. and Kaneniwa, N., Hepatic first-pass metabolism of hexobarbital in rabbits and dogs. *Int. J. Pharm.*, 18 (1984) 185–193.

Kaneniwa, N., Hiura, M. and Funaki, T., The absorption kinetics of barbiturates in rabbits. *Int. J. Pharm.*, 26 (1985) 157–164.

Melzak, Z.A., *Companion to Concrete Mathematics*, John Wiley and Sons, 1973.

Martis, L. and Levy, R.H., Bioavailability calculation for drugs showing simultaneous first-order and capacity-limited elimination kinetics. *J. Pharmacokin. Biopharm.*, 1 (1973) 283–294.

Pidgeon, C. and Pitlick, W.H., Unique approach for calculation of absorption rate constant. *Res. Commun. Chem. Pathol. Pharmacol.*, 18 (1977) 467–475.

Pidgeon, C. and Pitlick, W.H., Unique approach for calculation of first-order absorption rate constants from blood or urine data. *J. Pharmacokin. Biopharm.*, 8 (1980) 203–214.

Yamaoka, K. and Nakagawa, T., A non-linear least squares program based on differential equations, MULTI (RUNGE), for microcomputers. *J. Pharmacobio-Dyn.*, 6 (1983) 595–606.

Wagner, J.G. and Nelson, E., Per cent absorbed time plots derived from blood level and/or urinary excretion data. *J. Pharm. Sci.*, 52 (1963) 610–611.

Wagner, J.G., Properties of the Michaelis-Menten equation and its integrated form which are useful in pharmacokinetics. *J. Pharmacokin. Biopharm.*, 1 (1973) 103–121.