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Application of the Pidgeon-Pitlick method for calculation of the absorption rate constant of drugs whose disposition can be described by the two-compartment open model

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Summary

A method for calculating the absorption rate constant of drugs whose disposition can be described by the two-compartment open model was developed based on Pidgeon and Pitlick's method, which does not use data points prior to the maximum plasma concentration and therefore is not influenced by errors in the data before the peak concentration. It was shown that the method is applicable for estimation of the absorption rate constant of such drugs, and is particularly convenient when few data points are available in the absorption phase. The absorption properties of cimetidine in rats were also studied by means of the present method. The results suggested that the absorption rate of cimetidine is increased by increasing the volume of water taken with the drug and by co-administration of metoclopramide, and is decreased by co-administration of atropine.

Introduction

Cimetidine is a specific histamine H_2-receptor antagonist which inhibits gastric acid secretion and is used for the treatment of gastrointestinal peptic ulcer (Burland et al., 1975). Many reports dealing with the renal excretion mechanism (Mckinney et al., 1981; Weiner and Roth, 1981; Mckinney and Speeg, 1982; Cacini et al., 1982; Rennick et al., 1984) have been published, since cimetidine is mainly eliminated by renal excretion, but little is known about the absorption properties except for a report by Griffiths et al. (1977). On the other hand, many methods have been reported for the calculation of absorption rate constant (Wagner and Nelson, 1973; Loo and Riegelman, 1968; Wagner, 1974; Pidgeon and Pitlick, 1977, 1980; Gerardin et al., 1983). However, it is very difficult to obtain the absorption rate constant (k_a) accurately and usually the different methods yield dissimilar estimated values of k_a when applied to the same data set. This discrepancy is due to the differences in the algorithms used for calculation or to the error associated with the data. Since the absorption rate tends to be faster than the elimination rate, the rate of change of concentration with time will be most rapid during the

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absorption phase and measurements will be particularly susceptible to error. Most methods (Wagner and Nelson, 1963; Loo and Riegelman, 1968; Wagner, 1974; Gerardin et al., 1983) utilize primarily the data points in the absorption phase to obtain an estimate of k_a, and consequently, deviations from the true k_a may be expected.

Pidgeon and Pitlick (1977, 1980) reported a unique method for the calculation of k_a in the linear one-compartment model; in their method k_a is derived from the maximum plasma concentration (C_{max}), the area under the blood concentration time curve from the time of C_{max} to infinity ($\int_{T_{max}}^{\infty} C\,dt$), and the elimination rate constant (k_{el}). The method obviates the need for large numbers of data points in the absorption phase, and is less influenced by errors in data points prior to C_{max}. We (Kaneniwa et al., 1985a) calculated k_a values of six barbiturates in rabbits by the Pidgeon and Pitlick method (1977; 1980) and found a good correlation between k_a and partition coefficient. However, the Pidgeon and Pitlick method (1977, 1980) cannot be applied directly for the calculation of k_a of drugs whose disposition is described by the two-compartment model.

Since the disposition of cimetidine can be described by the two-compartment model in rats (Kaneniwa et al., 1985b), the Pidgeon and Pitlick method cannot be applied directly. However, in the present study, a method for calculating the absorption rate constant of drugs whose disposition is described by the two-compartment model was developed based on the Pidgeon and Pitlick method (1977, 1980), and the reliability of the present method was evaluated by comparing the results with those obtained by non-linear least-squares analysis (Yamaoka et al., 1981). We (Kaneniwa et al., 1985b) have already reported that the absorption of cimetidine is influenced by the gastric emptying rate, and thus k_a of cimetidine in rats was estimated by using the present method.

Theoretical

If the absorption of a drug can be approximated by a two-compartment model (see footnote b of Table 1), the mass-balances of the drug in the body at any time t are given by:

$$\frac{dA_1}{dt} = k_a D_g - (k_{10} + k_{12})A_1 + k_{21}A_2 \quad (1)$$

$$\frac{dA_2}{dt} = k_{12}A_1 - k_{21}A_2 \quad (2)$$

$$\frac{dD_g}{dt} = -\frac{k_a}{f} D_g \quad (3)$$

where A_1, A_2 and D_g are the amounts of drug in the central compartment, in the peripheral compartment, and in the gastrointestinal tract, respectively, k_a is the absorption rate constant, k_{10} is the elimination rate constant, and k_{12} and k_{21} are the microscopic rate constants associated with movements of drug from compartment 1 to compartment 2 and from compartment 2 to compartment 1, respectively. At time $t = 0$, the initial amounts of A_1 and A_2 are equal to zero and the initial amount of D_g is equal to $f' \cdot D$. The amount of drug absorbed (i.e. the amount reaching the general circulation) up to time t (A_{abs}) is given by:

$$A_{abs} = f(f' \cdot D - D_g) \quad (4)$$

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:

$$A_{el} = f \cdot f' \cdot D \frac{\int_0^T C\,dt}{\int_0^{\infty} C\,dt} \quad (5)$$

The amount of drug in the body at time t (A_b) is given by Eqn. 4 minus Eqn. 5:

$$A_b = f \cdot f' \cdot D - f \cdot D_g - f \cdot f' \cdot D \frac{\int_0^T C\,dt}{\int_0^{\infty} C\,dt} \quad (6)$$

At the time of maximum plasma concentration (T_{max}) the rate of change of the amount of drug in

the body is zero:

$$k_a \cdot D_{g \cdot T_{max}} = (k_{10} + k_{12})A_{1 \cdot max} - k_{21}A_{2 \cdot T_{max}} \quad (7)$$

The amount in the peripheral compartment at T_{max} ($A_{2 \cdot T_{max}}$) is given by the Loo-Riegelman method (1968):

$$A_{2 \cdot T_{max}} = A_{2 \cdot T_{max-1}} \cdot e^{-k_{21} \Delta t} + \frac{k_{12}A_{1 \cdot T_{max-1}}}{k_{21}}(1 - e^{-k_{21} \Delta t}) + \frac{k_{12}(\Delta t)^2 \Delta CV_1}{2\Delta t} \quad (8)$$

where $A_{1 \cdot T_{max-1}}$ and $A_{2 \cdot T_{max-1}}$ are the amounts in compartment 1 and compartment 2 at the time interval just prior to T_{max}, respectively. On the other hand, $A_b = A_1 + A_2$, and Eqn. 7 gives:

$$k_a D_{g \cdot T_{max}} = (k_{10} + k_{12} + k_{21})A_{1 \cdot max} - k_{21}A_{b \cdot T_{max}} = (\lambda_1 + \lambda_2)A_{1 \cdot max} - k_{21}A_{b \cdot T_{max}} \quad (9)$$

Substituting Eqn. 6 into $A_{b \cdot T_{max}}$ in Eqn. 9 and solving for D_g:

$$D_{g \cdot T_{max}} = \left[(\lambda_1 + \lambda_2)A_{1 \cdot max} - k_{21} \cdot f \cdot f' \cdot D\left(1 - \frac{\int_0^{T_{max}} C\,dt}{\int_0^{\infty} C\,dt}\right)\right] \times [k_a - k_{21}f]^{-1} \quad (10)$$

Equation 7 may be rearranged to:

$$D_{g \cdot T_{max}} = \frac{(\lambda_1 + \lambda_2 - k_{21})A_{1 \cdot max} - k_{21}A_{2 \cdot T_{max}}}{k_a} \quad (11)$$

From the relations between Eqns. 10 and 11:

$$\frac{k_a}{f} = \frac{A_{1 \cdot max}(k_{21} - \lambda_1 - \lambda_2) + k_{21}A_{2 \cdot T_{max}}}{A_{1 \cdot max} + A_{2 \cdot T_{max}} - f \cdot f' \cdot D\left(1 - \frac{\int_0^{T_{max}} C\,dt}{\int_0^{\infty} C\,dt}\right)} \quad (12)$$

Now

$$\int_0^{\infty} C\,dt - \int_0^{T_{max}} C\,dt = \int_{T_{max}}^{\infty} C\,dt$$

and

$$\int_0^{\infty} C\,dt = k_{21} \cdot f \cdot f' \cdot D/(V_1 \cdot \lambda_1 \cdot \lambda_2)$$

Substituting these relations into Eqn. 12 and solving for k_a/f, we have:

$$\frac{k_a}{f} = \frac{C_{max}(k_{21} - \lambda_1 - \lambda_2) + \frac{k_{21}A_{2 \cdot T_{max}}}{V_1}}{C_{max} + \frac{A_{2 \cdot T_{max}}}{V_1} - \lambda_1 \cdot \lambda_2 \int_{T_{max}}^{\infty} C\,dt/k_{21}} \quad (13)$$

The left hand side of Eqn. 13, k_a/f, represents the overall rate constant for all processes that occur during absorption which cause a decrease of the amount of drug in the gastrointestinal tract. If complete absorption can be presumed, the left hand side of Eqn. 13 represents k_a.

Materials and Methods

Materials

Cimetidine was obtained from Industrie Chimiche Farmaceutiche Italiane (Italy). Metiamide and metoclopramide were kindly supplied by Smith Kline Fujisawa Co. (Tokyo, Japan) and by Takeshima Pharmaceutical Co. (Tokyo, Japan), respectively. All other chemicals were of reagent grade.

Animal experiments

Male Wistar rats weighing ca. 250 g (9–11

weeks old) were fasted for 18 h before experiments, and a cannula (Atom disposable intravenous catheter 2 Fr; Atom Co., Tokyo, Japan) was inserted into the femoral artery under light ether anesthesia. Cimetidine (25.0, 50.0 or 100.0 mg/kg) was dissolved in 1 ml of distilled water; a minimum amount of hydrochloric acid was used for the dissolution of cimetidine (the concentrations of hydrochloric acid were 0.085 w/v% and 0.170 w/v% at the doses of 50.0 mg/kg and 100.0 mg/kg, respectively). The pH values of all drug solutions were almost 6.8 after preparation. After awakening of the rats, predetermined doses of cimetidine were administered orally through a gastric tube. The number of rats used for each study is shown in each table. Blood samples (ca. 0.25 ml) were collected periodically from the femoral artery into heparinized glass centrifuge tubes. Plasma was separated and kept frozen until analyzed.

Drug treatments

The doses of atropine sulfate and metoclopramide hydrochloride were 1 mg/kg in both cases and the drugs were dissolved in 1 ml of normal saline. Each dosage was administered intraperitoneally 30 min prior to cimetidine administration.

Analytical method

The concentrations of cimetidine in plasma were determined by high-performance liquid chromatography, as described in a previous report (Kaneniwa et al., 1985b). To a micro-centrifuge tube containing 100 μl of plasma, 100 μl of the internal standard solution (metiamide 50 μg/ml) and 100 μl of 6 N sodium hydroxide were added. Ethyl acetate (4.5 ml) was then added and the whole was shaken for 10 min. After centrifugation (3000 rpm, 10 min), 4 ml of the organic phase was transferred to a dry test tube and evaporated to dryness. The residue was dissolved in 100 μl of distilled water, and aliquots (10 μl) of this solution were injected into the chromatograph. A Shimadzu LC-3A (Shimadzu Seisakusho, Japan) connected to a Model 7125 sample loop injector (fitted with a 20 μl sample loop; Rheodyne) was used for the analytical system. A variable-wavelength UV detector (SPD-2A, Shimadzu Seisakusho, Japan) was used to monitor the effluent at 228 nm (sensitivity: 0.01 a.u.f.s). The chromatographic mobile phase, which consisted of acetonitrile–water–1/30 M sodium phosphate buffer (pH 4.9, 40:39:1 v/v), was pumped through a Hiber Lichrosorb RP-8 column (250 × 4.0 mm, 10 μm particle size; Merck) at the rate of 1.0 ml/min. The column temperature was kept at 40°C by using a CTO-2A column oven (Shimadzu Seisakusho, Japan). Peak areas for quantitation of cimetidine were integrated with a Chromatopac C-R1P (Shimadzu Seisakusho, Japan).

Data analysis

As the disposition of cimetidine in rats could be approximated by a two-compartment model (Kaneniwa et al., 1985b), the absorption rate constant was calculated by using Eqn. 13. The relative error in T_{max} can be calculated from Eqn. 14 as follows:

$$\text{Relative error} = T_{max \cdot est}/T_{max \cdot obs} \tag{14}$$

where $T_{max \cdot est}$ and $T_{max \cdot obs}$ are estimated and observed T_{max}, respectively. The absorption rate constant obtained by using Eqn. 13 was multiplied by the relative error (Eqn. 14), and thus corrected for the error of determination of T_{max}. Estimated T_{max} can be obtained by calculating Eqn. 15 sequentially at microscopic time intervals:

$$C = (C_1)_{po}\, e^{-\lambda_1 \cdot t} + (C_2)_{po}\, e^{-\lambda_2 \cdot t} - \left((C_1)_{po} + (C_2)_{po}\right) e^{-k_a \cdot t} \tag{15}$$

where

$$(C_1)_{po} = \frac{k_a \cdot F \cdot D(k_{21} - \lambda_1)}{V_1(k_a - \lambda_1)(\lambda_2 - \lambda_1)},$$

$$(C_2)_{po} = \frac{k_a \cdot F \cdot D(k_{21} - \lambda_2)}{V_1(k_a - \lambda_2)(\lambda_1 - \lambda_2)}$$

and $F = f \cdot f'$

As the rate of change of the concentration of drug is zero at T_{max} (i.e. $dC/dt = 0$), $T_{max \cdot est}$ can be

also obtained by differentiating Eqn. 15 (Wagner, 1979), in which successive values for $T_{max \cdot est}$ are substituted into the equation until the derivative is approximately equal to zero by the iterative trial and error method. In order to compare k_a calculated by Eqn. 13 with the result of non-linear least-squares analysis, the plasma data were fitted to Eqn. 15 with the use of the non-linear least-squares program MULTI (Yamaoka et al., 1981). The initial value of k_a was calculated by Loo-Riegerman method (1968) and other initial parameter values were obtained from intravenous data for non-linear least-squares analysis. Because it appears that cimetidine is completely absorbed from the gastrointestinal tract (Kaneniwa et al., 1985b), F is equal to unity in the present study. The overall correlation (r^2) for the fits was calculated from Eqn. 16:

$$r^2 = \left(\sum (\overline{obs} - obs_i)^2 - \sum (calc_i - obs_i)^2 \right) / \sum (\overline{obs} - obs_i)^2 \qquad (16)$$

where $\overline{obs}$ is the mean of observed plasma concentration obs_i is the i^{th} point of the observed plasma concentration, and $calc_i$ is the i^{th} point of calculated plasma concentrations (Eqn. 15). The statistical moments (MRT, the mean residence time; MAT, the mean absorption time) were calculated by using Eqns. 17 and 18 (Yamaoka et al., 1978; Riegelman and Collier, 1980)

$$MRT = \int_0^\infty tC\ dt / \int_0^\infty C\ dt \qquad (17)$$

$$MAT = MRT_{iv} - MRT_{po} \qquad (18)$$

Results and Discussion

Although it is known that the renal excretion of cimetidine involves a capacity-limited tubular secretion (Mckinney et al., 1981; Weiner and Roth, 1982; Mckinney and Speeg, 1982; Cacini et al., 1982; Rennick et al., 1984), in the dosage range used in the present study the disposition of cimetidine in rats can be approximated by a linear process (Kaneniwa et al., 1985b) and this is also evident from the results shown in Table 1; i.e. the areas under the plasma concentration–time curve (AUC) increased proportionally with the dose, and the rate constant was not dose-dependent. Plasma concentration–time course plots following the oral administration of cimetidine to rats are shown in Fig. 1. In both methods (i.e. Eqn. 13 and non-linear least-squares analysis), the calculated values were in good agreement with the observed values. The pharmacokinetic parameters used in the two methods for calculation of k_a are shown in Table 1; these parameters were obtained from the oral data based on the two-compartment model by the non-linear least-squares analysis. Although it appears that the oral data can be fitted to the one-compartment model, if the disposition of cimetidine is the same after oral and intravenous administrations, it should be fitted to the two-compartment model because the disposition of cimetidine following intravenous administration could be approximated by the two-compartment model in rats (Kaneniwa et al., 1985b). These problems for the modeling after oral administration have been discussed by Ronfeld and Benet (1977). Since these parameters are similar to the intravenous data (Kaneniwa et al., 1985b), it appears that these parameters could be obtained precisely from the oral data and were not influenced by the absorption phase in the present study. The absorption rate constant obtained by non-linear least-squares analysis and its attendant parameters are shown in Table 2; in these analyses, only k_a was varied as a parameter and other parameters were fixed at the values shown in Table 1 as constants. The absorption rate constant obtained by using Eqn. 13 with the parameter values shown in Table 1 and its attendant parameters are also shown in Table 2. Time courses of plasma concentration which showed more than one peak were omitted from the calculation of k_a in the present study. Since the hybrid parameters ($(C_1)_{po}$ and $(C_2)_{po}$) contain k_a, the values of $(C_1)_{po}$ and $(C_2)_{po}$ were affected by k_a and differ between both methods. In a comparison of k_a obtained by non-linear least-squares analysis with that obtained by the present method, no statistically significant difference was observed. Al-

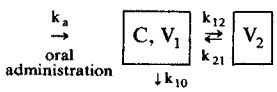
TABLE 1

PHARMACOKINETIC PARAMETERS OF CIMETIDINE IN RATS [a] FOLLOWING ORAL ADMINISTRATION [b,c]

Parameters	Dose (mg/kg)		
	25 (n = 5) [d]	50 (n = 4)	100 (n = 4)
λ_1 (min^{-1})	0.2098 ± 0.0103	0.1995 ± 0.0407	0.2140 ± 0.0173
λ_2 (min^{-1})	0.0126 ± 0.0005	0.0119 ± 0.0007	0.0124 ± 0.0005
k_{10} (min^{-1})	0.0334 ± 0.0039	0.0420 ± 0.0007	0.0367 ± 0.0031
k_{12} (min^{-1})	0.1070 ± 0.0111	0.1168 ± 0.0304	0.1177 ± 0.0129
k_{21} (min^{-1})	0.0822 ± 0.0088	0.0572 ± 0.0007	0.0720 ± 0.0023
V_1/F (ml/kg)	568.7 ± 69.6	450.2 ± 59.4	446.5 ± 25.2
k_a (min^{-1})	0.0179 ± 0.0007	0.0205 ± 0.0023	0.0207 ± 0.0018
MAT (min)	58.60 ± 6.90	50.39 ± 7.19	53.79 ± 5.81
AUC (μg min/ml)	1335.3 ± 25.2	2876.7 ± 177.8	6121.3 ± 314.6
F [e] (%)	96.7	97.6	100.5

[a] Data are from Kaneniwa et al. (1985), but the number of rats is different in the present study.

[b] Parameters for the model: $C = (C_1)_{po}\, e^{-\lambda_1 \cdot t} + (C_2)_{po}\, e^{-\lambda_2 \cdot t} - ((C_1)_{po} + (C_2)_{po})\, e^{-k_a \cdot t}$



where

$$(C_1)_{po} = \frac{k_a FD(k_{21} - \lambda_1)}{V_1(k_a - \lambda_1)(\lambda_2 - \lambda_1)} \qquad (C_2)_{po} = \frac{k_a FD(k_{21} - \lambda_2)}{V_1(k_a - \lambda_2)(\lambda_1 - \lambda_2)}$$

[c] Each value represents the mean ± S.E.

[d] n is the number of rats used.

[e] $F = AUC_{po}/AUC_{iv}$.

though the overall correlation of the fits obtained by non-linear least-squares analysis was slightly better than that obtained by the present method (statistically insignificant), it appears that k_a values obtained by the present method can also depict the plasma concentration–time course following oral administration accurately, as shown in Fig. 1. The inverse relationships between MAT and k_a were observed in both methods (i.e. non-linear least-squares analysis and Eqn. 13). In the previous report (Kaneniwa et al., 1985b), a lag time for initiation of absorption was included in the analysis, but it was shown that the lag time was extremely short. Consequently, in the present study, the lag time was not considered in the analysis.

In the previous report, we (Kaneniwa et al., 1985b) clarified that the absorption rate of cimetidine was influenced by the variation of gastric emptying rate in rats. Plasma concentration–time plots of data obtained after oral ad-

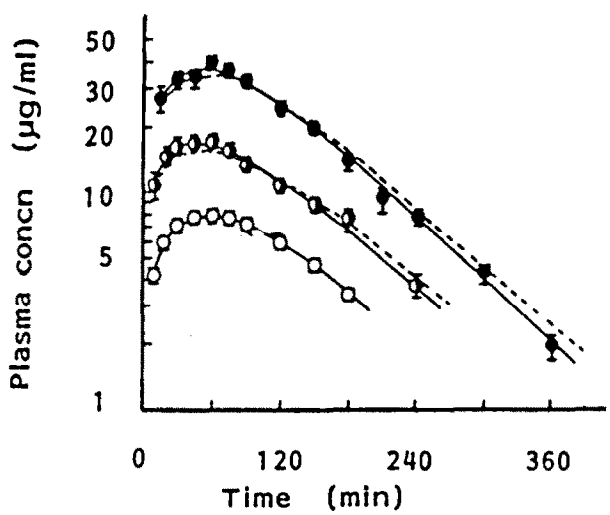


Fig. 1. Time courses of plasma concentration of cimetidine in rats following oral administration. Solid lines and dotted lines were calculated based on k_a obtained by the non-linear least-squares analysis and obtained by using Eqn. 13, respectively. Each point is the mean ± S.E. Dose (mg/kg): ○, 25.0; ◑, 50.0; ●, 100.0.

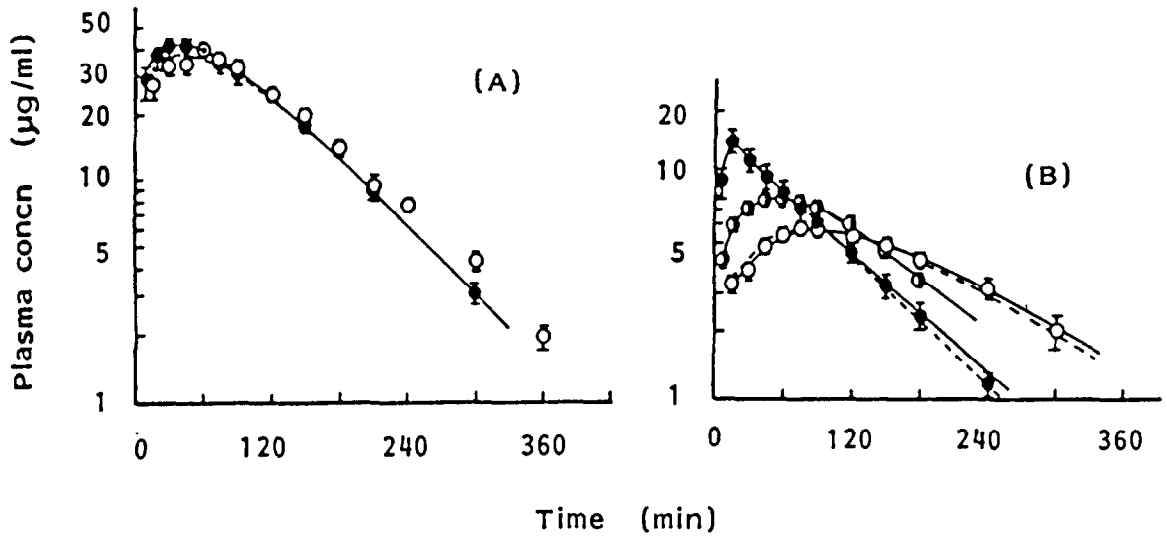


Fig. 2. Effects of water volume taken with the drug, and of atropine or metoclopramide co-administration on the time course of plasma concentration of cimetidine in rats following oral administration. In the case of water volume (A), the doses (100 mg/kg) were dissolved in 1 (○) or 2 (●) ml of distilled water (per head). In the case of atropine (○), or metoclopramide (●) co-administration (B), the doses of cimetidine were 25 mg/kg. The control (Φ), given cimetidine only, is also shown. Solid lines and dotted lines were calculated based on k_a obtained by the non-linear least-squares analysis and that obtained by using Eqn. 13, respectively. Each point is the mean ± S.E.

ministration of the drug with different volumes of water and after co-administration of atropine or metoclopramide are shown in Fig. 2. The pharmacokinetic parameters shown in Table 3 were used to calculate k_a by the two methods (i.e. non-linear least-squares analysis and Eqn. 13). The absorption rate constant obtained by the non-linear least-squares analysis and its attendant parameters, and k_a obtained by Eqn. 13 and its attendant parameters are shown in Table 4. The parameters used for the analyses in Table 4 (i.e. the values in Table 3) were obtained from the oral data in advance by non-linear least-squares analysis similar to the case shown in Table 1. From the

TABLE 2

ABSORPTION RATE CONSTANTS OF CIMETIDINE DERIVED BY NON-LINEAR LEAST-SQUARES ANALYSIS AND DERIVED BY USING EQN. 13, AND THEIR ATTENDANT PARAMETERS [a]

Parameters	Non-linear least-squares analysis [b]			Eqn. 13		
	Dose (mg/kg)			Dose (mg/kg)		
	25 (n = 5) [c]	50 (n = 4)	100 (n = 4)	25 (n = 5)	50 (n = 4)	100 (n = 4)
$(C_1)_{po}$ (μg/ml)	−2.87 ± 0.54	−10.65 ± 2.00	−16.40 ± 2.44	−2.78 ± 0.41	−8.61 ± 1.25	−14.39 ± 0.82
$(C_2)_{po}$ (μg/ml)	56.19 ± 5.45	73.31 ± 6.08	213.91 ± 41.09	50.74 ± 5.41	89.94 ± 7.24	260.25 ± 53.75
k_a (min^{-1})	0.0182 ± 0.0007	0.0204 ± 0.0020	0.0206 ± 0.0019	0.0185 ± 0.0011	0.0176 ± 0.0014	0.0178 ± 0.0006
r^2	0.980 ± 0.011	0.947 ± 0.040	0.961 ± 0.019	0.928 ± 0.024	0.876 ± 0.067	0.924 ± 0.024

[a] Each value represents the mean ± SE.

[b] In the analysis, the only variable (parameter) was k_a and other parameters were fixed at the values shown in Table 1.

[c] n is the number of rats used.

results shown in Table 4, it was found that the absorption rate of cimetidine was influenced by a change in the volume of water taken with the drug and by co-administration of atropine or metoclopramide, as is also clear from Table 4. It has been reported that the gastric emptying rate increases with increase of water volume taken with a drug (Henderson, 1966) or on co-administration of metoclopramide (Nimmo et al., 1973), but decreases on co-administration of atropine (Watari et al., 1984). These findings are also consistent with our previous study showing that the absorption rate constant of nitrofurantoin increased with increase in the volume of water taken with the drug and decreased on co-administration of atropine (Watari et al., 1984). Consequently, the results of the present study indicate that the absorption rate of cimetidine may be affected by a change in the volume of water taken with the drug, and by co-administration of atropine or metoclopramide, in the clinical setting. It is clear from the results in Table 4 that the k_a values obtained by Eqn. 13 and by non-linear least-squares analysis are essentially the same (no statistically significant difference) and these are inversely relation to MAT, and this confirms the validity of Eqn. 13 in the present study (assuming that F in the rats is equal to unity). Furthermore, in the case of metoclopramide where few data points are available in the absorption phase, the present method was more suitable than the non-linear least-squares method for the calculation of k_a, because the present method does not use data points prior to the maximum plasma concentration to estimate of k_a (however, minimum data points during the absorption phase are required in order to assess $T_{max \cdot est}$), whereas at least several data points are necessary for non-linear least-squares analysis to obtain k_a accurately.

In conclusion, the present method is applicable for the estimation of k_a of drugs whose disposition is described by the two-compartment model, and is particularly convenient when few data points are available in the absorption phase. The value of k_a obtained by Eqn. 13 is also useful as an initial value the non-linear least-squares analysis.

TABLE 3

PHARMACOKINETIC PARAMETERS OF CIMETIDINE IN RATS [a] WHEN THE VOLUME OF WATER TAKEN WITH THE DRUG WAS CHANGED [b], OR ATROPINE OR METOCLOPRAMIDE [c] WAS CO-ADMINISTERED [d]

Parameters	Water volume		Co-administered drug		
	1 ml [e] (n = 4) [f]	2 ml (n = 6)	Control [e] (n = 5)	Atropine (n = 4)	Metoclopramide (n = 5)
λ_1 (min^{-1})	0.2140 ± 0.0173	0.2251 ± 0.0132	0.2098 ± 0.0103	0.1896 ± 0.0426	0.2290 ± 0.0404
λ_2 (min^{-1})	0.0124 ± 0.0005	0.0123 ± 0.0005	0.0126 ± 0.0005	0.0123 ± 0.0006	0.0107 ± 0.0009
k_{10} (min^{-1})	0.0367 ± 0.0031	0.0390 ± 0.0058	0.0334 ± 0.0039	0.0362 ± 0.0072	0.0464 ± 0.0186
k_{12} (min^{-1})	0.1177 ± 0.0129	0.1217 ± 0.0118	0.1070 ± 0.0111	0.1032 ± 0.0308	0.1131 ± 0.0257
k_{21} (min^{-1})	0.0720 ± 0.0023	0.0768 ± 0.0083	0.0822 ± 0.0088	0.0626 ± 0.0058	0.0802 ± 0.0239
V_1/F (ml/kg)	446.5 ± 25.2	506.4 ± 97.1	568.7 ± 69.6	532.1 ± 101.4	567.2 ± 130.8
k_a (min^{-1})	0.0207 ± 0.0018	0.0282 ± 0.0038	0.0179 ± 0.0007	0.0112 ± 0.0004	0.0915 ± 0.0194
MAT (min)	53.79 ± 5.81	37.86 ± 3.40	58.60 ± 6.90	133.84 ± 21.34	14.36 ± 2.99
AUC ($\mu g \cdot min/ml$)	6 121.3 ± 314.6	5 948.4 ± 379.5	1 335.3 ± 25.2	1 310.6 ± 77.8	1 456.0 ± 177.7
F [g] (%)	100.5	102.8	96.7	98.4	95.9

[a] Data are from Kaneniwa et al. (1985), but the number of rats is different in the present study.
[b] Dose of cimetidine was 100 mg/kg to study the effect of water volume taken with the drug.
[c] Dose of cimetidine was 25 mg/kg to study the effects of co-administered drugs.
[d] Each value represents the mean ± S.E.
[e] Same as the values shown in Table 1.
[f] n is the number of rats used.
[g] $F = AUC_{po}/AUC_{iv}$.

TABLE 4

ABSORPTION RATE CONSTANTS OF CIMETIDINE DERIVED BY NON-LINEAR LEAST-SQUARES ANALYSIS AND DERIVED BY EQN. 13, AND THEIR ATTENDANT PARAMETERS WHEN THE VOLUME OF WATER TAKEN WITH THE DRUG WAS CHANGED [a], OR ATROPINE OR METOCLOPRAMIDE [b] WAS CO-ADMINISTERED [c]

Parameters	Non-linear least-squares analysis [d]				
	Water volume		Co-administered drug		
	1 ml (n = 4) [e]	2 ml (n = 6)	Control (n = 5)	Atropine (n = 4)	Metoclopramide (n = 5)
$(C_1)_{po}$ (μg/ml)	−16.40 ± 2.44	−21.37 ± 3.99	−2.87 ±0.54	−1.51 ±0.17	−17.16 ±3.56
$(C_2)_{po}$ (μg/ml)	213.91 ±41.09	123.69 ±12.48	56.19 ±5.45	−25.05 ±3.63	15.87 ±2.42
k_a (min^{-1})	0.0206± 0.0019	0.0312± 0.0045	0.0182±0.0070	0.0085±0.0008	0.0748±0.0161
r^2	0.961 ± 0.019	0.965 ± 0.011	0.980 ±0.011	0.929 ±0.026	0.908 ±0.047
Parameters	Eqn. 13				
	Water volume		Co-administered drug		
	1 ml (n = 4)	2 ml (n = 6)	Control (n = 5)	Atropine (n = 4)	Metoclopramide (n = 5)
$(C_1)_{po}$ (μg/ml)	−14.39 ± 0.82	−20.08 ± 3.70	−2.78 ±0.41	−1.80 ±0.18	−18.33 ±3.73
$(C_2)_{po}$ (μg/ml)	260.25 ±53.75	166.55 ±22.23	50.74 ±5.41	−43.31 ±6.81	14.92 ±2.31
k_a (min^{-1})	0.0178± 0.0006	0.0260± 0.0055	0.0185±0.0011	0.0092±0.0010	0.0915±0.0194
r^2	0.924 ± 0.024	0.923 ± 0.014	0.928 ±0.024	0.915 ±0.023	0.944 ±0.028

[a] Dose of cimetidine was 100 mg/kg to study the effect of water volume taken with the drug.

[b] Dose of cimetidine was 25 mg/kg to study the effects of co-administered drugs.

[c] Each value represents the mean ± S.E.

[d] In the analysis, the only variable (parameter) was k_a and other parameters were fixed at the values shown in Table 3.

[e] n is the number of rats used.

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