Journal of Pharmacokinetics and Biopharmaceutics, Vol. 14, No. 2, 1986

Estimation of Drug Absorption Rates Using a Deconvolution Method with Nonequal Sampling Times

Katsumi Iga,[1,2] Yasuaki Ogawa,[1] Takatsuka Yashiki,[1] and Tsugio Shimamoto[1]

Received February 5, 1985—Final January 16, 1986

A method affording direct estimation of the drug absorption rate from blood level data using arbitrary time intervals has been derived based on the staircase input principle. In the derivation, the drug was assumed to follow linear kinetics where the plasma concentration of the drug after an impulse input is expressed by a multiexponential function. Drug absorption was assumed to occur at a constant rate during each subsequent sampling interval. The absorption rate profiles obtained by the method using several numerical examples were expressed as a set of rectangular pulses. Divergence in the profiles reflected blood sampling measurement errors rather than errors due to the deconvolution. Smoothing of the rate profiles by calculating the mean of the absorption rates between adjacent time intervals gave realistic results. Absorption rate profiles for theophylline obtained by the method using published data gave information on the initiation and termination of the absorption as well as the extent of absorption from the dosage form.

KEY WORDS: estimation of drug absorption rate; staircase input; multiexponential function; absorption rate profile; theophylline tablet; initiation and termination of absorption.

INTRODUCTION

Several methods for estimating drug absorption rates from blood level data based on convolution-deconvolution theory have been reported (1-7). The Wagner-Nelson method (1) and the Loo-Riegelman method (2) have been used most often for drug absorption rate analysis. These methods do not employ an input function to obtain the absorption rate directly from the blood level data; rather, they derive the drug absorption rate from the cumulative amount absorbed.

[1]Pharmaceutical Development Laboratories, Central Research Division, Takeda Chemical Industries, 17-85, Jusohonmach 2-chome, Yodogawa-Ku, Osaka 532, Japan.
[2]To whom correspondence should be addressed.

0090-466X/86/0400-0213$05.00/0

Vaughan and Dennis (5) have described a deconvolution method using a staircase input function. The derivation of the deconvolution procedure was demonstrated for equal time intervals of the staircase input, and it was shown to be a simple and accurate method for the assessment of the cumulative *in vivo* drug input. Derivation of the deconvolution procedure for unequal time intervals was not fully demonstrated, although the authors suggested its possibility.

The purpose of this paper is to derive a deconvolution method based on the staircase input for arbitrary time intervals. This method affords direct estimation of the drug absorption rate from the actual blood level data. The applicability of this method is tested by analyzing *in vivo* absorption kinetics for oral dosage forms.

THEORY

Equations and Method for Calculation of the Absorption Rate

The principle of deconvolution using a staircase input function (5) can be used to derive the present method. In general, if the drug follows linear kinetics, then the concentration of drug in the plasma at time t, $Y(t)$, resulting from an arbitrary input (i.e., absorption) can be described by a convolution integral,

$$Y(t) = \int_0^t \mathrm{In}(x) G(t-x)\, dx \tag{1}$$

where $G(t)$ is the characteristic response function expressing the concentration of the drug in the plasma after impulse input and $\mathrm{In}(x)$ is the input rate function.

If drug absorption occurs at an arbitrary constant rate I_i during each subsequent sampling interval (i.e., between times t_{i-1} and t_i), where the amount absorbed changes linearly in each time interval, then, by applying Eq. (1) and letting $\mathrm{In}(x) = I_i$, one can express the drug concentration response at time t_n, $Y(t_n)$, as a summation of the integrals between the limits of $x = t_{i-1}$ and t_i,

$$Y(t_n) = \sum_{i=1}^{n} \int_{t_{i-1}}^{t_i} I_i G(t_n - x)\, dx = \sum_{i=1}^{n} I_i \int_{t_{i-1}}^{t_i} G(t_n - x)\, dx \tag{2}$$

The deconvolution of Eq. (2) with respect to I_i was demonstrated previously for the case where the pulse lengths were all equal (5); however, this procedure is not applicable for unequal pulse lengths. If $G(t)$ can be approximated by a multiexponential function, Eq. (2) can be solved in a

different manner for arbitrary time intervals (i.e., pulse lengths). For simplification, let $G(t)$ be a biexponential function ($A\,e^{-\alpha t} + B\,e^{-\beta t}$); then the integral term in Eq. (2) can be solved,

$$\int_{t_{i-1}}^{t_i} G(t_n - x)\,dx = a_i\,e^{-\alpha t_n} + b_i\,e^{-\beta t_n} \tag{3}$$

where a_i and b_i are defined as functions of the time interval and the characteristic response parameters (A, B, α, and β),

$$a_i = \frac{A}{\alpha}(e^{\alpha t_i} - e^{\alpha t_{i-1}}), \qquad b_i = \frac{B}{\beta}(e^{\beta t_i} - e^{\beta t_{i-1}})$$

By applying Eq. (3) to Eq. (2), one obtains $Y(t_n)$ as

$$Y(t_n) = \left(\sum_{i=1}^{n} I_i a_i\right) e^{-\alpha t_n} + \left(\sum_{i=1}^{n} I_i b_i\right) e^{-\beta t_n} \tag{4}$$

Transformation of Eq. (4) gives an equation for the input rate I_n between times t_{n-1} and t_n as follows:

For $n = 1$

$$I_1 = \frac{Y(t_1)}{a_1\,e^{-\alpha t_1} + b_1\,e^{-\beta t_1}}$$

For $n \geq 2$

$$I_n = \frac{Y(t_n) - (\sum_{i=1}^{n-1} I_i a_i)\,e^{-\alpha t_n} - (\sum_{i=1}^{n-1} I_i b_i)\,e^{-\beta t_n}}{a_n\,e^{-\alpha t_n} + b_n\,e^{-\beta t_n}} \tag{5}$$

where a_i and b_i are defined above. The cumulative amount absorbed at t_n is $\sum^{n} I_i(t_i - t_{i-1})$. Thus, the drug absorption rate as a function of time can be obtained by calculating input rates I_i in Eq. (5) from the drug concentration versus time data $Y(t_i)$ and the characteristic response parameters (A, B, α, and β).

Calculation is done stepwise: first, from the plasma concentration at the first time point, $Y(t_1)$,

$$I_1 = \frac{Y(t_1)}{a_1\,e^{-\alpha t_1} + b_1\,e^{-\beta t_1}} \tag{6}$$

where

$$a_1 = \frac{A}{\alpha}(e^{\alpha t_1} - 1), \qquad b_1 = \frac{B}{\beta}(e^{\beta t_1} - 1)$$

next, from I_1 obtained above and the drug concentration in the plasma at the second time point, $Y(t_2)$,

$$I_2 = \frac{Y(t_2) - a_1 I_1 e^{-\alpha t_2} - b_1 I_1 e^{-\beta t_2}}{a_2 e^{-\alpha t_2} + b_2 e^{-\beta t_2}} \tag{7}$$

where

$$a_2 = \frac{A}{\alpha}(e^{\alpha t_2} - e^{\alpha t_1}), \qquad b_2 = \frac{B}{\beta}(e^{\beta t_2} - e^{\beta t_1})$$

Next, from I_1 and I_2 obtained above and the plasma concentration at the third time point, $Y(t_3)$,

$$I_3 = \frac{Y(t_3) - (a_1 I_1 + a_2 I_2) e^{-\alpha t_3} - (b_1 I_1 + b_2 I_2) e^{-\beta t_3}}{a_3 e^{-\alpha t_3} + b_3 e^{-\beta t_3}} \tag{8}$$

where

$$a_3 = \frac{A}{\alpha}(e^{\alpha t_3} - e^{\alpha t_2}), \qquad b_3 = \frac{B}{\beta}(e^{\beta t_3} - e^{\beta t_2})$$

The $I_4, I_5, \ldots$ can be obtained in a similar manner as above. Such calculations may be performed by means of a digital computer.

Characteristic Response Function and Parameters for Calculation of Absorption Rate

In this example, the characteristic response function $G(t)$ is assumed to be a biexponential function, since the drug concentration versus time curve of many drugs after i.v. administration can be well fitted to a biexponential function. However, for some drugs, it might be necessary to assume tri- or higher-exponential functions as the characteristic response. Equations for the absorption rate assuming such a characteristic response can also be derived by the addition of terms such as $(\sum I_i c_i) \exp(-\gamma t_n)$ to the right-hand side of Eq. (4).

The calculation of the drug absorption rate by this method requires the characteristic response parameters. The most ideal instance is the case in which the i.v. administration data are available and can be fitted to mono- or biexponential functions ($A e^{-\alpha t} + B e^{-\beta t}$; for a monoexponential function, $B = 0$). The values of A, B, α, and β from the i.v. data can be directly used as the parameters.

If data on i.v. administration are not available, data on an oral solution may be used to obtain the characteristic response function, which might be a triexponential function, such as $A e^{-\alpha t} + B e^{-\beta t} + C e^{-\gamma t}$ $(A + B + C = 0)$, assuming that the absorption from the oral solution follows first-order

kinetics. However, the rate profile obtained by this procedure is applicable only for the analysis of *in vivo* dissolution kinetics for the test sample.

Some drugs exhibit nonlinear pharmacokinetics due to saturation of disposition. This method is not applicable for such drugs.

Application of the present method is not limited to the case where drug concentrations in plasma as a function of time are available, since minor modification of the method enables us to estimate the drug absorption rate from only urinary data as the cumulative amount excreted. The cumulative amount excreted into urine after i.v. administration of the drug can be expressed by an exponential function such as $A e^{-\alpha t} + B e^{-\beta t} + C$ ($A, B < 0$, $C = -A - B$) and the function can be used as the characteristic response function G. In this case, Y should be the cumulative amount excreted at time t after administration of the test sample. By a similar procedure in the derivation of Eq. (4), $Y(t_n)$ can be found by adding $\sum (I_i c_i)$, where $c_i = C(t_i - t_{i-1})$, to the right-hand side of Eq. (4). The equation for I_n can be similarly obtained from this equation as in Eq. (5); however, estimation of absorption rate based on urinary data might not be accurate.

RESULTS AND DISCUSSION

Application of the Method

The estimation of cumulative amounts absorbed was examined by comparing the results with two standard methods [the Loo-Riegelman method (2) and the Chiou method (4)]. A model previously reported (4) was used in which a first-order absorption rate ($k_a = 0.693\ \text{hr}^{-1}$) and a characteristic response function

$$0.23\ e^{-4.62t} + 0.15\ e^{-0.41t} + 0.062\ e^{-0.0225t}$$

had been assumed and the drug concentration versus time data generated theoretically using the first-order absorption rate constant. As shown in Table I, the present method tends to underestimate slightly the cumulative amounts absorbed, as does the Loo-Riegelman method. The underestimation by the present method is smaller than that by the Loo-Riegelman method; however, the accuracy is essentially the same for the three methods. The results support the applicability of the present method to estimate cumulative amounts absorbed.

When one analyzes the absorption kinetics of a drug, particularly the duration of its absorption, it may be more useful to obtain the absorption rate profile. The present method was derived assuming constant absorption between blood sampling time intervals t_{i-1} and t_i. However the assumption might be valid only between short time intervals. The validity of this

Table I. Comparison of Results of Cumulative Amount Absorbed Estimated by the Chiou Method, the Loo-Riegelman Method, and the Present Method[a]

Time (hr)	C_p	Cumulative amount absorbed (fraction)[b]			
			Calculated		
		Theoretical[c]	Chiou	Loo-Riegelman	Present work
0.5	0.0822	0.2928	0.3050	0.2767	0.2864
1.0	0.1106	0.5000	0.5135	0.4874	0.4918
1.5	0.1223	0.6464	0.6586	0.6339	0.6380
2.0	0.1253	0.7499	0.7604	0.7388	0.7418
2.5	0.1233	0.8232	0.8323	0.8132	0.8155

[a] A model previously reported (4) was used in which a first-order absorption rate $k_a = 0.693\ \text{hr}^{-1}$ and a characteristic response function $0.23e^{-4.62t} + 0.15e^{-0.41t} + 0.062e^{-0.0225t}$ had been assumed. C_p is the drug concentration based on data in ref. 4, which had been generated theoretically using the first-order absorption rate constant $k_a = 0.693\ \text{hr}^{-1}$.
[b] Based on data reported in ref. 4, except for the last column.
[c] Based on $(1 - e^{-0.693t})$.

assumption was examined by using a model in which a first-order absorption rate $k_a = 0.693\ \text{hr}^{-1}$ and a characteristic response function $5e^{-0.4t} + 5e^{-0.2t}$ were assumed. Drug concentration versus time data were theoretically generated at times that were likely to be used for the blood sampling in practice (column 2 in Table II). The influence of the selection of sampling times on the estimation of the absorption rate is summarized in Table II (columns 5 and 6). A comparison of the generated rate profiles to the theoretically obtained rate profiles is shown in Figs. 1a and 1b. The generated rate profiles are displayed as a set of rectangular pulses. The accuracy of the rate profile was dependent on the sampling time intervals and the sampling periods. It required shorter time intervals in the earlier sampling period; this was not as critical in the later sampling period.

The ability of the present method to generate accurate rate profiles from data generated with a significant random error was also examined. This error was produced by increasing and decreasing the hypothetical plasma concentrations of drug by 10% in alternate time intervals (column 3 in Table II). Divergences in the profile were significant, and the absorption rate between 4 and 5 hr was negative, although the rate of absorption cannot have a negative value (Fig. 1c). Divergences in the profile reflect errors in blood sampling measurements which are inevitable in practice. In such a case, smoothing of the rate profile by calculating the mean of the absorption rates between consecutive time intervals may be one way to obtain a realistic estimate of the absorption rate profile (dashed line in Fig. 1c).

Cutler (6) and Veng-Pedersen (7,8) have reported least squares deconvolution methods. Input rate profiles were compared between the present

Table II. The Influence of the Selection of Sampling Times and Error on the Estimation of Absorption Rate by the Present Method[a]

Time (hr)	C_p	$C_{p,e}$	Absorption rate (unit dose/hr)[b] Theoretical	Calculation A	Calculation B	Calculation C
0.25	1.531	1.377	0.582	0.635 (0-0.25)		0.571 (0-0.25)
0.5	2.708	2.978	0.490	0.534 (0.25-0.5)		0.705 (0.25-0.5)
1	4.252	3.826	0.346	0.412 (0.5-1)	0.491 (0-1)	0.270 (0.5-1)
2	5.310	5.841	0.173	0.245 (1-2)	0.246 (1-2)	0.343 (1-2)
3	5.061	4.554	0.086	0.123 (2-3)	0.123 (2-3)	0.018 (2-3)
4	4.366	4.802	0.043	0.061 (3-4)		0.155 (3-4)
5	3.594	3.232	0.021	0.030 (4-5)	0.043 (3-5)	−0.048 (4-5)
6	2.894	3.183	0.010	0.015 (5-6)		0.091 (5-6)
7	2.304	2.534	0.005	0.007 (6-7)	0.011 (5-7)	0.000 (6-7)
8	1.827	1.644	0.002	0.003 (7-8)		−0.037 (7-8)
9	1.448	1.592	0.001	0.002 (8-9)		0.034 (8-9)
10	1.149	1.034	0.000	0.000 (9-10)	0.002 (7-10)	−0.024 (9-10)

[a] A first-order absorption rate $k_a = 0.693\ \text{hr}^{-1}$ and a characteristic response function $5e^{-0.4t} + 5e^{-0.2t}$ were assumed. C_p is the plasma concentration generated theoretically using the absorption rate constant $k_a = 0.693\ \text{hr}^{-1}$. The $C_{p,e}$ is the concentration with error (±10%). The absorption rate is expressed as the mean absorption rate between time intervals as shown in parentheses.

[b] Theoretical rate is based on $0.693e^{-0.693t}$. Calculation A was performed using all the theoretical plasma concentrations shown in column 2. Calculation B was performed using some of the theoretical drug concentrations shown in column 2, i.e., concentrations at 1, 2, 3, 5, 7, and 10 hr. Calculation C was performed using the concentrations with errors shown in column 3.

method and the Veng-Pedersen method, using the test data generated by Cutler (6,8). As shown in Fig. 2, the present method appears inferior to the Veng-Pedersen method on the basis of the smoothness of the rate profile obtained. However, these least squares deconvolution methods actually employed a procedure of curve fitting for the drug concentration versus time data. The rate profiles obtained by such curve fitting might be highly dependent on the manner of weighting the data points. In this respect, the present method offers an advantage, since it employs the actual data points.

Analysis of Absorption Kinetics

As an example of the application of this method, the oral absorption kinetics of theophylline from tablets was analyzed from reported data after oral and i.v. administrations in male volunteers (9). A summary of the theophylline concentration in plasma following oral administration is shown in Table III. The values of A, B, α, and β in each subject were obtained by changing the characteristic response parameters for intravenous dose (208 mg), which were given as pharmacokinetic parameters in ref. 9, into

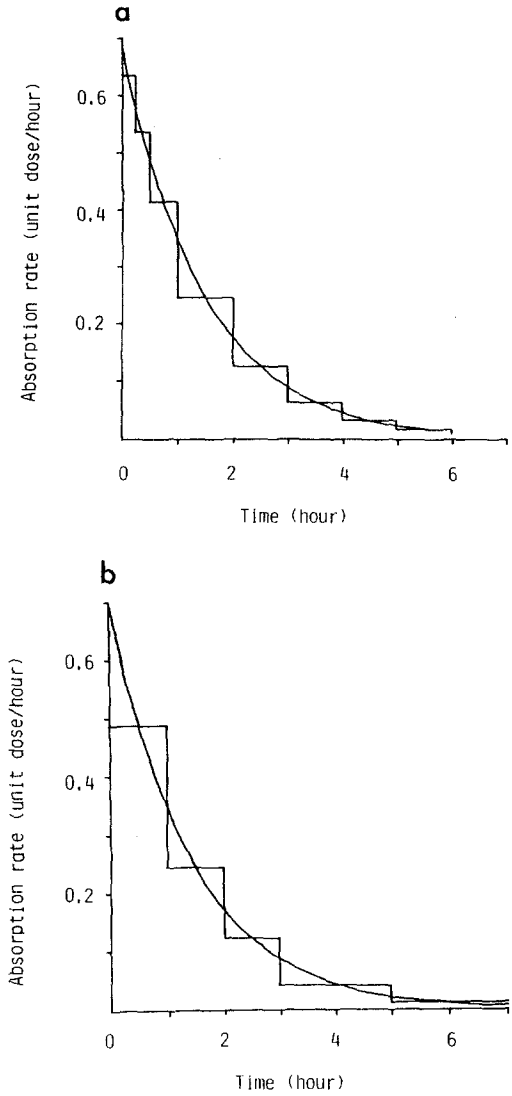

Fig. 1. The profiles of the absorption rate estimated by the present method (rectangular pulses) and the theoretical absorption rate. A first-order absorption rate $k_a = 0.693\,\mathrm{hr}^{-1}$ and a characteristic response function $5e^{-0.4t}+5e^{-0.2t}$ were assumed. (*a, b*) Profiles based on the theoretical plasma concentration data for (a) shorter and (b) longer sampling time intervals. (c) Theoretical plasma concentration data with errors (±10%); the broken line indicates the result of smoothing the rate profile.

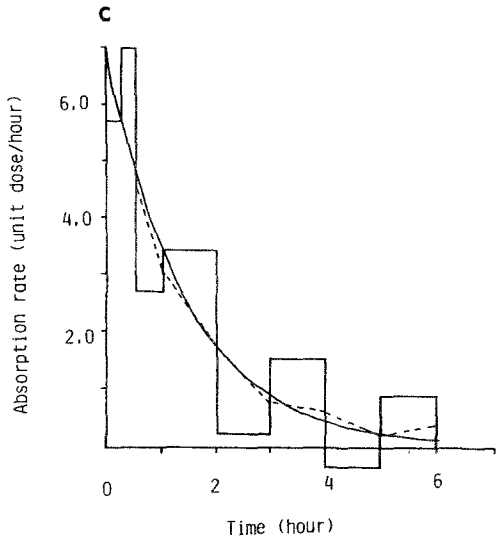

Fig. 1. Continued.

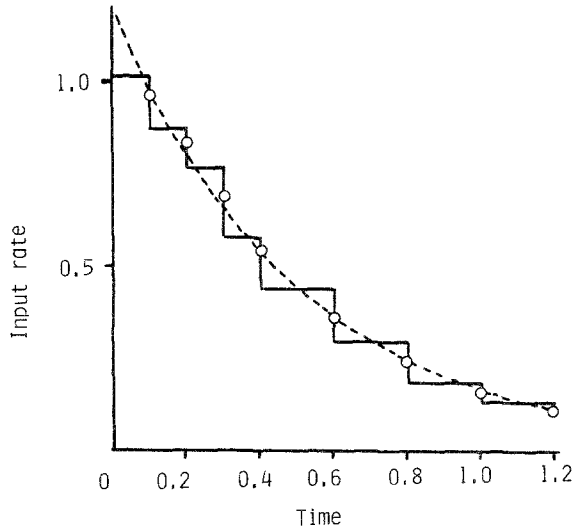

Fig. 2. Comparison of input rate profiles between (rectangular pulses) the present method and (circles) the Veng-Pedersen method, using the test data (data set 1) generated by Cutler (6,8). The dashed line shows the exact absorption rate profile.

Table III. Theophylline Concentration in Plasma following Oral Administration of a 225-mg Tablet in Three Subjects[a]

Time (hr)	Theophylline concentration (μg/ml)		
	Subject 1	Subject 2	Subject 3
0.08	—	—	—
0.17	—	0.88	1.26
0.33	—	2.79	4.80
0.50	—	3.54	5.33
0.75	1.48	3.94	5.07
1.00	0.97	4.70	4.87
1.25	3.88	4.80	4.56
1.50	5.70	5.69	4.24
2.00	5.82	4.53	3.81
3.00	5.92	4.33	3.10
4.00	5.16	4.22	2.43
5.00	4.67	3.54	2.10
6.00	4.55	3.12	1.55
8.00	3.53	2.40	1.00

[a] Data from ref. 9. Dashes signify a concentration below the detection limit.

parameters for the oral dose (225 mg) (Table IV). The estimates of the absorption rates are shown in Table V. The profiles of the absorption rate and the cumulative amount absorbed for the three subjects are shown in Fig. 3. Divergences in the profiles are found after 3 hr in subjects 1 and after 1.5 hr in subject 2, where the absorption rate is sometimes negative. These divergences may reflect random scatter in the data. Smoothing the rate profile as mentioned above might be a way to obtain a more realistic estimate of the absorption rate profile (curved lines in the figure). So far, input rate profiles obtained by any deconvolution method have not been evaluated as a tool for analyzing the different phases of absorption, such as the initial or the terminal absorption phases, or the duration of the

Table IV. Values of Characteristic Response Parameters A, B, α, and β of Theophylline in Three Subjects[a]

Parameter	Units	Subject 1	Subject 2	Subject 3
A	μg/ml	8.21	3.88	10.64
B	μg/ml	5.76	6.71	5.67
α	1/hr	16.9	7.2	15.4
β	1/hr	0.07	0.11	0.19

[a] These values were obtained by changing the characteristic response parameters for the intravenous dose (208 mg) which were shown as pharmacokinetic parameters in ref. 9 into parameters for the oral dose (225 mg).

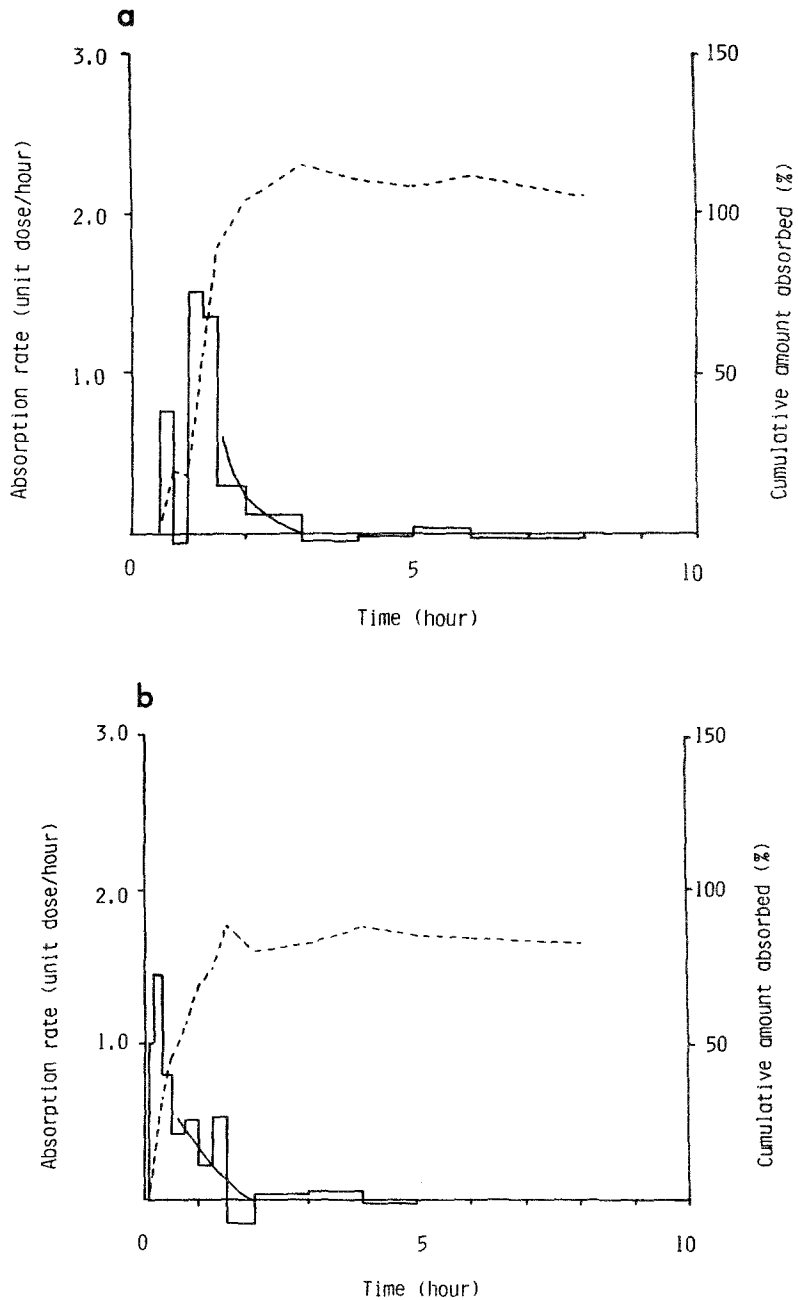

Fig. 3. The profiles of (solid line) the absorption rate and (dashed line) the cumulative amount absorbed after oral theophylline tablet dosing estimated by the present method from the data shown in Table IV. (a-c) The profiles for subjects 1-3, respectively. The curved line in each panel shows the result of smoothing the absorption rate profile in the terminal phase of the absorption.

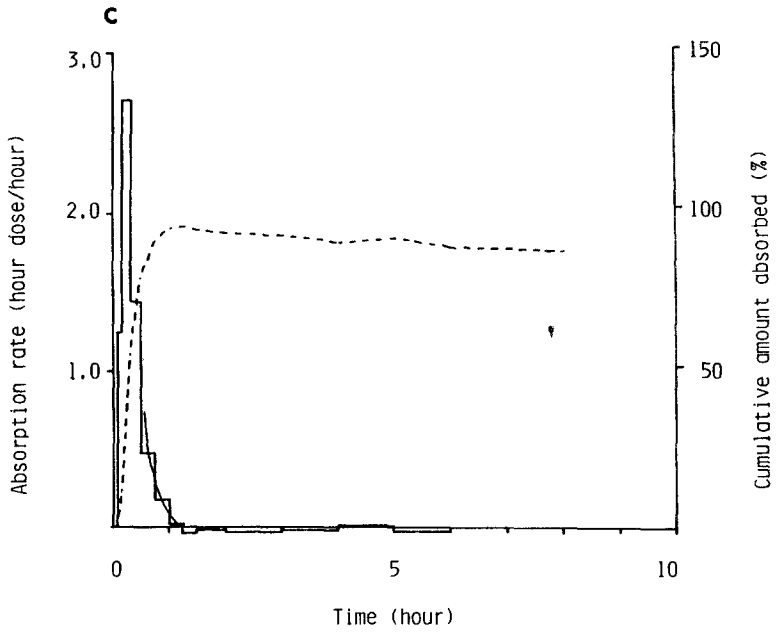

Fig. 3. Continued.

absorption. However, in this way, we could evaluate the initiation and termination of absorption from the rate profiles as well as the completion or incompletion of the absorption from the profiles of cumulative amount. In subject 1, absorption appears to have occurred around 30 min after administration and completed at around 3 hr. In subjects 2 and 3, absorption

Table V. Absorption Rates for an Oral Theophylline Tablet Estimated by the Present Method

Time (hr)	Absorption rate (unit dose/hr)		
	Subject 1	Subject 2	Subject 3
0.08	0	0	0
0.17	0	1.025	1.230
0.33	0	1.466	2.714
0.50	0	0.814	1.426
0.75	0.776	0.425	0.465
1.00	−0.065	0.516	0.169
1.25	1.522	0.214	0.014
1.5	1.359	0.539	−0.047
2.0	0.287	−0.161	−0.021
3.0	0.103	0.029	−0.010
4.0	−0.051	0.051	−0.023
5.0	−0.027	−0.009	0.013

appears to have occurred immediately after administration and been completed before 2 hr. It appears that the absorption of this dosage form might be rapid and complete, but it might be affected by gastric emptying, as in subject 1.

Such information on initiation and termination of absorption as estimated by the present method may help clarify absorption kinetics of a drug with poor aqueous solubility or a drug formulated in a sustained release dosage form as a function of GI transit time.

REFERENCES

1. J. G. Wagner and E. Nelson. Percent absorbed time plots derived from blood level and/or urinary excretion data. *J. Pharm. Sci.* **52**:610-611 (1963).
2. J. C. K. Loo and S. Riegelman. New method for calculating the intrinsic absorption rate of drugs. *J. Pharm. Sci.* **57**:918-928 (1968).
3. H. Kiwada, K. Morita, M. Hayashi, S. Awazu, and M. Hanano. A new numerical calculation method for deconvolution in linear compartment analysis of pharmacokinetics. *Chem. Pharm. Bull.* **25**:1312-1318 (1977).
4. W. L. Chiou. New compartment- and model-independent method for rapid calculation of drug absorption rates. *J. Pharm. Sci.* **69**:57-62 (1980).
5. D. P. Vaughan and M. Dennis. Mathematical basis of point-area deconvolution method for determining *in vivo* input functions. *J. Pharm. Sci.* **67**:663-665 (1978).
6. D. J. Cutler. Numerical deconvolution by least squares: Use of polynomials to represent the input function. *J. Pharmacokin. Biopharm.* **6**:243-263 (1978).
7. P. Veng-Pedersen. Model-independent method of analyzing input in linear pharmacokinetic systems having polyexponential impulse response I: Theoretical analysis. *J. Pharm. Sci.* **69**:293-305 (1980).
8. P. Veng-Pedersen. Model-independent method of analyzing input in linear pharmacokinetic systems having polyexponential impulse response II: Numerical evaluation. *J. Pharm. Sci.* **69**:305-312 (1980).
9. H. S. Kaumeier, O. H. Kehrhahn, G. Neugebauer, D. Shuppan, J. A. Shwarz, and A. H. Staib. A crossover study after oral and intravenous administration of theophylline in male volunteers (absolute bioavailability of Afonilum tablets). *Int. J. Clin. Pharmacol. Ther. Toxicol.* **21**:339-345 (1983).