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# Studies on the Absorption Kinetics of Theophylline in the Steady State, Following Multiple Oral Dosing of a Sustained-Release Theophylline Tablet Formulation to Asthmatic Patients

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The pharmacokinetics of theophylline in the steady state, following multiple oral dosing of a sustained-release theophylline tablet formulation, were studied in six asthmatic patients. The pharmacokinetic parameters were calculated by utilizing a one-compartment model with zero-order or first-order absorption according to the Davidon–Fletcher–Powell method. The computer-predicted theophylline concentrations based on the zero-order absorption model fitted the observed data points better than those based on the first-order absorption model. The nonlinear least-squares curve based on the first-order absorption model underestimated the maximum observed plasma concentrations of theophylline. Linear relationships were obtained between observed and calculated maximum plasma concentration ($C_{max}$) data based on the two absorption models. There was a highly significant relationship between observed and calculated time to $C_{max}$ data based on the zero-order absorption model. These results show that the drug absorption from the sustained-release theophylline tablet formulation used in this study is best described by an apparent zero-order rather than a first-order absorption model.

**Keywords**——theophylline pharmacokinetics; sustained-release theophylline tablet formulation; zero-order absorption model; first-order absorption model; asthmatic patient

Theophylline is regarded as being useful in the treatment of patients with reversible obstructive airway diseases and its bronchodilator effect is well established.[1,2] In the clinical use of theophylline, it is important to adjust the dosing schedule to keep the maximum and minimum concentrations in plasma within the treatment range of 10 to 20 $\mu$g/ml.[3,4] In general, the use of two doses daily rather than three or four should improve patient compliance. Therefore, there has been much interest in sustained-release theophylline formulations. In our earlier studies, we have investigated the bioavailability of sustained-release theophylline formulations and the pharmacokinetics of theophylline in asthmatic patients after multiple oral dosing of a sustained-release tablet formulation.[5] Moreover, we have also analyzed the pharmacokinetics of theophylline in terms of a first-order absorption model in asthmatic patients after multiple oral dosing of a sustained-release tablet formulation.[6]

In a number of recent studies,[7–10] a sustained-release theophylline formulation, Theo-Dur, which is now widely used clinically, has been shown to have complete bioavailability. The pharmacokinetic parameters for theophylline after oral dosing of Theo-Dur have been estimated on the assumption of first-order absorption kinetics by many investigators. It is well known that zero-order drug absorption is ideal for maintenance of a therapeutic plasma concentration of a drug, rather than first-order absorption. However, a detailed examination of theophylline disposition based on a zero-order absorption model after multiple oral dosing

of Theo-Dur has not yet been reported.

In the present study, we estimated the pharmacokinetic characteristics of theophylline in the steady state, following multiple oral dosing of Theo-Dur in asthmatic patients, in order to determine whether the absorption of the drug is best described by a zero-order or a first-order absorption model.

## Experimental

**Drug**——The sustained-release theophylline tablet formulation (Theo-Dur, theophylline 100 mg per tablet) was obtained from Nikken Chemicals Co., Ltd., Tokyo.

**Procedure Used with Asthmatic Patients**——Characteristics of the asthmatic patients tested are given in Table I. These subjects were inpatients at Nagoya University Hospital. We obtained informed consent from each person after full explanation of the procedures. Each subject received an oral dose of the drug described above as the maintenance dose twice daily at 12-h intervals. Blood samples for determination of the concentration of theophylline in the plasma were obtained at 72 (9:00 a.m.), 72.5, 73, 74, 76, 78, 80, 82 and 84 h after the first administration and the plasma samples obtained were kept frozen at −20 °C until analyzed. Total theophylline concentration in the plasma was measured by means of a commercially available substrate-labeled fluorescence immunoassay (SLFIA), the results of which correlate well with those of high-performance liquid chromatography.[11] The subjects in the present study took normal drink and food throughout the experiments. Clinical laboratory data, including bilirubin, blood urea nitrogen (BUN), serum creatinine, glutamic oxalacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), total proteins and serum albumin were within normal limits.

**Pharmacokinetic Analysis**——Plasma concentration data after the multiple oral dosing of the drug were fitted to a one-compartment model[12] with zero-order or first-order absorption using Eq. 1 or 2, respectively. The pharmacokinetic parameters were calculated by use of the Davidon–Fletcher–Powell method (DFP method).[13]

$$C_n = \sum_{i=1}^{n} C_i \tag{1}$$

if $(t_i - t_{lag}) < 0$ $\quad C_i = 0$

if $0 < (t_i - t_{lag}) < LD$ $\quad C_i = \dfrac{k_0}{Vd \cdot k_{el}} [1 - e^{-k_{el}(t_i - t_{lag})}]$

if $LD < (t_i - t_{lag})$ $\quad C_i = \dfrac{k_0}{Vd \cdot k_{el}} (1 - e^{-k_{el} \cdot LD}) \cdot e^{-k_{el}(t_i - t_{lag} - LD)}$

where $k_0$ is the zero-order rate of absorption, $Vd$ is the apparent volume of distribution in the steady state, $k_{el}$ is the apparent elimination rate constant, and $t_i$ is time after administration of the $i$-th dose. $LD$ is calculated by dividing the dose administered by the $k_0$.

TABLE I. Characteristics of Asthmatic Patients

| Subject | Sex | Age (Years) | Height (cm) | B.W. (kg) | Dose[b] (mg) |
|---|---|---|---|---|---|
| WA | M | 61 | 158 | 48 | 300 |
| HA | M | 30 | 160 | 71 | 350 |
| SH | M | 36 | 170 | 70 | 400 |
| OS | F | 69 | 152 | 52 | 200 |
| OH | M | 43 | 162 | 57 | 300 |
| TA | M | 46 | 165 | 60 | 400 |
| Mean | | 47.5 | 161.2 | 59.7 | 325.0 |
| S.E.M. | | 6.1 | 2.5 | 3.8 | 31.0 |
| C.V. %[a] | | 31.3 | 3.8 | 15.7 | 23.3 |

*a*) Coefficient of variation. *b*) Maintenance dose.

$$C_n = \frac{D \cdot F \cdot k_a}{Vd(k_a - k_{el})}\left[\left(\frac{1-e^{-n \cdot k_{el} \cdot \tau}}{1-e^{-k_{el} \cdot \tau}}\right) \cdot e^{-k_{el}(t_n - t_{lag})} - \left(\frac{1-e^{-n \cdot k_a \cdot \tau}}{1-e^{-k_a \cdot \tau}}\right) \cdot e^{-k_a(t_n - t_{lag})}\right] \quad (2)$$

where

$D$ = the dose (oral administration)
$C_n$ = plasma concentration–time units after oral administration of the $n$-th dose
$t_n$ = time after administration of the $n$-th dose
$t_{lag}$ = lag time for absorption
$k_a$ = apparent first-order absorption rate constant
$\tau$ = dosage interval
$Vd$ = apparent volume of distribution
$F$ = fraction of the oral dose absorbed

It was assumed that $F = 1.0$. The plasma theophylline clearance was calculated as $k_{el} \cdot Vd$ using the computer-derived constant $k_{el}$ and $Vd$. The predicted time to reach maximal plasma theophylline concentration, $T_{max}$, after the multiple oral dosing, was obtained by using the computed estimates of $k_a$ and $k_{el}$ according to Eq. 3. The $T_{max}$ value calculated with the zero-order absorption model is equal to $LD$ plus $t_{lag}$. The steady-state maximal theophylline concentration, $C_{max}$, was calculated by substituting the $T_{max}$ value into Eq. 1 or 2, respectively.

$$T_{max} = \frac{1}{(k_a - k_{el})} \cdot \ln\left[\frac{k_a}{k_{el}} \cdot \frac{(1-e^{-k_{el} \cdot \tau})}{(1-e^{-k_a \cdot \tau})}\right] + t_{lag} \quad (3)$$

The following data were analyzed by means of the paired $t$-test, with $p < 0.05$ taken as the minimum level of significance. Values in the present study are expressed as the mean ± standard error.

## Results and Discussion

Figure 1 shows individual plasma theophylline concentration–time data in the steady state, following multiple oral dosing of the drug in six subjects. The maintenance dose of theophylline used in the present study was tolerated well by the subjects. The overall mean plasma theophylline concentrations in the steady state were maintained within the range of 8—20 μg/ml. In particular, three of the subjects (WA, HA and OH) maintained concentrations in the therapeutic range at all times, while two subjects (SA and OH) showed concentrations below 10 μg/ml at times.

The trough plasma concentrations in five of the six subjects were higher in the morning (72 h) than in the evening (84 h). Although there was no significant difference between in the morning and in the evening, the mean plasma concentration in the morning was approximately 10% higher than in the evening. It is likely that there is diurnal variation in the trough theophylline concentrations.

The pharmacokinetic parameters of theophylline following administration of sustained-release theophylline formulations are generally calculated by assuming a simple first-order absorption model. In the present study, in order to determine whether the gastrointestinal absorption of the drug is best described by an apparent zero-order or a first-order absorption model, both models were used for the pharmacokinetic analysis of theophylline after multiple oral dosing of the drug. As a measure of the fit between the observed and the simulated concentrations of theophylline, we used the residual sum of squares ($SS$) value in the ordinary least-squares, analysis.

The pharmacokinetic parameters calculated by using the first-order absorption model are shown in Table II. The mean values of the apparent absorption rate constant ($k_a$) and the apparent elimination rate constant ($k_{el}$) were 0.193 and 0.124 $h^{-1}$, respectively. The volume of distribution based on total body weight, $Vd$, 0.340 l/kg, is smaller than that normally observed, 0.5 l/kg, but is similar to that observed for obese, adult asthmatic patients.[14] In fact, two of the six subjects (HA and OS) were considered to be obese.

On the other hand, Table III also shows the pharmacokinetic parameters calculated by

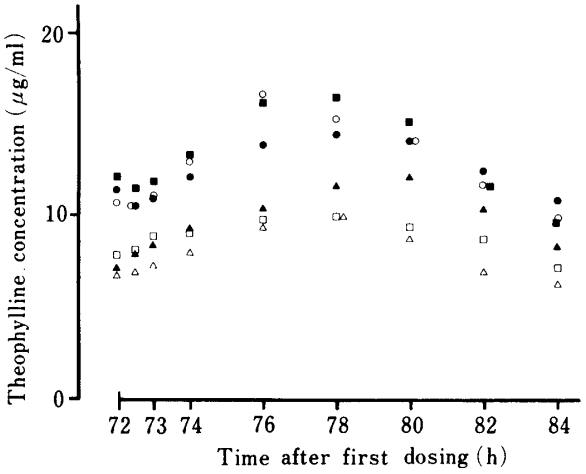


Fig. 1. Individual Plasma Theophylline Concentration–Time Data in Asthmatic Patients after Multiple Oral Dosing of the Sustained-Release Theophylline Tablet Formulation

●, subject WA; ○, subject HA; □, subject SH; ■, subject OS; △, subject OH; ▲, subject TA.

TABLE II. Pharmacokinetic Parameters of Theophylline Calculated on the Basis of First-Order Absorption in the Steady State after Oral Administration of the Sustained-Release Theophylline Tablet Formulation

| Subject | $k_a$ (1/h) | $k_{el}$ (1/h) | $Vd$ (1/kg) | $CL$ (ml/kg/h) | $t_{lag}$ (h) | $SS^{a)}$ |
|---|---|---|---|---|---|---|
| WA | 0.140 | 0.129 | 0.341 | 43.99 | 0.88 | 0.658 |
| HA | 0.300 | 0.104 | 0.294 | 30.58 | 0.70 | 2.422 |
| SH | 0.131 | 0.119 | 0.442 | 52.60 | 0.00 | 0.664 |
| OS | 0.255 | 0.104 | 0.220 | 22:88 | 0.69 | 7.040 |
| OH | 0.159 | 0.154 | 0.336 | 51.74 | 0.31 | 1.421 |
| TA | 0.171 | 0.136 | 0.406 | 55.22 | 0.92 | 4.925 |
| Mean | 0.193 | 0.124 | 0.340 | 42.84 | 0.58 | 2.860 |
| S.E.M. | 0.028 | 0.008 | 0.032 | 5.41 | 0.15 | 1.061 |
| C.V. %$^{b)}$ | 32.5 | 14.3 | 21.3 | 30.9 | 56.0 | |

*a*) Residual sum of squares. *b*) Coefficient of variation.

TABLE III. Pharmacokinetic Parameters of Theophylline Calculated on the Basis of Zero-Order Absorption in the Steady State after Oral Administration of the Sustained-Release Theophylline Tablet Formulation

| Subject | $k_0$ (mg/kg/h) | $k_{el}$ (1/h) | $Vd$ (1/kg) | $CL$ (ml/kg/h) | $t_{lag}$ (h) | $SS^{a)}$ |
|---|---|---|---|---|---|---|
| WA | 0.997 | 0.060 | 0.726 | 43.56 | 0.47 | 0.757 |
| HA | 1.208 | 0.069 | 0.444 | 30.64 | 0.37 | 0.999 |
| SH | 0.894 | 0.052 | 0.990 | 51.48 | 0.00 | 1.654 |
| OS | 0.742 | 0.073 | 0.314 | 22.92 | 0.06 | 4.874 |
| OH | 0.960 | 0.074 | 0.722 | 53.43 | 0.00 | 0.555 |
| TA | 0.772 | 0.148 | 0.369 | 54.61 | 0.11 | 0.546 |
| Mean | 0.929 | 0.079 | 0.594 | 42.77 | 0.17 | 1.564 |
| S.E.M. | 0.069 | 0.014 | 0.107 | 5.39 | 0.08 | 0.083 |
| C.V. %$^{b)}$ | 18.3 | 43.7 | 44.0 | 30.9 | 119.8 | |

*a*) Residual sum of squares. *b*) Coefficient of variation.

using the zero-order absorption model. The mean values of zero-order absorption rate constant ($k_0$), $t_{lag}$ and $k_{el}$ were 0.929 mg/kg/h, 0.17 h and 0.079 $h^{-1}$, respectively. The mean plasma theophylline clearance ($CL$) determined based on the two absorption models was appro-

ximately 42 ml/kg/h. The value is nearly equal to the previously reported value,[14,15] but somewhat lower than the average clearance, 50 ml/kg/h, obtained by other investigators.[16,17]

The experimental plasma concentration data were also compared with the calculated plasma concentration data based on the zero-order and first-order absorption models. The regression curve computer-fitted to the experimental data for subject OH are shown in Fig. 2. The results show that the nonlinear least-squares curve based on the first-order absorption model underestimates the maximum observed plasma concentrations of theophylline and provides a poorer fit of the data as compared to that obtained with the regression curve based on the zero-order absorption model.

There were highly significant relationships between the observed and calculated maximum plasma concentration ($C_{max}$) data based on the two absorption models as shown in Fig. 3. On the other hand, there was a highly significant relationship between the observed and calculated values of the time to maximum plasma concentration ($T_{max}$) based on the zero-order absorption model; the equation of the regression line was calculated to be $y=1.08x-0.27$. The correlation coefficient was greater for the zero-order absorption model than for the first-order absorption model (Fig. 4). Further, the mean $SS$ value obtained in the first-

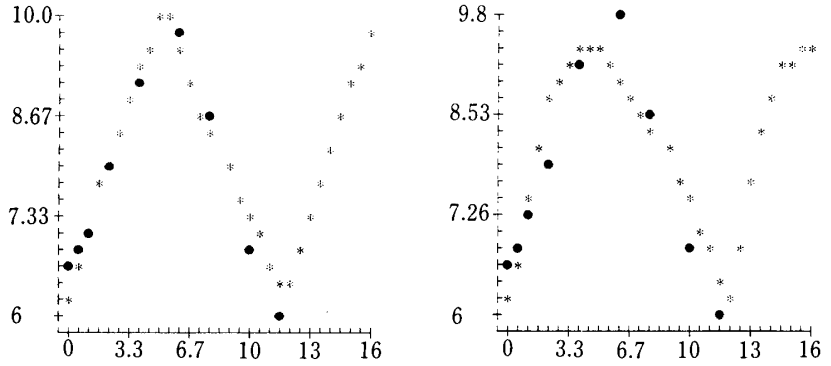


Fig. 2. Computer-Simulated Plot of Plasma Theophylline Concentration–Time Data after Multiple Oral Dosing of the Drug to Subject OH Fitted to the One-Compartment Model with Zero-Order Absorption (Left) or First-Order Absorption (Right)

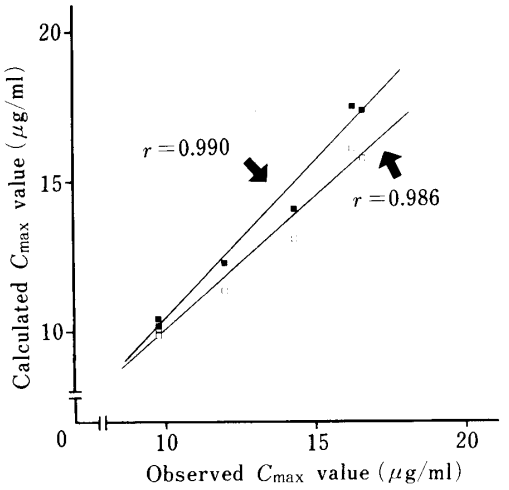


Fig. 3. Relationship between the Observed and Calculated $T_{max}$ Values Obtained with Zero-Order and First-Order Absorption Models

The regression lines were calculated by least-squares analysis. ■ and □ represent zero-order and first-order absorption models, respectively.

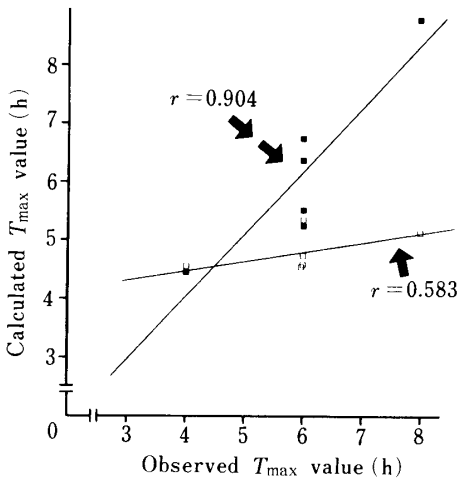


Fig. 4. Relationship between the Observed and Calculated $C_{max}$ Values Obtained with Zero-Order and First-Order Absorption Models

The regression lines were calculated by least-squares analysis. ■ and □ represent zero-order and first-order absorption models, respectively.

order absorption model was larger than that obtained in the zero-order absorption model as indicated in Tables II and III. The best fit was obtained with the zero-order absorption model in four subjects (HA, OS, OH and TA). Thus, the zero-order absorption model used in this study gave better fits than the first-order absorption model; the latter model fitted better only in the case of subject SH. These results clearly show that the gastrointestinal absorption of the drug used is better described as an apparent zero-order rather than a first-order process. Moreover, the overall agreement between the model simulation and observed data seemed acceptable, judging from the *SS* values.

It is generally thought that the *SS* value can not be used to evaluate curve fitting. However, when the relationship between observed and calculated data such as $C_{max}$ and $T_{max}$ is examined, the *SS* value might be useful as an indicator of whether or not the computer-simulated plots of plasma concentrations fit the observed plasma concentrations.

In conclusion, the results of the present study indicate that the absorption of the drug may be better described by an apparent zero-order rather than a first-order model. It is likely that the dissolution process of theophylline from the drug formulation is the rate-limiting step. On the basis of these observations, we recommend that the pharmacokinetic parameters for theophylline after multiple oral dosing of the drug should be estimated by utilizing the one-compartment model with apparent zero-order absorption, even though the assumption of first-order absorption in pharmacokinetics is more usual. It is clearly possible in principle to achieve and maintain constant concentrations in the steady state. Moreover, the pharmacokinetic data obtained in this study can be used to predict the steady-state plasma concentration and to determine the optimal dosage schedule for the drug in therapy at 12-h dosing intervals.

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