TIME-DEPENDENT PHARMACOKINETICS OF THEOPHYLLINE: FAILURE OF APPLICATION OF THE TEST-DOSE CONCEPT

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A comparative pharmacokinetic study of theophylline between the first and repeated oral administration and the assessment of clinical utility of theophylline test-dose concept were performed in 6 (study I) and 4 (study II) healthy male volunteers with different dosing schedules. In study I, although the average of theophylline systemic clearance (Cl_{sys}) was significantly ($p < 0.05$) lower in the repeated dosing than in the first dosing, large intersubject variations were observed. Plasma free fatty acids which inhibit drug metabolizing enzyme activity were not influenced by theophylline chronic administration. In study II, the volunteers received oral multiple doses of a theophylline powder preparation to maintain 5 to 15 $\mu\text{g/ml}$ plasma concentration on the basis of the pharmacokinetic parameters calculated from the single oral test-dose. A good prediction of the plasma concentration was observed only in one case and the maximum levels in the rest exceeded 20 $\mu\text{g/ml}$, a toxic concentration. Throughout the Studies, a stable Cl_{sys} was obtained in smokers, but the Cl_{sys} in non-smokers decreased by one third to a half during multiple dosing. These findings suggest that theophylline showed time-dependent pharmacokinetics and that test-dose concept for theophylline may not be applicable in all cases because of a large intersubject variation in the Cl_{sys} change between single and multiple dosing.

Keywords — theophylline; single dose; multiple dose; time-dependent pharmacokinetics; test-dose concept; pharmacokinetics; smoking

INTRODUCTION

Theophylline systemic clearance (Cl_{sys}) shows large intra- and inter-individual variations because it is influenced by various factors such as age, diet, smoking, concomitant disease, other drugs¹⁾ and the bronchodilator concentration.²⁾ Recently, conflicting data have been accumulated on theophylline disposition. Efthimiou *et al.* have shown that the Cl_{sys} may alter with time³⁾ and on the other hand, Vestal *et al.* have reported that it is independent of elapsed time.⁴⁾ There are many successful reports with respect to the theophylline test-dose method to maintain plasma levels within the therapeutic range on the basis of linear pharmacokinetics.⁵⁾ Considering the finding by Efthimiou and others,³⁾ the test-dose concept⁵⁾ would not be applicable to theophylline dosage regimen calculation.

The aims of this study were (i) to compare theophylline pharmacokinetics between single and multiple dosing and (ii) to assess the clinical utility of theophylline test-dose concept.⁵⁾

MATERIALS AND METHODS

Subjects — Six healthy men (age range 23–37 years, weight range 55.0–72.5 kg) and four healthy men (age range 27–59 years, weight 44.0–62.0 kg), from whom informed written consent had been obtained, participated in studies I and II, respectively. Two volunteers in study I and one in study II were smokers (15 to 20 cigarettes/d). Pre-study physical examination and pre- and post-drug laboratory findings were within normal range. None had taken any drugs during at least one month before the investigational period. Foods and beverages containing xanthines were prohibited for 2 d prior to and during the studies.

Drugs — Aminophylline tablets (Neophylline[®] 100 mg tablet, lot no. 4103, Eisai Co., Ltd., Tokyo, Japan) and aminophylline powder (Neophylline[®] powder, lot no. C20 EFA, Eisai Co., Ltd.) were used throughout studies I and II, respectively. Complete bioavailability has been documented for these preparations.^{6a)} The dose

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FIG. 1. *Experimental Protocol of Studies*

is expressed as equivalent of theophylline in the following description.

Protocol — Experimental designs are illustrated in Fig. 1. In study I, each volunteer received orally a Neophylline[®] tablet every eight h at 2.18 to 2.87 mg/kg dose. Blood specimens were drawn from an arm vein using a disposable syringe (Terumo Co., Ltd., Tokyo, Japan) just prior to and at 0.5, 1, 2, 4, 6, 8, 48, 48.5, 49, 50, 52, 54, and 56 h after the first dose. The blood obtained was immediately transferred into a vacuumed blood collection tube (Venoject[®], VT-050DIC, Terumo Co., Ltd.) containing ethylenediaminetetraacetic acid dipotassium salt as an anticoagulant. The blood sample was centrifuged to separate plasma and a part of the plasma was used to assay for free fatty acids (FFA) as soon as possible. The remaining plasma was frozen at -40°C until the assay for drug concentration was performed.

In study II, after a single oral theophylline administration of 3.95 mg/kg as a test-dose to each volunteer in the morning, blood specimens were collected following the same procedures in study I just before and at 0.5, 1, 2, 4, 6, and 8 h after the dose. Based on the pharmacokinetic parameters obtained from the test-dose, the dosage regimen was calculated to make the steady state concentration between 5 and 15 $\mu\text{g/ml}$. After a one week washout period, the volunteers received the calculated dose every

eight hours. Plasma levels at 0.5, 1, 2, 4, 6, and 8 h after the last drug administration in the morning on the third day were monitored and subsequently kinetic parameters at steady state were calculated.

Assays — Theophylline assay was carried out by the method developed in our laboratory using a high pressure liquid chromatograph⁷⁾ [a LC-4A system (Shimadzu Co., Ltd., Kyoto, Japan) equipped with an ultraviolet (UV) detector (SPD-2AS type) and a Zorbax ODS column (25 cm $\times$ 4.6 mm i.d., Du Pont Instruments, Wilmington, Del., U.S.A.)]. Plasma FFA levels were immediately determined on the same day of plasma collection with a NEFA kit U (Nippon Shoji Kaisha Ltd., Osaka, Japan) applying enzymatic analysis based on the method of Mizuno *et al.*⁸⁾

Pharmacokinetic Analysis — Unweighted plasma concentration data after an oral theophylline dose were fitted to a one-compartment open model by using the following equation⁹⁾:

$$C_t = \frac{F \cdot D \cdot k_a}{V_d(k_a - K)} \left(\frac{1 - \exp(-K \cdot n \cdot \tau)}{1 - \exp(-K \cdot \tau)} \cdot \exp(-K(t - t_0)) - \frac{1 - \exp(-k_a \cdot n \cdot \tau)}{1 - \exp(-k_a \cdot \tau)} \cdot \exp(-k_a(t - t_0)) \right)$$

where k_a is the apparent first-order absorption rate constant (h^{-1}), K is the apparent first-order elimination rate constant (h^{-1}), V_d is the apparent volume of distribution (l/kg), F is the bioavailability, t is the time after administration (h), t_0 is the time to absorption (h), n is the number of administration and τ is the dosing interval (h). The value of V_d was calculated assuming F equals 1.0 because its bioavailability is almost 100%.⁶⁾ The Cl_{sys} was calculated as the product of K and V_d ⁹⁾ to compare the Cl_{sys} in the present study with that in a previous study¹⁰⁾ having insufficient sampling points.

The best fitting values of various pharmacokinetic parameters were calculated by the iterative least squares computer program, MULTI,¹¹⁾ adapted for a microcomputer FM-11EX (Fujitsu Co., Ltd., Tokyo, Japan).

Statistical Analyses — All data were statistically treated and each value was presented as the mean $\pm$ the standard error of the mean (S.E.M.). The Student's paired t -test and the Wilcoxon signed rank test were used for statistical analyses. The values of p less than 0.05 were considered to be significant.

RESULTS

Comparison of Theophylline Pharmacokinetic Parameters between the First and Repeated Dosing

Table I summarizes the results of study I showing theophylline pharmacokinetic parameters following the first and repeated dosings. Significant difference ($p < 0.05$) between the dosings was found only in the Cl_{sys} , which is the

FIG. 2. Typical Plasma Concentration-Time Curves for Theophylline

The solid lines and asterisks indicate the simulated levels obtained by using the pharmacokinetic parameters after the first dosing and the observed levels, respectively.

most important kinetic parameter for dosage regimen calculation. Although the average reduction of the Cl_{sys} was about 24%, the non-smokers showed marked decrease at steady state. Large intersubject variations in the change of Cl_{sys} between both doses were observed and the decrease at steady state ranged from 4.8 to 52.8%.

In light of the results presented in Table I, the volunteers could be classified into two groups; one, the observed levels at steady state were pre-

TABLE I. Comparison of Pharmacokinetic Parameters for Theophylline between First and Repeated Oral Administration

Subject	Age (y)	Body weight (kg)	Dose (mg/kg)	Smoking habit	k_a (h^{-1})		K (h^{-1})		V_d (l/kg)		Lag time (h)		Cl_{sys} (ml/kg/h)	
					First	Repeated	First	Repeated	First	Repeated	First	Repeated	First	Repeated
1	24	65.0	2.44	+	4.03	4.62	0.097	0.124	0.556	0.414	0.43	1.96	53.9	51.3
2	26	69.0	2.29	+	3.32	2.69	0.096	0.113	0.509	0.396	0.27	0.46	48.9	44.7
3	37	72.5	2.18	—	2.02	3.33	0.110	0.093	0.431	0.356	0.93	0.34	47.4	33.1
4	30	57.0	2.77	—	3.02	1.76	0.123	0.108	0.511	0.449	0.28	0.00	62.9	48.5
5	24	56.0	2.82	—	1.17	4.26	0.062	0.055	0.466	0.375	0.00	0.32	28.9	20.6
6	23	55.0	2.87	—	0.43	1.81	0.161	0.061	0.320	0.398	0.29	0.31	51.5	24.3
Mean	27	62.4	2.56		2.33	3.08	0.108	0.092	0.466	0.398	0.37	0.57	48.9	37.1
S.E.M.	2	3.0	0.12		0.56	0.49	0.013	0.012	0.034	0.013	0.13	0.29	4.6	5.3
p					N.S.		N.S.		N.S.		N.S.		<0.05	

Statistical comparisons were performed between first and repeated dosing by using paired t -test. N.S. means not significant. +, smoker; —, non-smoker.

FIG. 3. Plasma Free Fatty Acids Levels Following the First (●) and the Multiple (*) Theophylline Administrations

Each value is the mean $\pm$ S.E.M. Statistical comparisons between the first and repeated dosing were conducted by using Wilcoxon signed rank test and no significant differences were observed.

dictable from the first dosing and the other the steady state levels were higher than the simulated values. Figure 2 illustrates theophylline observed levels and the simulation levels calculated with the pharmacokinetic parameters obtained from the first dose in the respective groups.

These observations demonstrate that time-dependent pharmacokinetics¹²⁾ for the bronchodilator was observed, but not always in all case.

Effect of Theophylline on Plasma FFA Levels

The comparative data of FFA between the first and repeated theophylline administration

are presented in Fig. 3. It has been previously demonstrated that the drug increased plasma FFA levels¹³⁾ which can interrupt cytochrome P-450 system in rats.¹⁴⁾ However, these values were within their normal range and no significant difference was found between both dosings (Wilcoxon signed rank test). This indicates that time-dependent pharmacokinetics of theophylline may not result from the metabolic inhibition due to the elevation of plasma FFA levels.

Test-Dose Study

The results of study II are tabulated in Table II. Comparisons of pharmacokinetic parameters after the test- and multiple calculated-dose were made. Only the Cl_{sys} decreased significantly ($p < 0.02$) as was observed in study I. All subjects who showed mild side effects due to the marked reduction in the Cl_{sys} were also non-smokers. The maximum and minimum plasma concentrations in these three non-smokers were 23.1 ± 0.4 and 13.4 ± 3.0 $\mu\text{g/ml}$, respectively.

Throughout studies I and II, the degree of reduction in Cl_{sys} varied individually from 4.8 to 52.8% and the reduction was dependent on cigarette smoking but independent of age and body weight.

DISCUSSION

We have previously shown that the mean oral Cl_{sys} at steady state, was 18.5% smaller than the Cl_{sys} after a loading administration of double the chronic dose in 8 patients with asthma.¹⁰⁾ Efthimiou *et al.* have also studied intravenous theophylline clearance at steady state in acute and chronic phases at a constant test con-

TABLE II. Comparison of Pharmacokinetic Parameters for Theophylline between Test and Multiple Oral Administration

Subject	Age (y)	Body weight (kg)	Smoking habit	Dose (mg/kg)		k_a (h^{-1})		K (h^{-1})		V_d (l/kg)		Lag time (h)		Cl_{sys} (ml/kg/h)	
				Test	Multiple	Test	Multiple	Test	Multiple	Test	Multiple	Test	Multiple	Test	Multiple
A	27	62.0	+	3.95	3.82	9.54	1.43	0.145	0.104	0.355	0.390	0.13	0.24	51.5	40.6
B	59	60.0	—	3.95	4.84	4.54	8.28	0.160	0.106	0.403	0.327	0.01	0.85	64.5	34.7
C	29	55.0	—	3.95	6.17	0.71	8.20	0.315	0.117	0.251	0.410	0.39	0.91	79.1	48.0
D	30	44.0	—	3.95	4.48	0.41	0.93	0.207	0.102	0.252	0.282	0.30	0.12	52.2	28.8
Mean	36	55.3		3.95	4.83	3.80	4.71	0.207	0.107	0.315	0.352	0.21	0.53	61.8	38.0
S.E.M.	8	4.0		0.00	0.49	2.13	2.04	0.038	0.003	0.038	0.029	0.09	0.20	6.5	4.1
p				N.S.		N.S.		N.S.		N.S.		N.S.		<0.02	

Statistical comparisons were performed between test and multiple dosing by using paired *t*-test. means not significant.

+, smoker; —, non-smoker.

N.S.

centration of 15 $\mu\text{g}/\text{ml}$, excluding significant concentration dependence, and found that the Cl_{sys} in the chronic phase decreased by 26%.³⁾ These reports suggest that the decrease of Cl_{sys} may not result from concentration-dependent pharmacokinetics. In contrast, Vestal *et al.* have recently reported that no significant difference in Cl_{sys} was observed between single and multiple intravenous dosings using stable isotopes⁴⁾ although the *AUC* after oral dosing was 25% higher in the multiple dose study than in the single dose study as was seen in other reports.^{3,15)} Based on the pharmacokinetic simulations used to predict *AUC* and trough plasma concentration after chronic oral dosing, Vestal and others have indicated⁴⁾ that time-dependent pharmacokinetics in the oral study may be due to diurnal variation in the clearance and/or absorption rate.

In two intravenous studies, a slight increase in Cl_{sys} was reported after the morning administration in comparison with the evening administration.¹⁶⁾ On the contrary, some authors have reported¹⁷⁾ that the intravenous Cl_{sys} between the morning and evening doses was identical, but not for oral Cl_{sys} , and that the circadian variation described was due to delayed absorption at night. Thus, the existence of a circadian change in the plasma concentration was demonstrated when a slow-release tablet was administered¹⁷⁾ but reports concerning diurnal change of theophylline metabolism are confusing.^{16,17)} In addition, a 3-h lag in the absorption assumed in the report of Vestal and others⁴⁾ seems unlikely because they used a plain aminophylline tablet which is rapidly and completely absorbed.⁶⁾ Therefore, a large reduction of the Cl_{sys} observed in this study may not be explained by the hypothesis proposed by Vestal *et al.*⁴⁾

Based on the change of Cl_{sys} between single and multiple dosings, our volunteers were roughly classified into two groups, those with constant and others with marked reduction. This classification also appeared to be related to the smoking habit which can induce the P-448 system.^{1, 18a)} Theophylline metabolism is affected by the activity of the P-448 system^{1, 18a)} and secondarily enhances the elimination of the bronchodilator, implying that theophylline time-dependent pharmacokinetics may be associated with its metabolism.

Nonlinear metabolism of theophylline has been reported to occur within the therapeutic

range, particularly in the formation of 3-methylxanthine (3-MX) and 1-methyluric acid (1-MU) which are major metabolites of theophylline¹⁸⁾ in humans, suggesting that theophylline elimination may be dominated by the metabolic saturation. It has been also reported that the fraction of 3-MX recovered in the urine decreased as the steady state plasma concentration of theophylline increased.¹⁹⁾ This might indicate the Michaelis-Menten type formation of 3-MX and/or the contribution of a negative feedback effect of 3-MX on the enzyme system of theophylline metabolism, as reported for exogenous 5-*p*-hydroxyphenylhydantoin, the major metabolite of phenytoin, can inhibit phenytoin metabolism.²⁰⁾ In view of these findings, it seems likely that theophylline is metabolized faster in the first or test administration in studies I and II in which 3-MX would not exist enough to inhibit theophylline metabolism and/or the N-demethylation pathway to 3-MX or 1-MU might not be limited. Our speculation was supported by the fact that the Cl_{sys} increased by 17.9% with time after chronic dosing in rats (T. Kuzuya, I. Johno, and S. Kitazawa, unpublished data) in which the 3-MX formation pathway is completely lacking.²¹⁾

Cigarette smoking leads to about a two-fold increase in theophylline metabolic clearance to 1-MU, 3-MX and 1, 3-dimethyluric acid (1, 3-DMU).²²⁾ In our studies presented here, the average Cl_{sys} in the smokers was almost identical to that in the non-smokers after the single dose, but the smokers showed 34% larger values in the Cl_{sys} during the multiple doses. This also supports our speculation that sufficient accumulation of 3-MX following chronic dosing may inhibit theophylline metabolism. If the effect of negative feedback by the increased 3-MX is found in smokers, theophylline metabolism would be compensated enough since the absolute change of metabolic clearance to 1-MU or 1, 3-DMU was larger than that to 3-MX.²²⁾

The role of oxygen tension (Po_2) in blood has become of major interest lately in theophylline metabolism. The decrease of Po_2 increased theophylline half-life in rat liver perfusion study.²³⁾ This finding is in accordance with the observation that a 2- to 3-fold increase in the Cl_{sys} paralleled the elevation of Po_2 in some patients.²⁴⁾ On the other hand, Nakahara *et al.* have shown that the mean Cl_{sys} in a remission period with higher

Po₂ levels decreased by approximately 30% in comparison with the Cl_{sys} in an asthmatic attack period with lower Po₂ levels.²⁵⁾ The reduction of Cl_{sys} after chronic dosing in the present study might be related to high Po₂ level.

In any case, further investigations are necessary to elucidate the change of theophylline pharmacokinetics associated with time.

Many authors have reported successful examples on the prediction of an oral maintenance dose from a single intravenous or oral test-dose.⁵⁾ However, the present study demonstrated a large intersubject variation of the Cl_{sys} reduction in the multiple administration, ranging from 4.8 to 52.8% (Tables I and II). Similar variation was also found in our previous study.¹⁰⁾ The Cl_{sys} for six patients decreased 4.2 to 62.6% and for two patients increased during chronic doses (4.0 and 11.0%).

In conclusion, because a large interindividual variation of Cl_{sys} change associated with time, the theophylline test-dose concept must be practiced carefully and monitored frequently until stable plasma levels are obtained.

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