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Pharmacokinetics of Oral Theophylline in Thai Asthmatic Children

Renu Koysooko*, Montri Tuchinda, Suprida Habanananda, Theerawut Pinthong*, Jonggonnee Wattanapermpool*, and Sirikul Geadsomnuig

Summary **Pharmacokinetic studies of theophylline were carried out in 12 Thai asthmatic children after oral administration of Elixir Quibron and Tablet Aminophylline. No significant differences in any of the pharmacokinetic parameters between these two dosage forms were observed. Peak serum concentrations of theophylline were reached in an average time of 3.16 hours (range 1.71 – 7.71). It was shown that the elimination half-life of theophylline in Thai asthmatic children (average 7.21 hours) was longer than that observed for subjects in western countries. Variations in elimination half-lives ranging from 4.44 to 14.34 hours were intersubject variations.**

Due to the slow elimination of theophylline in Thai patients, a dosage regimen of 5 mg/kg every 8 hours was recommended as more suitable than 5 mg/kg every 6 hours. Using data from this study, the predicted maximum and minimum serum theophylline concentrations at steady state were calculated to be 16.53 μg/ml and 9.96 μg/ml, respectively. This dosage regimen should be suitable not only for Thai people but also for Asian people of similar races and under similar environmental conditions.

Theophylline is an effective bronchodilator used widely in acute attacks and long term treatment of asthma. It has been shown that the intensity of the effect of theophylline on pulmonary function is related to the concentration of drug in plasma or serum.[1-5] The minimum effective plasma concentration of theophylline is generally considered to be about 5 μg/ml, and the average therapeutic concentration is about 10 μg/ml.[2] Concentrations in excess of 20 μg/ml may produce nausea and other adverse effects.[6] To achieve maximum therapeutic benefit with minimum adverse effects, plasma theophylline should be maintained within the therapeutic range. The therapeutic concentration of theophylline for children appears to be in the same range as for adults. Weinberger *et al.*[7] showed that a theophylline dosage regimen which produced average serum concentrations of 13 μg/ml and 9 μg/ml at 2 and 4 hours was highly effective in relieving signs and symptoms of asthma in children.

The plasma theophylline concentrations will fluctuate as a result of absorption, distribution and elimination. Studies in adults and children[6,8] have shown appreciable intersubject variation in the biological half-life of theophylline. Erratic absorption, incomplete bioavailability, and inadequate compliance may further complicate the achievement and maintenance of theophylline concentrations in the therapeutic range. Considering the importance of maintaining plasma theophylline concentrations within a relatively narrow range, it is necessary to have pharmacokinetic data from asthmatic patients. Lack of such information may lead to subtherapeutic plasma concentrations in some and toxic concentrations in other asthmatic patients. One study in asthmatic outpatient children on the same prescribed theophylline dosage regimen revealed 4 with plasma concentrations above 10 μg/ml, 16 with concentrations less than 5 μg/ml, and 10 with no detectable theophylline in the plasma.[9]

In Thailand, few studies[10,11] have been done concerning serum theophylline levels in asthmatic patients after oral and intravenous

From the Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, and *Division of Medical Research, Department of Medical Sciences, Ministry of Public Health, Bangkok, Thailand.

administrations of the drug. Following oral administration, the maximum serum level with no observed side effects was reported to be 11.0 μg/ml.[10] In another study,[11] adverse effects of nausea, vomiting and headache were observed in patients with serum theophylline concentrations above 15 μg/ml. Since pharmacokinetic studies were not carried out thoroughly, the study only indicated that the elimination half-life of theophylline in Thai asthmatic children was longer than that observed in European or Caucasian children. Therefore, the purpose of this study was to determine the pharmacokinetic parameters in Thai asthmatic children after oral administration of elixir or tablet forms of theophylline. Special emphasis was placed on analysis of the parameter variations in order to determine the dosage regimen for maximal therapeutic benefit with minimal risk.

MATERIALS AND METHODS

The study was carried out on 12 Thai asthmatic children, 10 to 14 years old and weighing between 25 and 44 kg, who attended the Allergy Clinic at the Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand, between 1985-1986. All patients and parents gave verbal consent for the study. They had been off theophylline medication for at least one week and had received no other drugs or caffeine containing beverages for 2 days before the study.

Every subject received two preparations of theophylline, Elixir Quibron* and Tablet Aminophylline**, 1 hour after a light breakfast, firstly to prevent gastric disturbance due to the side effect of theophylline and secondly to obtain the pharmacokinetic parameters from asthmatic patients under the same conditions should they come to the hospital for treatment. The two preparations were given in a crossover design with a one week wash out period. The dose administered was 5 mg theophylline/kg body weight.

Five milliliter blood samples were collected immediately before and at 10 mins, 30 mins, 1, 2, 4, 6 and 8 hours subsequent to drug administration. The serum was separated and assayed for theophylline concentration by the ultraviolet spectrophotometric method.[12]

Pharmacokinetic analysis

Previous studies[8,13] showed that the pharmacokinetics of theophylline following intravenous bolus administration could be described by a two-compartment model. However, in the present oral study, a clearly distributive phase was not evident in any serum concentration-time profile. Therefore, the data were analyzed using a simple linear one-compartment open model[14] to determine the pharmacokinetic parameters, comprising of absorption rate constant, elimination rate constant, elimination half-life, peak serum concentration, and time to peak concentration. The area under the serum concentration-time curve from the time of drug administration to 8 hours afterwards was calculated using the linear trapezoidal method. The area from 8 hours to infinity was estimated by dividing the serum concentration at 8 hours by the slope of the terminal log-linear phase of the semilogarithmic plots of concentrations versus time.

The average serum concentration at steady state ($\overline{C}_{ss}$) after multiple oral doses given at a constant dosing interval was calculated from[15]

$$\overline{C}_{ss} = \frac{[AUC]_{0-\infty}}{\tau}$$

where $[AUC]_{0-\infty}$ is the area under the concentration time curve from time zero to infinity after a single dose administration and τ is the dosing interval.

The serum concentration of drug at any time during a multiple dosage regimen was determined as follows:[14]

$$C_n = \frac{FX_0Ka}{V(Ka-K)}\left[\left(\frac{1-e^{-nK\tau}}{1-e^{-K\tau}}\right)e^{-Kt} - \left(\frac{1-e^{-nKa\tau}}{1-e^{-Ka\tau}}\right)e^{-Kat}\right]$$

where Ka = the apparent first order absorption rate constant
K = the apparent first order elimination rate constant
τ = the dosing interval
t = t_{max} when maximum concentration during a dosing interval was determined.
= T when minimum concentration during a dosing interval was determined.
F = the fraction of the administered dose absorbed
Xo = the dose administered
and V = the volume of distribution

In this study the term $\frac{FXo}{V}$ was determined from

$$\frac{FXo}{V} = [AUC]_{0-\infty}\,K$$

* Elixir Quibron (Bristol - Myers LTD.,) containing 50 mg theophylline/5 ml

** Tablet Aminophylline (The Government Pharmaceutical Organization) containing 85% theophylline.

Statistical analysis

The results were expressed as the mean ± standard error. Student's paired *t*-test[16] was used to determine the significant difference.

RESULTS

The mean serum theophylline concentrations-time profiles following oral administration of single doses of 5 mg theophylline/kg body weight in elixir or tablet form are shown in Figures 1 and 2, respectively. The serum data of individual subject were fitted to a one compartment open model system for the calculation of pharmacokinetic parameters. The mean values, standard errors of the means, and coefficients of variation for the parameters obtained from 12 asthmatic children administered elixir or tablets of theophylline are summarized in Table 1. The pharmacokinetic values obtained showed bioequivalence of the two preparations. No significant difference was observed in either speed or extent of drug absorption ($p > 0.05$).

Substantial variations in the absorption rate constants of theophylline for elixir (0.4426-1.6703 hr^{-1}) and for tablets (0.1829-1.7299 hr^{-1}) were observed. Intersubject variation in absorption rate constants was less with elixir (CV, 42.72%) than tablets (CV, 52.22%). There was no statistically significant correlation of the absorption rate constants either with the ages or weights of the children.

Mean theophylline peak concentrations following administration of elixir and tablets were 7.75 and 7.16 μg/ml, respectively. The intersubject variations in the peak concentrations (CV, 21.01% and 25.16%, respectively) were considerably smaller than the variations in the absorption rate constants (CV, 42.72% and 52.22%, respectively).

For elixir and tablets, the elimination rate constants as well as the elimination half-lives of theophylline following administration were not significantly different. The mean elimination half-lives were 6.57 and 7.84 hours, respectively. The individual half-life values are graphically presented in Figure 3. Variations in elimination half-lives ranging from 4.44 to 14.34 hours were observed. This variation appeared to be an intersubject variation (intersubject SD = 2.15 and 2.49) rather than an intrasubject variation (intrasubject SD = 1.42) as shown in Table 2.

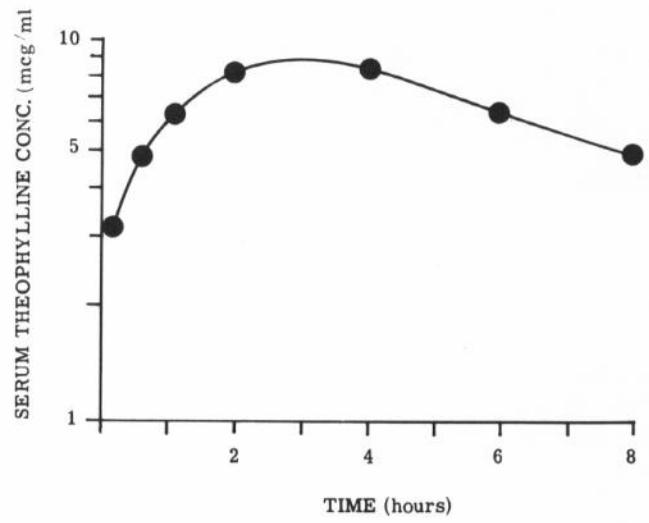

Fig. 1 Mean serum theophylline concentrations in 12 asthmatic children as a function of time after a 5 mg/kg single oral administration of elixir.

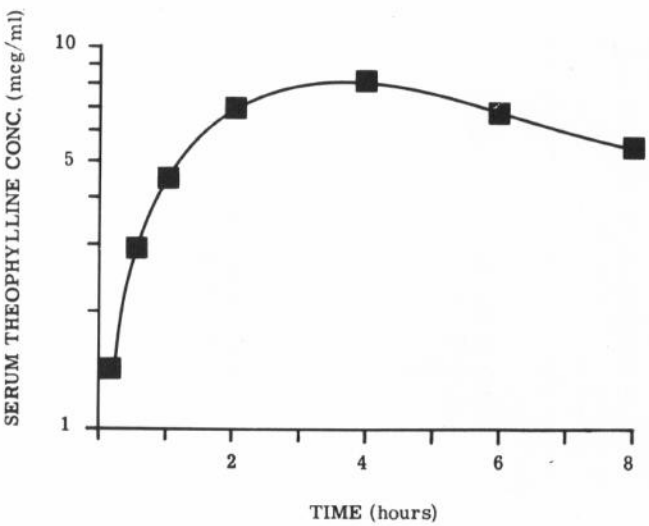

Fig. 2 Mean serum theophylline concentrations in 12 asthmatic children as a function of time after a 5 mg/kg single oral administration of tablets.

There was no statistically significant correlation between the elimination half-lives and the ages of the children, but a correlation was observable between the half-lives and the weights of the subjects ($r = 0.4508$, $p < 0.05$) as illustrated in Figure 4.

DISCUSSION

Since the pharmacokinetic parameters obtained after administration of theophylline in elixir and tablet forms were not significantly different, the two mean values were computed to get the average value of each parameter (Table 1).

Table 1 Summary of pharmacokinetic constants of theophylline in 12 Thai asthmatic children

Constant	Elixir		Tablets		Average
	Mean (SE)	% CV	Mean (SE)	% CV	
Absorption rate const. (Ka), hr^{-1}	0.9536 (0.1176)	42.72	0.8292 (0.1250)	52.22	0.8914
Elimination rate const. (K), hr^{-1}	0.1136 (0.0084)	25.61	0.0956 (0.0076)	27.54	0.1046
Elimination half-life ($T_{1/2}$), hr	6.57 (0.62)	32.69	7.84 (0.72)	31.81	7.21
Time to maximum conc. (T_{max}), hr	2.77 (0.21)	26.26	3.55 (0.49)	47.81	3.16
Maximum conc. (C_{max}), μg/ml	7.75 (0.47)	21.01	7.16 (0.52)	25.16	7.46
Area under curve $(AUC)_{0\rightarrow\infty}$ μg-hr/ml	104.11 (9.56)	31.81	115.96 (11.59)	34.62	110.04

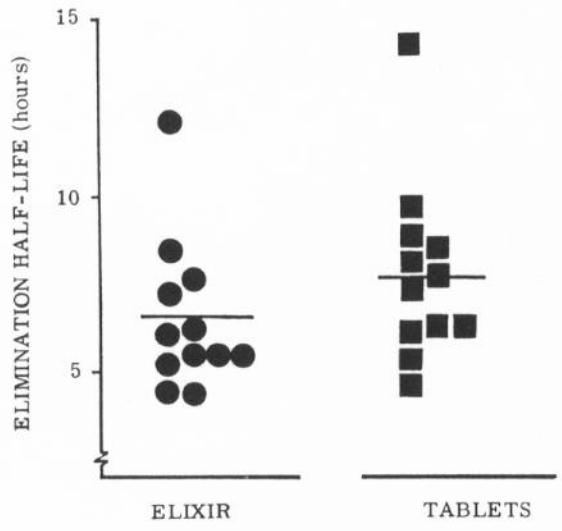

Fig. 3 Variation in elimination half-lives of theophylline after oral administration of elixir or tablets.

The peak serum concentrations of theophylline were reached in an average of 3.16 hours (range 1.71-7.71). Some investigators[6,17,18] studying adult asthmatic patients have reported that oral elixirs and solutions are absorbed rapidly with peak plasma concentrations being reached in 30 minutes to 2 hours, whereas uncoated tablets give peak plasma concentrations between 1 to 3 hours after drug administration. Weinberger and Bronsky[7] found that a mean peak serum concentration of 12.7 μg/ml was observed 2 hours after oral administration of Aminophylline Tablets to asthmatic children. The slower rate of absorption observed in this study may probably be due to the effect of food ingestion before drug administration. The absorption parameters obtained represent the absorption characteristic in general asthmatic patients usually taking the drug after meal.

The results also showed that intersubject variation in absorption rate constant was less with elixir than tablets. Since the drug in tablet form has to disintegrate and be dissolved before absorption can occur. Therefore, disintegration and dissolution are additional factors contributed to the intersubject variation in absorption rate constant of tablet form.

The elimination half-lives of theophylline ranged from 4.44 to 14.34 hours, with an average value of 7.21 hours in our study. Jenne *et al*[6] reported wide intersubject variations in theophylline half-lives of 3.01-9.51 hours (mean = 5.2 hours) based on a one compartment model and following constant intravenous infusion of 42.5 mg of theophylline per hour to 10 asthmatic children. Mitenko and Ogilvie[13] determined the pharmacokinetic parameters of theophylline following

Table 2 Intersubject and intrasubject variations in elimination half-life values of theophylline after administration to 12 Thai asthmatic children

Patient	Age (yr)	Weight (kg)	Elimination Half-life, hours	
			Elixir	Tablets
1	13	41.5	4.48	8.74
2	11	29.9	7.24	6.08
3	12	25.9	5.28	6.08
4	12	28.7	6.08	4.72
5	13	38.3	6.27	5.57
6	13	32.7	4.44	7.66
7	14	38.6	12.12	14.34
8	13	44.0	8.49	9.64
9	11	25.1	5.68	6.32
10	9	30.9	7.69	8.54
11	10	25.9	5.59	7.88
12	12	25.4	5.50	6.39
		Mean	6.57	7.84
		SD.	2.15	2.49
		% CV	32.69	31.81
		SD, intrasubject	1.42	

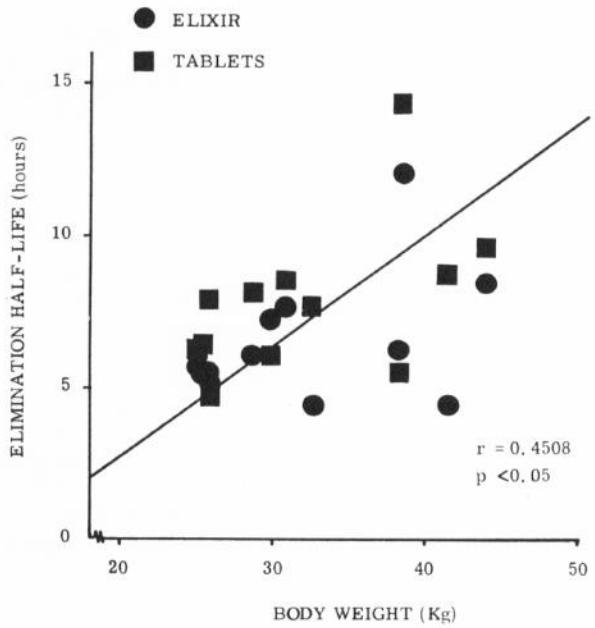

Fig. 4 Relationship between elimination half-lives of theophylline and body weights of the patients.

intravenous injection into 7 asthmatic patients and 9 normal volunteers. A mean beta disposition constant of 0.159 hr^{-1} and a corresponding plasma half-life of 4.36 hours were observed. Ellis *et al*[8] reported that biological half-lives of theophylline following intravenous injection of aminophylline to 30 asthmatic children ranged from 1.42 to 7.85 hours with a mean value of 3.69 hours. The elimination half-life following a single oral administration of Elixophylline to 12 healthy volunteers was reported to be 4.62 hours.[19] From these observations it can definitely be concluded that Thai asthmatic children eliminate theophylline at a slower rate than subjects in studies from western countries. Differences in metabolism are suspected to be responsible for this half-life variation because metabolism accounts for over 85% of the elimination of theophylline in man.[20] It is known that genetic factors and environmental factors such as diet and nutrition play important roles for individual differences in drug metabolism.[21] Thai diet is always high in carbohydrate and low in protein. Juan *et al*,[22] in the study of effect of dietary protein on theophylline pharmacokinetics, reported that with a low protein diet the mean theophylline half-life in 6 young men was longer than that with high protein diet. This observation supports the result obtained in our study.

Peak serum concentrations after a single oral administration of elixir or tablet form of theophylline were 5.69-11.83 μg/ml and 3.35-9.93 μg/ml, respectively. Only one subject taking tablets had a serum concentration below the minimum effective concentration of 5 μg/ml. Based on the average data in Table 1, the expected average serum concentration at steady state ($\overline{C}_{ss}$)[15] after multiple dosing in a conventional

regimen of 5 mg/kg every 6 hours was calculated to be 18.34 μg/ml. Maximum and minimum serum concentrations at steady state were also calculated and expected to be 20.10 μg/ml and 14.94 μg/ml, respectively. This calculated range of serum concentrations (14.94-20.10 μg/ml) was unfortunately within the range for which adverse effects had been observed in Thai asthmatic children.[11] If the dosage regimen were changed to 5 mg/kg every 8 hours, an average steady state serum concentration of 13.76 μg/ml and maximum and minimum steady state values of 16.53 μg/ml and 9.96 μg/ml, respectively, would be obtained. Figure 5 shows the predicted blood level curves following multiple theophylline dosing in 2 regimens (5 mg/kg every 6 hours and 5 mg/kg every 8 hours). This is a simulation derived by using the average pharmacokinetic parameters obtained from our study. Details of the calculation are shown in the pharmacokinetic analysis section. It was found that a dosing interval of 8 hours was more suitable for Thai asthmatic children due to slow elimination of the drug. People in Southeast Asian countries are under more or less similar environmental conditions. Therefore, the dosage regimen suggested in this study may be suitable not only for Thai people but also for other Southeast Asian people.

From a practical point of view, due to the great intersubject variation in elimination half-life of theophylline and due to possibly erratic absorption and compliance problems, particularly with chronically ill patients under long-term maintenance therapy, it is advised that theophylline dosage regimens be individualized. This would assure that plasma theophylline concentrations were in the therapeutic range. For easy monitoring, serum theophylline concentrations can be estimated indirectly by measuring theophylline concentrations in saliva.[23]

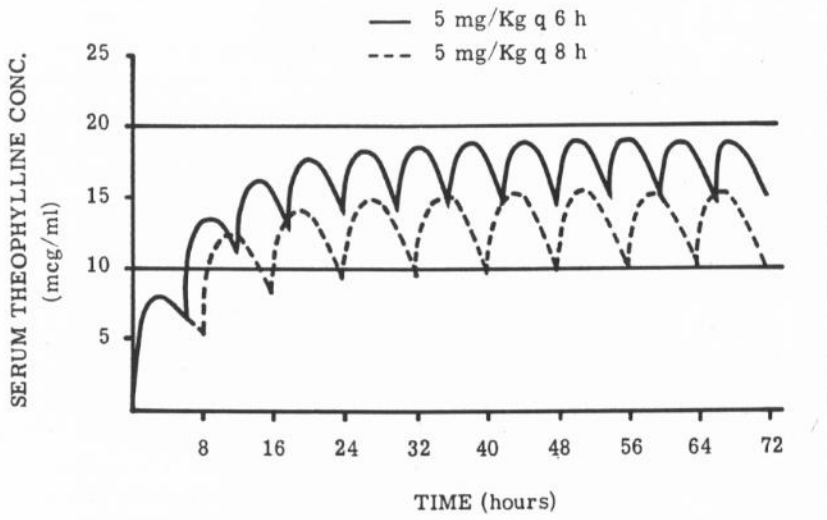

Fig. 5 Predicted serum level curves following multiple theophylline dosing in 2 regimens of 5 mg/kg every 6 hours (———) and 5 mg/kg every 8 hours (------). The simulation is based on the average pharmacokinetic parameters from this study.

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