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Theophylline Pharmacokinetics in Thai Children

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SUMMARY **To validate a previously suggested dosing regimen of aminophylline administration for Thai children[1], we enrolled 13 asthmatic Thai children (5 girls and 8 boys) between the ages of 7.5-13.4 years (mean=10.4 years) into a 36-hour, multiple-dose, oral theophylline pharmacokinetic study using plain aminophylline tablets at a dosage of 5 mg of theophylline base/kg every 8 hours. All patients were studied in the steady state. Blood samples were obtained every 2 hours for 24 hours; thereafter, samples were obtained more frequently for another 12 hours to determine theophylline pharmacokinetic parameters. Serum theophylline concentrations (STC) were assayed with a fluorescence polarization immunoassay method (TDX). Significant interpatient variations in STCs were observed. Five patients had peak STCs in the toxic range (>20 μg/ml). Most patients had reproducible STC patterns during the study period; however, marked variations of STCs were observed with a mean percent of fluctuations {(Cmax-Cmin)/Cmin *100} of 535.6%. Using the PC Nonlin computer interpolation program by a modification with a baseline decay method and the Lagrange polynominal interpolation technique, approximate pharmacokinetic parameters were calculated and the results were as follows: plasma half life (t1/2) = 3.08 hours, elimination rate constant (Kel) = 0.26 hour-1, absorption rate constant (Ka) = 2.21 hour-1, volume of distribution (Vd) = 0.23 l/kg and plasma clearance (Cl) = 56 ml/kg/hour. Since these calculated parameters could be imprecise due to delayed absorption of oral theophylline dosages, a single-dose intravenous theophylline pharmacokinetic study was further examined in another 13 patients (age range = 7-12 years, mean = 8.9 years) to determine more accurate pharmacokinetic data using intravenous aminophylline at dosage of 5.8 mg/kg. Data derived from this part of the study were t 1/2 = 4.25 hours, Kel = 0.19 hour-1, Vd = 0.44 l/kg, Clp = 90 ml/kg/hour and a mean residence time (MRT) of 5.84 hours. From these data, we conclude that theophylline pharmacokinetic data in this group of Thai children did not differ significantly form Caucasian children in the same age range. We therefore suggest that the routine dose regimen as recommended for Caucasian children in this age group may be applicable to Thai children as well.**

Increasing awareness of clinical toxicity of theophylline, together with its less active bronchodilatory effect compared to beta-adrenergics has led to a decline in the popularity of its use in adult asthmatics.[2] Inspite of this, theophylline continues to be a commonly prescribed drug in the treatment of asthma in pediatric patients,[3] perhaps due of the ease of administering oral sustained-release theophylline preparations, twice daily, compared with the difficulty of administering beta-adrenergic aerosol, four times daily. Moreover, daily administration of theophylline has been shown to reduce symptoms of asthma and to reduce the need for additional bronchodialators in children with moderately severe asthma.[4-7]

Pharmacokinetics of theophylline have been thoroughly examined in Caucasian children.[8-11] Theophylline metabolism decreases with age and its elimination half-life was determined to be approximately 4 hours. On the contrary, data on theophylline pharmacokinetics in Asian children have been sparse. During the past decade, preliminary studies from Thailand have suggested that theophylline metabolism in Thai children may be slower than in their Caucasian counterparts.[1,12] The reason for this discrepancy in metabolism is unclear; however, it has been speculated that it could be the result of differences in the composition of the Thai diet which is rich in carbohydrate and low in protein content.[13,14] Because of the slow elimination half-life, Koysooko *et al.*[1] have suggested that aminophylline tablets can be given on a q 8 hour schedule in lieu of a

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more familiar q 6 hour schedule to Thai children. Such knowledge has become increasingly essential not only because of a relatively high prevalence of allergic diseases among Asian populations[15] but also due to the current migration of Asian people to countries all over the world, particularly to in the European and North American continents.

This investigation was initially designed to validate the previously proposed, computer-simulated dosage regimen of aminophylline administration for Thai children (multiple-dose oral theophylline pharmacokinetic study). Since the results of our oral study were unusual, a single-dose intravenous pharmacokinetic study was then carried out in another, similar group of children to calculate accurately the pharmacokinetic parameters in Thai children.

MATERIALS AND METHODS

Patient selection

Thirteen asthmatic children (8 boys and 5 girls) were recruited from the Pediatric Allergy Clinic of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand for the oral part of the study. Their ages ranged from 7.5 to 13.4 years with the mean ± SD of 10.4 ± 2 years. Their demographic characteristics are outlined in Table 1. Their height and weight were between the 10th and 90th percentiles for Thai children; all patients had weight percentiles corresponding to their height percentiles.[16] Their diet was a typical Thai diet, the composition of which has been previously determined to consist of approximately 55% carbohydrate, 30% fat, and 15% protein.[17]

For the second part of the study (intravenous study), a separate group of 13 patients (7 boys and 6 girls) was studied. Their demographic characteristics, also shown in Table 1, were similar to those enrolled into the oral study.

Exclusion criteria for patients participating in both parts of the study were those with unstable asthma, those with hypersensitivity to methylxanthines, those with previous upper respiratory tract infections and those with acute asthmatic attack within the previous week prior to the time of the study. Most patients used inhaled beta-adrenergics on an irregular basis (not more often than every 6 hours). Liver function (SGOT, SGPT and alkaline phosphatase) and renal function data (blood urea nitrogen and creatinine) were obtained; the results were within the normal range for age. None of the patients took any drugs which would interfere with theophylline metabolism (such as erythromycin or barbiturates) at or close to the time of the study. Written informed consent was obtained from the parents. Both parts of the study were conducted on an in-patient basis, in the Pediatric Research Unit of the Department of Pediatrics Siriraj Hospital throughout the entire study period. The study was reviewed and approved by the Human Ethic Review Committee of the Siriraj Hospital, Bangkok Thailand.

Oral pharmacokinetic study

Plain aminophylline tablets (The Thailand Government Pharmaceutical Organization, Bangkok, 100 mg/tablet) were administered orally at a dosage and intervals as suggested by Koysooko *et al.*[1] ie 5.8 mg/kg (5 mg/kg of theophylline base, with dose rounded off to the nearest 50 mg) every 8 hours. These doses were given under nursing supervision for 72 hours prior to the study time to ensure that the steady state level had been reached. During the pharmacokinetic study, aminophylline tablets were continued every 8 hour for another four doses (Fig. 1). All doses of aminophylline were given at least one half hour before meal. Side effects from theophylline such as headache, vomiting, palpitation and restlessness were thoroughly monitored by research nurses and staffs throughout the entire study period.

At the steady state (72 hours after the first oral dose), an indwelling intravenous plastic catheter was inserted into an arm vein and 2 ml-blood samples were obtained every 2 hours for 24 hours starting at 8 am of the study day (due to the limit blood volume that could be sampled out from each child, blood specimen at 4th hour after each dose was not sampled). After the final aminophylline dose (Fig. 1), samples were obtained at 15, 30, 60, 120 minutes, and 4, 6, 8, and 12 hours to determine the Kel, t 1/2, Cl and Vd. Total duration for blood sampling was 36 hours. The appro-

Table 1. Anthropometric data of Thai children in theophylline study.

	Oral	Intravenous
1. No. of patients	13	13
2. Age		
range	7.5-13.4	7-12
mean	10.4	8.96
3. Height (mean)	137	131
4. Weight (mean)	32.8	28.7

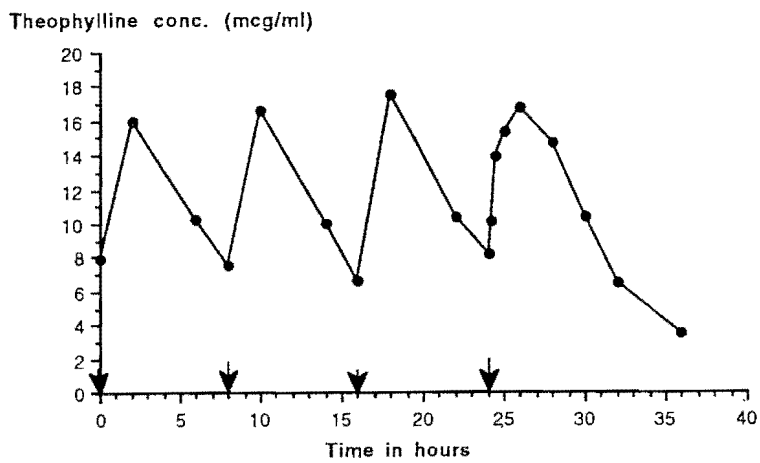

Fig. 1. Mean theophylline concentrations of the oral theophylline pharmacokinetic study in 13 children using plain aminophylline tablets with dosage of 5.8 mg/kg/dose every 8 hours. Arrows indicate times of administrations of dosages. See text for detail.

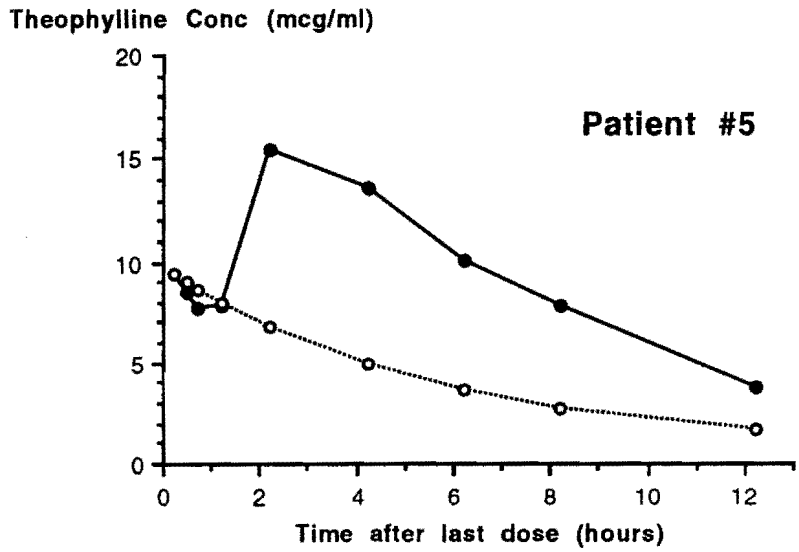

Fig. 2. A serum theophylline concentration-time curve (filled circles) of the terminal part the oral aminophylline pharmacokinetic profile in one patient. The hatched line (open circles) illustrates a conceptual plot of the decay of the baseline theophylline level calculated by using formula $Ct = Coe^{-kt}$ (see text for details).

ximate amount of blood sampled from each patient was 40 ml. Samples were centrifuged with serum separated and kept frozen at -20°C until the time of theophylline analysis. STCs were assayed by fluorescence polarisation immunoassay (FPIA, TDX, Abbott Laboratories, North Chicago, Illinosis[18,19]). The coefficient of variation was determined to be less than 5%.

Since the baseline values of the final 12 hours of the study were not zero, data from the last 12 hours were then modified by calculation of metabolic decay of baseline STCs utilizing the formula $Ct = Coe^{-kt}$ whereas Ct = concentration at time t, Co = concentration of baseline theophylline at 24th hour (prior to the last dose of theophylline) and k = elimination rate constant (estimated with the least square method). These derived values were then subtracted from the actual values at each time point (Fig. 2); the substracted values were then plotted on a semilogarithmic scale versus time. A best curve was constructed and was extended to intercept the abscissa and the ordinate to determine Cp0 and beta, respectively. Volume of distribution was calculated from the formula Cp0 = Dose/Vd and the absorbtion rate constant (Ka) was estimated from the formula beta = (-Ka)/2.303.[20] Elimination rate constant (Kel) was determined by the lease square regression of the terminal logarithm of the serum concentration over time curve during the terminal portion of elimination. These data were then fitted into the one compartment module with first order-input, first order-output with no lagtime of the PC Nonlin program (Statistical Consultant, Lexington, Ky) on a microcomputer; after the fitting, the program calculated a set of more precise relevant pharmacokinetic parameters (Kel, Ka, Vd and AUC). Clearance and t1/2 were then calculated from these parameters using formulas:

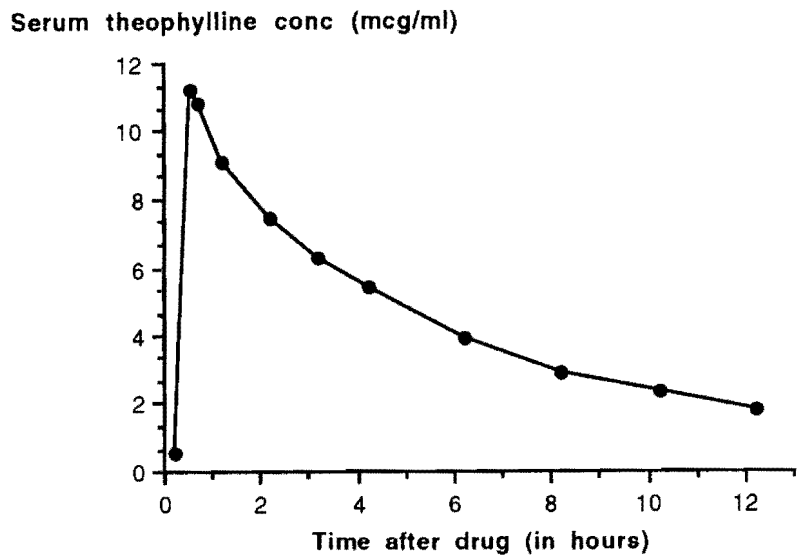

Fig. 3. Result of an intravenous theophylline pharmacokinetic study in 13 children. Dosage of aminophylline used was 5.8 mg/kg administered as a single dose via IV drip over 15 minutes. Pharmacokinetic parameters are tabulated in Table II.

clearance = Vdss x Kel, and t1/2 = 0.693/Kel.

Also, the unaltered data during the last 12 hours of the study were simultaneously fitted into the Lagrange polynomial interpolation computer program[21] (see detail description of the calculation below). The pharmacokinetic results obtained from this latter method of calculation were similar to those obtained with the PC Nonlin. Thus, only data from PC Nonlin calculation are presented in the result section.

Intravenous pharmacokinetic study

Intravenous preparation of aminophylline (Atlantic Laboratories, Bangkok Thailand) 25 mg/ml at a dosage of 5.8 mg/kg (5 mg/kg of theophylline base diluted with sterile water to 20 ml) was slowly administered intravenously over 15 minutes. Blood samples were obtained from an indwelling plastic intravenous catheter placed in the contralateral arm vein at 0, 15, 30, 60, 120 minutes, and 3, 4, 6, 8, 10, and 12 hours after the dose as previously recommended.[22] Samples were processed in a similar manner as in the oral pharmacokinetic study.

Data were fitted into a single compartment pharmacokinetic model utilizing the Lagrange polynominal interpolation computer program.[21] The program calculated the area under the concentration time curve (AUC) using the least-squares terminal slope to extrapolate to time infinity. The first moment of the curve and the area under the time-concentration-time-moment curve (AUMC) was also calculated by the program. These values permitted the calculation of the total body clearance (Cl) from dose/AUC, the mean residence time (MRT) from AUMC/AUC, and the steady state volume of distribution (Vdss) from (Clp) (MRT). The terminal elimination phase which is linear, allows calculation of the elimination rate constant (Kel) and elimination half-life (t1/2).

RESULTS

Oral theophylline pharmacokinetic data

Thirteen patients completed the oral study. The mean STCs at various time points is illustrated graphically in Fig. 1. Significant interpatient variations of the baseline STCs were observed (range 1.4-17.59 μg/ml). Five patients with low trough STCs (≤6 μg/ml) had low peak STCs (≤13 μg/ml). Four patients with higher trough STCs had peak STCs in desirable range (15-20 μg/ml). Four patients with high trough STCs (10-17 μg/ml) had toxic peak STCs (20-32 μg/ml); although no adverse reaction was observed in any patients during the entire study. One patient demonstrated a significant variability in the absorption pattern. Peak STCs in general occurred at 2 hours post dose. Although a consistent pattern of rise and fall of STCs was observed in each patient, significant variations of STCs defined as differences between peak and trough STCs expressed as percents of the trough STCs[23] were 535%. By excluding 4 patients with extreme fluctuations of STCs (patients #8 through #11), the mean variation of STCs in the remaining 9 patients was still unacceptably high (204.6%). We then calculated pharmacokinetic parameters of theophylline by using methods described as above. As stated the results of pharmacokinetic data from both methods of calculation (PC Nonlin and Lagrange methods) were similar; the data obtained with a single compartment module from PC Nonlin are shown in Table 2. The mean ± SD values of half life is 3.09 ± 1.35 hour with Kel = 0.26 ± 0.09 hour^{-1},

Table 2. Theophylline pharmacokinetic results (mean with range).

	Oral (PC Nonlin) (Lagran)	Intravenous	Oral (Koysooko, 1)	Intravenous (Ellis, 8)	
1. Clearance	56.08 (29.2-118.7)	90 (40-200)	45.5	87 (30.6-221)	ml/kg/hr
2. Vdss	0.23 (0.12-0.47)	0.44 (0.37-0.66)	0.475	0.42 (0.27-0.51)	l/kg
3. Kel	0.26 (0.12-0.47)	0.20 (0.1-0.35)	0.1	0.4 (0.19-0.8)	hr-1
4. t1/2	3.08 (1.47-5.98)	4.11 (1.96-7.0)	7.21	3.69 (1.42-7.85)	hours

Ka = 2.21 ± 4.89 hour^{-1}, Vd = 0.23 ± 0.1 l/kg and Cl of 56 ± 25 ml/kg/hour. The t1/2 from our study is similar to that found in caucasian children[8-11] and differed from that observed by Koysooko *et al.*[1] Since the absorption of aminophylline could be delayed due to food effect and could have resulted in the slow clearance calculated {(Cl = (Dose x F)/AUC}, we, therefore, proceeded with an intravenous theophylline pharmacokinetic study in order to obtain more accurate and more precise data in Thai children.

Intravenous pharmacokinetic data

The demographic characteristics of children participated in this part of the study (a separate group of children from the oral study), are shown in Table 1. As in the oral study, their heights, weights and diet composition represented those of normal Thai children. By using the Lagrange computer model, we confirmed our hypothesis that the clearance and volume of distribution calculated from the oral part were underestimated. The mean (±SD) of Vd, Cl, Kel and t1/2 are shown in Table 2. It is apparent that Vd derived from the IV kinetic study did not differ from those observed in Caucasian children. In fact, total body clearance, Kel and t1/2 of our children were similar to those previously reported in children by investigators from western countries.[8-11]

DISCUSSION

Our attempt to validate the proposed theophylline regimen by Koysooko *et al.* revealed extremely variable theophylline concentrations among our group of patients. Only 4 of 13 patients had both peak and trough STCs within the acceptable therapeutic range. Several patients had high degrees of STCs fluctuation suggesting high plasma clearance.[24] Indeed, in examining data from our patients with extreme degree of variability, their Kels were all over 0.3 hour^{-1}, indicating a rapid elimination phase (t1/2 ≤ 2.3 hours). Due to these unexpected results, we attempted to calculate pharmacokinetic parameters from our patients in this oral study to find an explanation for the discrepancy between our results and that previously published. We used two methods for the calculation of these parameters (PC Nonlin and Lagrange methods) since we realized that the first method (PC Nonlin with base line decay modification) might not have been the ideal method due to the hypothetical Cp0 value which could have led to an imprecisely calculated Vd. Surprisingly, pharmacokinetic data from these two methods yielded very similar results, particularly on the Kels which was notably greater than that found in Koysooko's study (0.26 hour^{-1} vs 0.1 hour^{-1}). Consequently, t1/2 from our study was much shorter (4 hours) from that of Koysooko's (7 hours). The aminophylline administration in both studies was by the oral route which can be subjected to an imprecise calculation of Vd, Cl and t1/2 possibly due to interference of theophylline absorption by concomitant food intake.[25,26] With this possibility in mind, we therefore elected to proceed with an intravenous pharmacokinetic study which is the most reliable method to calculate pharmacokinetic data to settle this dispute. Although it would have been ideal to recruit the same group of children who had been studied in our oral study, we were not able to convince the parents of all these

children to be restudied. Therefore, another group of children with similar demographic data were recruited. From Table 2, it is apparent that Kel and t1/2 in patients from our IV study were similar to those obtained in our oral study and also were similar to those previously reported in Caucasian children. These results suggest that our calculations were indeed correct and there could be some factor(s) explaining prolonged half lives in Koysooko's study. We believed that this apparently prolonged half lives were mainly due to the food effect as described above since aminophylline tablets in that study were given with food so as to avoid gastrointestinal upset.

Since the pharmacokinetic results of our study were quite similar to those studied in Caucasian children, it is reasonable to assume that theophylline recommendations for Caucasian children at this age group (9-11 years) may be applicable to Thai children for the same age group as well[27] (20 mg/kg/d, equally divided into q 6 hour doses). Although validity of this recommendation was verified a decade by Milavetz *et al.*[28] after it was initially proposed, it is prudent to recommend monitoring of STCs to ensure therapeutic concentrations since it has been shown as in our study that STC could vary widely among individuals. It is to be noted that in responding to an increase in the publicity of theophylline toxicity in the United States, a revision of dose schedule with a slightly lower doage range has been proposed.[29]

Whether the recommendations for younger Caucasian children (less than 9 years) could be applied to younger Thai children of the same age is not clear. Since diets of infants and younger children in Thailand contained the highest protein content in their diet (breast milk, infant formula and protein supplement) relative to diet for other age groups, it is reasonable that their theophylline requirement should not differ from those suggested by Wyatt *et al.*[27] In our preliminary observations (Vichyanond, unpublished data), the total body clearance in Thai children aged 2-6 years was extremely high (mean = 230 ml/kg/hour with very short half-lives (mean t1/2 = 2.1 hours). We therefore are following the recommendation from Wyatt *et al.*[27] and Hendeles *et al.*[29] in prescribing theophylline to our pediatric patients of all age ranges.

Currently, insufficient data exist to make a firm recommendation for the dosage of slow-release formulations to be used in Thai children. However, examination of data from Tuchinda's study[30] utilizing a low dose (10 mg/kg/day) of Theodur tablets (200 mg) has suggested that the absorption characteristics of Theodur might not be different from that in Caucasian children.[31] From this study, it could be observed that dosage for Theodur for Thai children may have to be increased to 16 mg/kg/day to attain concentrations within the therapeutic range.

Since pharmacokinetic data from intercontinental cohorts have yielded very similar results, we therefore feel that theophylline metabolic characteristics among Asian children should be uniform as well although to reach such a conclusion requires studies of another populations in addition to the Thai. Needlessly to say, STCs should be monitored to ensure that therapeutic range has been reached and to avoid toxicity from theophylline.

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