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A Single-Dose Comparison of Three Slow-Release Theophylline Oral Preparations in Healthy Thai Volunteers

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SUMMARY **The study was done to compare the pharmacokinetic characteristics of three slow-release theophylline (SRT) preparations. Twelve healthy nonsmokers were randomly assigned a single dose of the following treatments at weekly intervals: Theo-Dur, Theo-24 or Xanthium orally, or aminophylline intravenously. Serially collected serum samples were analyzed for theophylline with use of fluorescence polarization immunoassay (FPIA). All three SRT preparations showed reliable absorption characteristics, but Theo-Dur had a shorter T_{max} and MRT, and a higher K_a. The pharmacokinetic characteristics of Theo-24 and Xanthium were similar except that Xanthium had lower bioavailability. Using single dose data for simulation of steady state pharmacokinetics, we found that a once-a-day dosage regimen with either Theo-24 or Xanthium would maintain serum levels within the therapeutic range for average nonsmoking young adults whereas more frequent dosing intervals with Theo-Dur would be more appropriate. Our results argue against open substitution of SRT preparations without close monitoring of the serum theophylline concentrations when a change is made.**

Theophylline has been shown to be effective for the control of asthma and both its efficacy and toxicity correlate with serum concentrations.[1-4] Slow-release formulations of theophylline (SRT) can decrease fluctuations in serum concentration and allow longer dosing intervals[5-7] with resultant improvement in patient compliance. The absorption characteristics of some SRT preparations are affected by food and dietary composition.[3,8,9] However, the effects of race on the pharmacokinetic characteristics of SRT products have not been established. One recent study of conventional theophylline preparations in Thai children[10] revealed similar pharmacokinetic parameters compared with previous studies in Caucasians.[11,12] Little information is available on the pharmacokinetic characteristics and bioavailability of SRT preparations in Thai subjects eventhough some of these SRT preparations have been available for clinical use in Thailand since the 1980's. Substitution of one sustained release product for another at the same dosage could result in a change in serum concentration possibly leading to a subtherapeutic or toxic level.[13] We conducted this study to assess the pharmacokinetic characteristics and bioavailability after a single oral dose of 3 different SRT products in Thai subjects

MATERIALS AND METHODS

Subject selection

Twelve healthy, non-smoking volunteers (6 males, 6 females) between 20 and 33 years of age (median age 23 yrs) were recruited. Their health was judged on the basis of a prestudy medical history, physical examination, clinical laboratory tests, and electrocardiograms. No subjects received any drug during the study period, and abstained from tea, coffee and other caffeine containing beverages at least 48 hours before and during each study day. All subjects signed a written

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consent form and the study was approved by the Medical Ethics Committee of the Faculty of Medicine, Chiang Mai University.

Study design

The study was a randomized, 4-period crossover design. Each of the following treatments was given in a single dose during each study visit, at weekly intervals in a randomized balanced design : Theo-Dur [200 and 300 mg tablets; Astra-Olic (Thai)], Theo-24 (200 and 300 mg capsules; Searle), and Xanthium (200 and 400 mg capsules; Galephar, Belgium) orally, and aminophylline infusion drip over 30 minutes. All subjects received aminophylline at 5 mg/kg BW of theophylline. Each subject received the same dose of different SRT products during each study day, either with a single dose of 400 or 600 mg, whichever was close to 8-10 mg/kg BW. The mean dose of SRT given was 9.1 ± 1.0 mg/kg BW. Oral preparations were given after an evening meal typically consisting of 60% carbohydrate, 25% fat and 15% protein.

Sample collections and determination of serum theophylline levels

Blood samples were collected before and at 2, 4, 6, 8, 10, 12, 18, 24, and 36 hours after an oral SRT administration and at 0, 15, 30 minutes during the aminophylline infusion, and 0.5, 1.5, 2.5, 3.5, 5.5, 7.5, 9.5, 11.5, 17.5 and 23.5 hours after the end of the infusion. Blood samples were allowed to clot at room temperature for 6 hours and centrifuged. The serum was decanted and frozen at -21°C until it was assayed. Serum theophylline was determined by a fluorescence polarization immunoassay[14] (FPIA-TDx theophylline system assay, Abbott, USA). The same lot of reagent was used throughout the study. The coefficient of variation for the theophylline assay from levels of 6.3 to 28.6 μg/ml are <5%(n = 81).

Data analysis and statistical methods

The pharmacokinetic parameters including apparent absorption rate constant (K_a), maximal plasma concentration (C_{max}) and time to peak (T_{max}), elimination rate constant (K_{el}), plasma elimination half-life ($T_{1/2}$), and mean residence time (MRT) were estimated with use of the TopFit 2.0 (A pharmacokinetic and pharmacodynamic data analysis system for PC). The mean cumulative fraction of the dose absorbed following a single dose of different SRT preparations was also calculated from serial serum concentration measurements by a modification of the Wagner-Nelson equation, a process-independent method of comparing rates of absorption of different products after single doses.[15] Area under the curve from 0-36 hr (AUC_{0-36}) for the SRT administration was calculated using linear trapezoidal rule and $AUC_{36-\alpha}$ was determined by division of the final plasma concentration by the apparent elimination rate constant estimated after an intravenous administration. The relative bioavailability (F_{rel}) of Theo-24 and Xanthium in relation to Theo-Dur, were also determined. Analysis of variance and paired Students' *t*-tests were used to compare the pharmacokinetic values observed with the three different SRT products. A *p* value of less than 0.05 was considered statistically significant. The serum concentration-time profile at steady state was also predicted with use of the modified Wagner-Nelson Equation for the absorption characteristics of theophylline from the single dose data[15] and the effect of the formulation on serum concentrations during multiple dosing was also determined.

RESULTS

Pharmacokinetic parameters observed in 12 non-smoking young Thai adults after a single intravenous administration of 5 mg/kg BW of theophylline are shown in Table 1 and the pharmacokinetic characteristics of 3 different SRT preparations in Table 2. The apparent T_{max}, C_{max}, K_{el} and plasma $T_{1/2}$. K_a, MRT and AUC_{0-36} observed after Theo-24 and Xanthium administrations were significantly different from those values observed with the same dose of Theo-Dur. The $AUC_{0-\alpha}$ observed with Theo-Dur was not different from that of Theo-24 (p = 0.47) but was significantly higher than that of Xanthium (p = 0.003). The mean $F_{rel\ 0-\alpha}$ for Theo-24 and Xanthium in comparison to Theo-Dur were 97.4 ± 12.8 and 78.7 ± 15.3%, respectively. The absorption characteristics of each SRT preparation expressed as a fraction of the dose absorbed following a single oral dose are shown in Fig. 1 and the plasma theophylline concentration-time profiles after a single dose of each SRT product are shown in Fig. 2. Transient caffeine-like effects such as a mild headache or palpitations were reported in 5 subjects receiving Theo-Dur and 4 subjects receiving Theo-24 whereas only 2 subjects reported the symptoms with Xanthium. The symptoms appeared to correlate with peak plasma concentrations. When steady-state pharmacokinetics were predicted with use of single dose data,[15] the once-a-day dosage regimen to achieve 14-15 μg/ml peak concentration would be 500 mg, 600 mg, and 700 mg, for Theo-Dur, Theo-24, and Xanthium, respectively. The predicted steady state plasma concentration-time profiles for each SRT product are shown in Fig. 3. The fluctuation in serum concentrations (peak-trough/trough) at steady state were estimated to be 218%, 88.5%, and 99.14% for Theo-Dur, Theo-24, and Xanthium, respectively.

Table 1. Pharmacokinetic parameters after a single intravenous administration of aminophylline (5 mg of theophylline per kg BW) in 12 healthy subjects.

Parameters	Values
C_{max} (μg/ml)	12.2 ±3.1[a] (8.5 –17.3)[b]
V_d (L/kg)	0.53 ±0.07 (0.43 –0.63)
K_{el} (hr^{-1})	0.074 ±0.016 (0.045 –0.095)
$T_{1/2}$ (hr)	9.9 ±2.6 (7.3 –15.4)
Cl_p (ml/kg/hr)	0.643 ±0.148 (0.44 –0.762)

[a]mean ± SD
[b]range

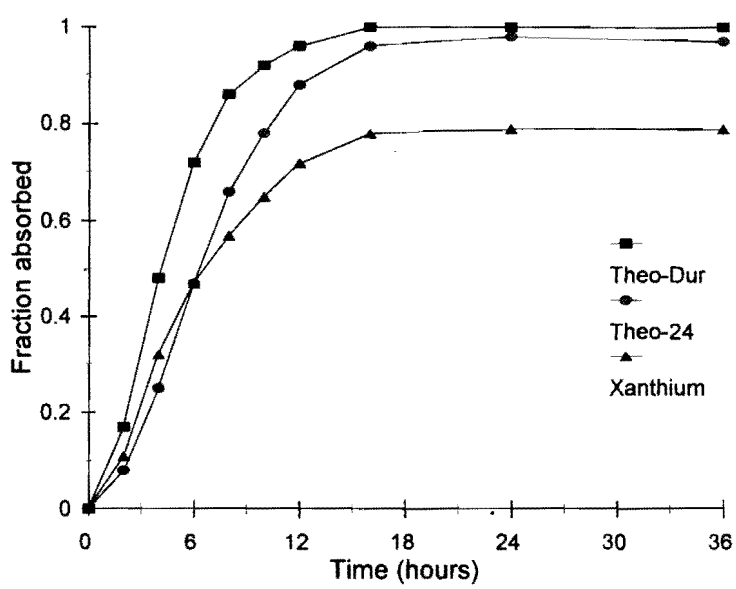

Fig. 1 The mean cumulative fraction of the dose absorbed following a single oral dose of 3 different SRT preparations in 12 healthy young adults. The fraction absorbed was calculated from serial serum concentration measurements by a modification of the Wagner-Nelson equation.[15] The extent of absorption is represented by the last data point.

DISCUSSION

The pharmacokinetic parameters of theophylline observed after a single intravenous administration in this study appeared to be very similar to the results previously reported in non-smoking young adult Caucasians.[16-20] All of three SRT preparations studied showed reliable slow absorption characteristics without "dose-dumping". Nonetheless, the absorption rate appeared to be higher for Theo-Dur compared to those of Theo-24 and Xanthium (Fig. 1), resulting in the higher apparent K_a and shorter T_{max} observed with Theo-Dur. The pharmacokinetic characteristics of Theo-24 and Xanthium were similar except that Xanthium had lower bioavailability and was incompletely absorbed compared to Theo-Dur. Our results with Theo-Dur and Theo-24 were similar to previous reports in nonsmoking adults. Theo-24 had a longer T_{max} than Theo-Dur and was completely absorbed under postprandial conditions.[21] Another study with Theo-Dur[8] found a shorter $T_{1/2}$ and higher K_{el} values than we measured.

When single dose pharmacokinetic data was used to predict the steady-state plasma theophylline concentration-time profile, we found that different daily dosage regimens of these SRT preparations would be required to achieve the same peak plasma concentrations. The daily dosage of Xanthium should be higher because of its lower oral bioavailability. Both efficacy and toxicity of theophylline depend on its plasma concentrations[1-4] and therapeutic theophylline concentrations of 10 to 20 μg/ml should be maintained[15] to achieve the greatest benefit for chronic asthma. We then compared the steady-state plasma concentration-time profile after a once-a-day dosage regimen of these SRT preparations at the dosage that would result in peak theophylline concentrations between

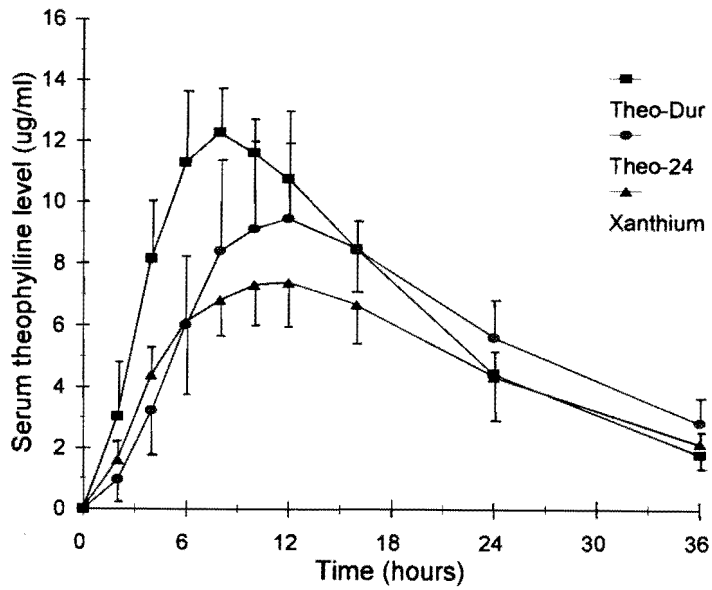

Fig. 2 Plasma concentration-time profiles after a single dose of three different SRT preparations (8-10 mg theophylline per kg BW) in 12 healthy young adults.

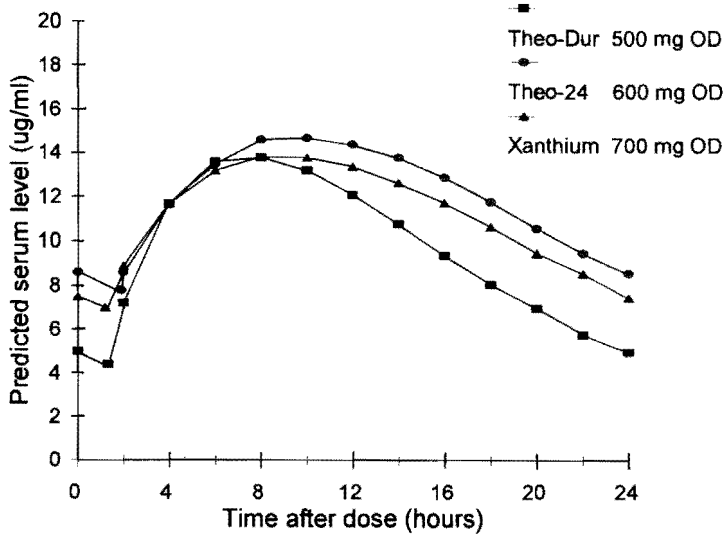

Fig. 3 Predicted plasma concentration-time profiles at steady state with once-a-day dosage regimen of the three different SRT preparations in an average young adult. The daily dosage regimen for each preparation was estimated with use of the single dose data to achieve the peak concentration between 14-15 μg/ml.

14 to 15 μg/ml. For average young Thai adults, we found that a once-a-day dosing interval with either Theo-24 or Xanthium would maintain plasma theophylline concentrations within the therapeutic range (above 10 μg/ml) for a longer period during the daily dosing interval (Fig. 3), thus providing around-the-clock stabilization of hyperreactive airways. Increasing the dose of Theo-Dur would allow serum concentrations to stay within the therapeutic range longer but the chance of toxicity is increased because of higher peak concentrations. Pharmacokinetic simulation of serum theophylline concentration-time profile at steady state when a 600 mg once-a-day dose of Theo-Dur was replaced with a 300 mg twice-a-day dose revealed decreased fluctuation of the serum levels from 218 to 39.2% with a longer time during which serum theophylline levels remained above the subtherapeutic level (22 vs 10.5 hours). There were also lower peak concentrations (13.1 vs 16.8 μg/ml). Theo-Dur has received approval for once-daily dosing even though supporting data indicated fluctuation in serum concentrations compatible with remaining within or near the 10 to 20 μg/ml therapeutic range only for non-smoking adult patients with slower than average rates of elimination.[21] Nonetheless, more frequent dosing intervals with both Theo-24 and Xanthium might also be necessary for rapid metabolizers such as smoking adults, children, or some nonsmoking adults. The clinical use of SRT preparations requires careful consideration of the pharmacokinetics and pharmacodynamics of the drug and the clinical and pharmacokinetic concerns of 24-hour dosing with theophylline have been discussed previously.[22]

In conclusion, these three SRT preparations were shown to be reliable in their slow-release charac-

Table 2. Pharmacokinetic characteristics of 3 different SRT preparations in 12 healthy subjects receiving 8-10 mg/kg dose of theophylline. Data represent mean (SD).

Paramaters	Theo-Dur	Theo-24	Xanthium
T_{max} (hr)	8.2 (1.3) (6-10)[a]	11.5 (2.7)* (8-16)	10.7 (1.8)* (6-12)
C_{max} (ug/ml)	12.7 (1.5) (10.3-15.0)	10.0 (2.6)* (6.4-13.9)	7.6 (1.2)*† (6.3-9.2)
$T_{1/2}$ (hr)	9.4 (1.3) (7.4-11.5)	13.8 (4.0)* (7.2-18.9)	12.9 (3.2)* (8.0-19.1)
MRT (hr)	17.7 (1.8) (14.5-20.3)	25.9 (6.2)* (16.9-36.4)	21.8 (6.0)* (15.4-36.2)
K_{el} (hr^{-1})	0.075 (0.011) (0.06-0.094)	0.055 (0.018)* (0.037-0.097)	0.057 (0.014)* (0.036-0.086)
K_a (hr^{-1})	0.241 (0.098) (0.115-0.392)	0.090 (0.025)* (0.061-0.127)	0.099 (0.038)* (0.039-0.129)
AUC_{0-36} (μg.hr/ml)	231.9 (23.1) (191.4-263.5)	208.4 (29.7)* (162.3-267.8)	171.9 (32.4)*† (121.3-209.0)
$AUC_{0-\alpha}$ (μg.hr/ml)	259.0 (35.5) (203.4-315.9)	251.5 (44.8) (200.2-350.5)	204.2 (47.9)*† (128.6-271.3)

*$p<0.05$ vs Theo-Dur
†$p<0.05$ vs Theo-24
[a]range

teristics, but had differences in pharmacokinetic properties. The oral bioavailbilty of Xanthium was significantly lower than those of Theo-24 and Theo-Dur, thus a higher dose is required to achieve the same plasma concentration . A once-a-day dosage regimen with either Theo-24 or Xanthium appears adequate to maintain plasma theophylline levels within the therapeutic range most of the time for an average non smoking young Thai adult. More frequent dosing intervals are more appropriate for Theo-Dur. We strongly recommended that serum theophylline concentrations be closely monitored when switching between these three SRT preparations.

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