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Comparative Steady-State Bioavailability of Sustained-Release Theophylline Preparations: Theo-Dur®, Uni-Dur® and Xanthium®

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SUMMARY **Steady-state bioavailability of sustained-release theophylline (SRT); Theo-Dur®, Uni-Dur® and Xanthium® were compared in 10 healthy males with theophylline clearance ranged from 0.3 - 0.8 ml/min/kg. Each of 400-mg SRT was administered once daily before breakfast for 7 consecutive days, one-week washout period in a crossover fashion. Serial blood samples were collected over 24 hours on days 6 and 7. Serum theophylline concentrations were determined by fluorescence polarized immunoassay. We found that the oral bioavailability relative to Franol®, (%F [90% CI]) of Theo-Dur®, Uni-Dur® and Xanthium® were 97 (93-106), 85 (79-96) and 77 (72-87), respectively. Average bioequivalence revealed that the Css_{min} (μg/ml) of Uni-Dur® (5.07) was higher than Theo-Dur® (4.29), and Xanthium® (4.18), while the Css_{max} and Css_{av} (μg/ml) of Theo-Dur® (11.02, 7.87) were statistically higher than Uni-Dur® (8.51, 6.91) and Xanthium® (7.65, 6.27). The extent of absorption assessed by $AUCss_{0-24}$ of Theo-Dur® was significantly greater than Uni-Dur® and Xanthium®. However, fluctuation index (% FI) of Theo-Dur® (232) was twofold higher than Uni-Dur® (137) and Xanthium® (113). The median Tss_{max} of Uni-Dur® was 12 hours which was significantly longer than Xanthium® (7 hours) and Theo-Dur® (8 hours). There were no statistically significant differences between Uni-Dur® and Xanthium® regarding bioavailability, Css_{max}, Css_{av} as well as % FI. Moreover, 400 mg OD of Uni-Dur® and Xanthium® are suitable for subjects with a theophylline clearance of 0.3-0.55 ml/min/kg while 400 mg OD Theo-Dur® can be used in subjects with slower clearance rates of 0.3-0.39 ml/min/kg. Subjects with rapid theophylline clearance rates of 0.65-0.8 ml/min/kg required a higher dose of theophylline and twice-daily dosing was more appropriate.**

Theophylline is a bronchodilator commonly used in the treatment of asthma. Its therapeutic effects are closely related to its serum theophylline concentration (STC) ranging from 5-20 μg/ml.[1] Since STC of > 20 μg/ml are potentially associated with theophylline toxicity, drug monitoring to maintain a peak STC between 10-15 μg/ml are required. An oral solution and an immediate-release tablet form of theophylline are rapidly and completely absorbed after oral administration.[1] Theophylline does not undergo any appreciable first-pass metabolism and its elimination pathways are primarily by liver metabolism. A large number of factors such as age, gender, cigarette smoking, concomitant medications and disease status may influence theophylline metabolisms. In addition due to a wide intersubject and intrasubject variability in the rate of its metabolisms, non-linearity of elimination has been reported at therapeutic STC level. The range (mean ± SD) for its elimination half-life (hours) and clearance (ml/min/kg) are 6.1-12.9 (9.1 ± 2.1) and 0.27-1.03 (0.65 ± 0.20), respectively.[1] The maximum STC after oral administration of immediate-release products usually occurs within 2 hours. However, these plain preparations are no longer recommended since they require frequent dosing and do not provide

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constant blood levels. Moreover, they produce wide differences between peak and trough concentrations that may alter the ability to stabilize the airway and increase the risk of toxicity. Oral sustained-release theophyl-line (SRT) preparations have been developed to compensate for its rapid absorption and elimination. The SRT preparations can be administered twice or once daily and are suitable for long term use.[1-6] They are designed to release theophylline slowly and continuously so that the patients can maintain a STC within therapeutic range with little fluctuation throughout the day and night. Most of the SRT products are completely absorbed, however, they vary greatly in their intestinal release characteristic and the rate of absorption.[7-8] For the products that require a longer duration of absorption, once daily or twice daily dosing is usually acceptable. Nevertheless, maintenance of STC within therapeutic range is not only due to a function of the rate of theophylline release from the product, but also depends on the theophylline clearance rate of the patient.[1] Generally, the use of a twice-daily product will result in less fluctuation in STC than a once-daily product.[8] Moreover, patients who require STC above 10 μg/ml or patients with a rapid theophylline clearance may experience a greater therapeutic effect with twice daily dosing. Nonetheless, for patients showing a normal or slow theophylline clearance, control of asthma symptoms can be achieved by using once-daily products.[1] The SRT preparations available in Thailand are Theo-Dur®, Theo-24® and Xanthium®. Recently, Theo-24® has been withdrawn from the Thai Market and Uni-Dur® was introduced. Theo-Dur® (200, 300 mg) is an extended-release tablet available for 12-hour dosing, while Uni-Dur® and Xanthium® (200, 400, 600 mg) are ultraslow sustained-release formulation designed for 24-hour dosing. The disadvantage of once-daily products is the possibility of incomplete bioavailability. Food also has a variable effect on the rate and extent of their absorption.[10] Concurrent administration of Theo-24® with high-fat meals can accelerate its absorption to toxic STC levels, known as "dose dumping effects".[11] Previous studies showed that Uni-Dur® provided stable STC over a 24-hr period and that the time of administration either morning or evening dosing did not affect its release characteristics.[8,9] In addition its absorption was not affected by food since no evidence of dose dumping was observed.[9] However, the oral bioavailability characteristics of Uni-Dur® have never been investigated in Thai subjects. Therefore, this study was aimed to compare the steady-state (SS) pharmacokinetic profiles of Uni-Dur® to those of the SRTs available in Thailand, Theo-Dur® and Xanthium®, in healthy Thai volunteers. The protocol of this study was reviewed and approved by the Ethics Committee of the Chiang Mai University, Thailand.

SUBJECTS AND METHODS

Drug formulations

The drug formulations are shown in Table 1.

Subjects

Since age and gender affected theophylline clearance,[1-12] only male volunteers aged between 18-30 years old were enrolled. They were non-smokers, non-alcohol consumers and were judged healthy based on their medical history, physical examination, routine blood chemistry and urinalysis. In addition, screening for theophylline clearance was performed to exclude subjects with very low clearance rates since their STC might reach toxic levels that lead to zero-order elimination after multiple dosing.

Table 1 Drug formulations used in the study

Brand name	Manufacturer	Distributor	Preparation
Theo-Dur® (T)	Astra Sodertaje (Sweden)	Astra-Olic (Thailand)	2 x 200 mg tablet Lot No. AB 558
Uni-Dur® (U)	Schering-Plough Inc. (USA)	Schering-Plough Ltd. (Thailand)	400 mg tablet Lot No. 91058
Xanthium® (X)	SMB Technolody (Belgium)	Berlin Pharmaceutical Industry Co., LTD. (Thailand)	400 mg capsule Lot No. 98D03

Target STCs of 5-20 μg/ml after administration of a SRT 400 mg per day were desired, therefore, only subjects with a theophylline clearance ranged from 14 - 55 ml/min were enrolled. Their elimination half-life ($T_{1/2}$) had to be less than 15 hours. Theophylline pharmacokinetic parameters of subjects were obtained following oral administration of 400 mg of an immediate-release preparation, Franol® (Sanofi, Zuellig Thailand) in the morning after an overnight fast. Serial blood samples were obtained predose and 24 hours postdose. Ten healthy males were selected to participate in this study. Their theophylline clearance (ml/min/kg) and half-life (hours) ranged from 0.3 - 0.8 (0.5 ± 0.15) and 5.7 - 14.1 (10.0 ± 2.8), respectively. Demographic data and theophylline pharmacokinetic parameters of the subjects were shown in Table 2.

Study design

This multiple-dose study was an open, three-period crossover design with one-week washout period. The assigned treatments were; T: Theo-Dur® (2 x 200 mg tablets), U: Uni-Dur® (1 x 400 mg tablet) and X: Xanthium® (1 x 400 mg capsules). The sequences of SRT administration are shown in Table 2. Each subject received a once daily dose of one of the SRTs at 7:00 a.m. after an overnight fast for 7 consecutive days. After a week long drug free interval, each subject was crossed over to receive a different SRT in the same manner. Blood samples were collected prior to the morning doses of days 4, 5 and 6 to ascertain a steady state. On days 6 and 7, after a single dose of 400-mg SRT with 240 ml of water, subjects had to fast for 2 hours. Serial blood samples were collected before drug administration and at 2, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14,16 and 24 hours after dose. Water and lunch were served at 2-hours and 4-hours after SRT administration, respectively. Meal and fluid intake were identical for all study visits. Alcohol and xanthine-containing foods or beverages were prohibited for 48 hours before and during the study period.

Determination of serum theophylline concentrations

Serum theophylline concentrations were determined by fluorescence polarization immunoassay (FPIA) technique, using the Abbott TDx clinical analyzer (Abbott Laboratory, North Chicago, IL, USA). The FPIA procedure was an automated method and the assay was conducted according to the manufacturer's protocol with-

Table 2 Age, weight, screening theophylline pharmacokinetic parameters and sequence of SRT administration (Theo-Dur [T], Uni-Dur [U], Xanthium [X]) in 10 subjects

Subject number	Age (years)	BW (kg)	C_{max} (μg/ml)	T_{max}* (hours)	$T_{1/2}$ (hours)	Vd (l/kg)	AUC (0-∞) (μg.hr/ml)	CL** (ml/min/kg)	Sequence of SRT
2	26	55	13.19	3.0	9.5	0.42	239.5	0.51	UTX
3	24	65	16.88	0.5	8.4	0.35	213.8	0.48	XTU
4	22	60	9.74	4.0	7.9	0.45	171.6	0.65	XTU
6	18	65	13.69	4.0	8.4	0.40	186.6	0.55	UTX
7	19	68	10.51	3.0	5.7	0.40	122.2	0.80	XTU
9	20	60	12.06	4.0	9.5	0.42	218.1	0.51	UTX
10	21	55	12.86	3.0	14.1	0.47	313.4	0.39	UTX
11	30	67	15.43	1.5	13.7	0.39	301.9	0.33	XTU
12	20	57	18.69	3.0	13.1	0.34	391.0	0.30	UTX
13	20	66	16.09	1.5	9.6	0.37	248.4	0.45	XTU
Mean	22	61.2	13.91	3.0	10.0	0.40	240.6	0.50	
SD	3.7	4.8	2.84	1.2	2.8	0.04	77.9	0.15	

The mean of T_{max}* = The median of T_{max}
CL** = Clearance = Dose/AUC(0-∞), normal values = 0.27-1.03 (0.65) ml/min/kg/[1]
Normal value for theophylline $T_{1/2}$ = 6.1-12.8 (8.7) hours[1]

out modification. Calibration standard samples were ranged from 0-40 μg/ml with 3 quality controls (low 7 μg/ml, medium 12 μg/ml, high 26 μg/ml) running with each carousel of serum samples. The coefficient of variation between the measurements was less than 5%, the average recovery and the correlation with reference assays were 97.39% and 0.998, respectively.

Pharmacokinetic parameter measurement and bioequivalence analysis[13-14]

Pharmacokinetic parameters of the SRT products were determined from the serum concentration-time profiles on study days 6 and 7. The time to reach the maximal concentration (Tss_{max}, hours), the maximal serum concentrations (Css_{max}, μg/ml) and the minimum serum concentrations (Css_{min}, μg/ml) were obtained directly by visual inspection of individual subject's serum concentration-time profile. The area under the curve 0-24 hrs ($AUCss_{0-24}$, μg.hr/ml) was calculated using the trapezoidal rule with the aid of a pharmacokinetic program (TopFit V. 2.0; Gustav Fisher Verlag; New York, NY). The bioavailability (% F) of the SRT relative to Franol® was determined from the equation: % F = ($[AUC_{SRT0-24}]/[AUC_{Franol®0-24}]$) x 100. The average steady-state STC (Css_{av}, μg/ml) was calculated as $AUCss_{0-24}$/dosing interval (24 hours).

Percentage of fluctuation in serum theophylline concentrations normalized to trough concentration (fluctuation index [% FI]) were calculated as ($[C_{max} - C_{min}]/ C_{min}$) x 100. The Css_{min}, Css_{max}, and AUC_{0-24} which represented the rate and extent of theophylline absorption were logarithmically transformed and performed an analysis of variance (ANOVA). Thereafter, using the variance estimate (S^2) obtained from the ANOVA, the 90% confidence interval (90% CI) for the mean difference between a pair of the SRT preparations (Uni-Dur® versus Theo-Dur® (U:T), Xanthium® versus Theo-Dur® (X:T) and Uni-Dur® versus Xanthium® (UX)) were calculated. The antilogarithm of the 90% CI ex-presses the bioequivalence as a ratio of the test and reference products (μ_T/μ_R). Bioequivalence acceptance criteria require that 90% CI (μ_T/μ_R) fell within the bioequivalence interval of 0.8-1.25.

RESULTS AND DISCUSSION

Trough STC on days 4, 5 and 6 of each SRT preparation showed no statistically significant differences ($p > 0.5$) and were used to verify the achievement of a steady state (Table 3). Fig. 1 depicts the average theophylline concentration-time curves at steady-state after once daily dosing of 400 mg Theo-Dur®, Uni- Dur® and Xanthium. Theophylline pharmacokinetic parameters of the three SRTs and the 90% CI of the ratio (μUni-Dur®/μTheo-Dur®), (μXanthium/μ Theo-Dur®) and (μUni-Dur®/μ Xanthium®) are summarized in Tables 4-6 and Table 7, respectively.

The oral bioavailability relative to an immediate-release product Franol®, (% F [90% CI]) of Theo-Dur®, Uni-Dur® and Xanthium® were 97 (93-106), 85 (79-96) and 77 (72-87), respectively. Since acceptable bronchodilator response will be achieved if a SRT product has an oral bioavailability of 70-90%,[15] the three SRT products were considered effective in controlling asthma. Average bioequivalence analysis of pharmacokinetic parameters on day 6 and day 7 revealed that the Css_{min} (μg/ml) of Uni-Dur® (5.07) was higher than those of Theo-Dur® (4.29), and Xanthium® (4.18) while the Css_{max} and Css_{av} (μg/ml) of Theo-Dur® (11.02, 7.87) were statistically higher than those of Uni-Dur® (8.51, 6.91) and Xanthium® (7.65, 6.27). Moreover, the extent of absorption assessed by $AUCss_{0-24}$ of Theo-Dur® was significantly greater than with Uni-Dur® and Xanthium®. Lower bioavailability of Xanthium® was confirmed by the other studies.[16-17] The result complied with the fact that Uni-Dur® and Xanthium® are ultra-slow SRT products designed for once-daily dosing (OD), while Theo-Dur® is designed for twice-daily dosing (BID). Since Uni-Dur® and Xanthium® are designed for very slow absorption, the possibility of incomplete bioavailability can occur because the duration of absorption might exceed the gastrointestinal transit time. There were no statistically significant differences between Uni-Dur® and Xanthium® regarding bioavailability, maximal and average steady-state STCs as well as % FI. However, the median Tss_{max} of Uni-Dur® (12 hours) was significantly longer than Xanthium® (7 hours) and Theo-Dur® (8 hours). In order to control nocturnal asthma, the STC should reach its highest concentration during late night-time. Through this critical time (e.g. 2 a.m.-6 a.m.), the airflow and pulmonary functions are naturally worse and higher therapeutic level of theophylline is required to maximize the lung function.[18-20] The higher theophylline level attained at that time could be achieved only by

Table 3 Trough STC (μg/ml) after once daily doses of 400 mg Theo-Dur®, Uni-Dur® and Xanthium®

Theo-Dur

Day	S2	S3	S4	S6	S7	S9	S10	S11	S12	S13	Mean	SD
4	4.52	4.30	1.16	3.31	1.97	4.45	7.44	5.80	8.20	3.19	4.43	2.23
5	5.96	5.88	1.97	3.02	1.74	3.85	7.87	4.84	8.67	2.95	4.68	2.40
6	4.77	4.87	1.87	2.62	0.49	3.91	6.79	5.65	10.00	3.06	4.40	2.71

Uni-Dur

Day	S2	S3	S4	S6	S7	S9	S10	S11	S12	S13	Mean	SD
4	6.42	6.66	0.62	4.10	1.70	5.34	7.63	6.87	10.40	5.91	5.57	2.85
5	7.04	4.76	0.76	4.66	3.20	5.22	9.18	7.42	6.29	5.67	5.42	2.34
6	6.90	5.57	0.45	5.27	1.46	4.72	10.51	6.77	10.16	4.89	5.67	3.21

Xanthium

Day	S2	S3	S4	S6	S7	S9	S10	S11	S12	S13	Mean	SD
4	3.75	4.47	1.66	2.51	2.60	4.30	7.21	6.94	9.58	5.81	4.88	2.49
5	2.32	3.51	1.25	2.46	1.26	4.70	7.88	7.71	7.93	5.17	4.42	2.68
6	2.94	4.36	1.38	2.80	1.48	4.96	7.35	7.04	5.34	4.94	4.26	2.09

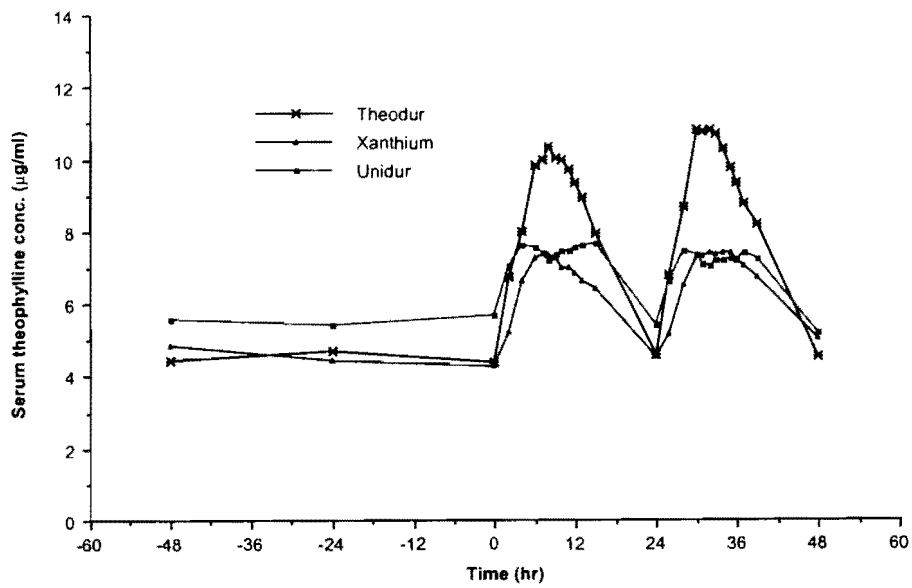

Fig. 1 Mean steady-state (Day6 - Day7) theophylline concentration-time curves following a once daily dose of 400 mg Theo-Dur®, Xanthium® and Uni-Dur®.

Table 4 Steady-state theophylline pharmacokinetic parameters after a once daily dose of 2 x 200 mg Theo-Dur®

Subject number	C_{min} (µg/ml)		C_{max} (µg/ml)		% FI*		$C_{ss,\ av}$ (µg/ml)		T_{max} (hours)		$AUC_{(0\text{-}24\ hours)}$		% F**	
	Day 6	Day 7	Day 6	Day 7	Day 6	Day 7	Day 6	Day 7	Day 6	Day 7	Day 6	Day 7	Day 6	Day 7
2	4.77	5.46	11.64	13.56	144	148	8.70	9.39	10.0	8.0	208.8	225.4	107	116
3	4.87	3.26	11.73	8.93	141	174	8.68	6.58	10.0	7.0	208.4	158.0	112	85
4	1.87	1.98	7.42	8.93	297	351	4.89	4.99	6.0	9.0	117.4	119.8	79	81
6	2.62	2.72	8.97	9.83	242	261	5.89	6.41	6.0	6.0	141.4	153.8	90	98
7	0.49	0.79	4.45	5.94	808	652	2.41	4.35	9.0	8.0	57.8	104.4	51	92
9	3.91	4.21	10.90	10.37	179	146	7.63	7.43	6.0	7.0	183.0	178.4	103	100
10	6.48	6.48	13.31	12.67	105	96	10.05	10.30	8.0	8.0	241.1	247.3	113	116
11	5.65	5.68	12.51	12.46	121	119	8.98	9.43	6.0	9.0	215.6	226.2	101	106
12	9.25	8.47	15.83	19.44	71	130	12.80	14.09	11.0	6.0	307.1	338.3	110	121
13	3.06	3.69	11.42	10.17	273	176	7.32	7.15	8.0	8.0	175.8	171.6	86	84
Mean	4.30	4.27	10.82	11.23	238	225	7.74	8.01	8.0	8.0	185.6	192.3	95	100
SD	2.51	2.29	3.19	3.63	214	168	2.87	2.87	1.9	1.1	69.0	69.0	19	15
Mean D6-D7		4.29		11.02		232		7.87		8		189.0		98
SD		2.34		3.33		187		2.80		1.5		67.2	90% CI	93-106

*FI = Fluctuation index = $([C_{max}-C_{min}]/C_{min}) \times 100$
**F = oral bioavailability compared to Franol®
Mean T_{max} = Median T_{max}

Table 5 Steady-state theophylline pharmacokinetic parameters after a once daily dose of 400 mg Uni-Dur®

Subject number	C_{min} (μg/ml)		C_{max} (μg/ml)		% FI*		Css, av (μg/ml)		T_{max} (hours)		$AUC_{(0\text{-}24\ h)}$		% F**	
	Day 6	Day 7	Day 6	Day 7	Day 6	Day 7	Day 6	Day 7	Day 6	Day 7	Day 6	Day 7	Day 6	Day 7
2	6.59	6.14	11.17	10.32	69	68	8.75	8.08	13.0	13.0	210.0	194.0	108	100
3	4.73	4.73	8.71	8.88	84	88	6.23	6.44	4.0	4.0	149.4	154.6	81	83
4	0.45	0.40	3.16	2.88	602	620	1.89	1.25	7.0	4.0	45.4	30.0	31	20
6	5.27	4.90	6.99	8.28	33	69	6.14	6.70	15.0	15.0	147.3	160.8	94	102
7	1.46	1.26	5.36	4.49	267	256	3.68	2.76	12.0	4.0	88.4	66.2	78	58
9	4.67	4.67	8.27	7.48	77	60	6.52	6.40	6.0	15.0	156.5	153.7	88	86
10	8.60	8.60	11.54	11.44	34	33	10.45	10.23	15.0	15.0	250.8	245.6	118	115
11	6.77	7.37	9.93	10.45	47	42	8.66	9.50	12.0	9.0	207.7	227.9	97	106
12	10.16	5.76	13.23	11.54	30	100	12.02	9.12	15.0	4.0	288.4	219.0	103	79
13	4.45	4.45	6.96	9.06	56	104	6.15	7.15	6.0	13.0	147.6	171.5	72	84
Mean	**5.32**	**4.83**	**8.53**	**8.48**	**130**	**144**	**7.05**	**6.76**	**12.0**	**11.0**	**169.1**	**162.3**	**87**	**83**
SD	**2.94**	**2.49**	**3.05**	**2.87**	**180**	**179**	**3.02**	**2.86**	**4.3**	**5.1**	**72.5**	**68.7**	**24**	**28**
Mean D6-D7		**5.07**		**6.51**		**137**		**6.91**		**12.0**		**165.7**		**85**
SD		**2.67**		**2.68**		**175**		**2.87**		**4.6**		**68.8**	**90% CI**	**79-96**

*FI = Fluctuation index = $([C_{max}-C_{min}]/C_{min}) \times 100$
**F = oral bioavailability compared to Franol®
Mean T_{max} = Median T_{max}

Table 6 Steady-state theophylline pharmacokinetic parameters after a once daily dose of 400 mg Xanthium®

Subject number	C_{min} (μg/ml)		C_{max} (μg/ml)		% FI*		Css, av (μg/ml)		T_{max} (hours)		$AUC_{(0\text{-}24\ h)}$		% F**	
	Day 6	Day 7	Day 6	Day 7	Day 6	Day 7	Day 6	Day 7	Day 6	Day 7	Day 6	Day 7	Day 6	Day 7
2	2.94	3.80	6.52	7.49	122	97	5.18	5.93	7.0	8.0	124.4	142.3	64	73
3	3.42	3.42	6.80	6.08	99	78	5.53	5.14	7.0	8.0	132.6	123.3	72	67
4	1.38	1.48	4.03	4.88	192	230	2.97	3.36	8.0	6.0	71.2	80.5	48	54
6	2.17	2.17	5.68	5.85	162	170	4.06	4.76	6.0	6.0	97.5	114.2	62	73
7	1.08	1.08	3.56	3.71	230	244	2.44	2.55	7.0	6.0	58.5	61.2	51	54
9	4.65	4.62	9.21	6.84	98	48	6.84	5.78	6.0	7.0	164.2	138.6	92	78
10	7.35	6.97	10.97	11.20	49	61	9.79	9.24	8.0	6.0	235.0	221.6	110	104
11	7.04	7.58	10.32	11.31	47	49	8.95	10.07	11.0	11.0	214.8	241.7	100	113
12	5.34	7.19	9.70	12.38	82	72	8.43	10.85	9.0	10.0	202.2	260.4	73	93
13	4.94	4.92	8.84	7.63	79	55	7.25	6.33	7.0	10.0	174.0	152.0	85	75
Mean	4.03	4.32	7.56	7.74	116	110	6.14	6.40	7.0	7.5	147.4	153.6	76	78
SD	2.20	2.37	2.62	2.94	61	76	2.53	2.79	1.5	1.9	60.7	67.1	21	20
Mean D6-D7		4.18		7.65		113		6.27		7.0		150.5		77
SD		2.23		2.71		67		2.60		1.7		62.3	90%CI	72-86

*FI = Fluctuation index = $([C_{max}-C_{min}]/C_{min}) \times 100$
**F = oral bioavailability compared to Franol®
Mean T_{max} = Median T_{max}

Table 7 90% CI of the steady-state (Day 6 + Day 7) theophylline pharmacokinetic parameters of Uni-Dur®:Theo-Dur®, Xanthium®:Theo-Dur®, and Uni-Dur®:Xanthium®.

PK Parameters	90% CI (U:T)	90% CI (X:T)	90% CI (U:X)
C_{min}	1.06 - 1.33 (U >T)	0.92 - 1.13 (X = T)	1.07 - 1.39 (U > X)
C_{max}	0.67 - 0.84 (U < T)	0.64 - 0.73 (X < T)	0.99 - 1.22 (U = X)
AUC (0-24)	0.71 - 0.96 (U < T)	0.72 - 0.84 (X < T)	0.94 - 1.21 (U = X)

giving a once daily preparation that provided a long plateau-shaped serum theophylline concentration given at an appropriate time.[20-22] Since the average T_{max} of Uni-Dur® and Xanthium® are approximately 12 hours and 7 hours, the best time to administer the drugs would be around 6 p.m. ± 2 hours and 8 p.m. ± 2 hours, respectively.

Although OD Theo-Dur® provided better bioavailability, its absorption profile produced an unfavorable high fluctuation index (average % FI of Theo-Dur®, Uni-Dur® and Xanthium® were 232%, 137% and 113%, respectively). Since the upper limit of % FI is usually accepted at 100% where fluctuation in STC can stay within therapeutic range of 10-20 μg/ml,[6] the use of slow released theophylline preparations should be individualized. Nevertheless, once-daily dosing (OD) of Theo-Dur® has received approval from the US-FDA for selected patients such as adult nonsmokers with appropriate theophylline clearance or patients who required low dose theophylline after being satisfactorily titrated to therapeutic levels with twice daily dosing (BID).[1] Our study complied with this recommendation, since 400 mg OD dose of Theo-Dur® could be used in subjects 10, 11 and 12 who had a low theophylline clearance ranging from 0.3-0.39 ml/min/kg. In these subjects, the range of %FI and Css_{av} of 71-130% and 10.05-14.1 μg/ml, were within an acceptable range. Similarly, the use of OD 400 mg Uni-Dur® and Xanthium® for these subjects resulted in acceptable ranges of % FI and Css_{av} of 30-100%, 8.66-12.02 μg/ml and 47-82%, 8.43-10.85 μg/ml, respectively. Moreover, for subjects 2, 3, 6, 9 and 13 who had a theophylline clearance ranging from 0.45 to 0.55 ml/min/kg, the use of OD Uni-Dur® and Xanthium® also resulted in acceptable ranges of % FI and Css_{av} of 33-104%, 6.14-8.75μg/ml and 48-122%, 4.06-7.25 μg/ml, respectively. On the other hand, although the use of OD Theo-Dur® resulted in a therapeutic range of Css_{av} of 5.89-9.39 μg/ml, their % FI fell outside the acceptable range (141-273%), hence the use of OD Uni-Dur® and Xanthium® in these subjects would be more appropriate than OD Theo-Dur®. For subjects 4 and 7 who had a higher theophylline clearance rate of 0.65 and 0.8 ml/min/kg, administration of OD SRT resulted in an unacceptable high peak-trough fluctuation ranged from 297-808%, 256-620% and 192-244% for Theo-Dur®, Uni-Dur® and Xanthium®, respectively. In these cases, twice-daily dosing of the SRT will be appropriate, even though the product is labeled for once-daily use. Moreover, their Css_{av} (μg/ml) ranging from 2.41-4.99 (Theo-Dur®), 1.25-3.68 (Uni-Dur®) and 2.44-3.36 (Xanthium®) did not reach therapeutic levels, therefore higher doses of > 400 mg theophylline per day would be required. Our study underlines that the use of SRT preparations for maintaining the STC within therapeutic ranges is not only a function of the rate of theophylline release from the product, but also depends on the theophylline clearance rate of the individual subjects.

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