P' = Permeability constant of the drug in the distal tubule and collecting ducts, centimeter per minute
P_w = Reabsorption flux of water in the proximal tubule, centimeter per minute
P'_w = Reabsorption flux of water in the distal tubule and collecting duct, centimeter per minute
pK_a = The dissociation constant of the drug
U = Urine flow rate, millimeter per minute
U_{Ap} = Luminal fluid flow rate at the end of the proximal tubule, milliliter per minute
U_x = Luminal fluid flow rate in annulus at point x, millimeter per minute
α = Unbound fraction of drug in plasma
δ = Ratio of P/P_w
ϵ = Product of $P'A_d$, ml/min

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Absorption Kinetics and Steady-State Plasma Concentrations of Theophylline Following Therapeutic Doses of Two Sustained-Release Preparations

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Received October 5, 1981, from the *Department of Clinical Chemistry, Centralsygehuset i Naestved, DK 4700 Naestved, Denmark.* Accepted for publication March 19, 1982.

Abstract □ Ten healthy volunteers received two sustained-release preparations as a single and multiple dose regimen in an open crossover study. Plasma theophylline concentrations were measured by an enzyme immunoassay. The limited fluctuation of the theophylline levels at steady state, with twice daily administration, clearly demonstrated the marked sustained release properties of both preparations. Results indicate similar properties for the two preparations. Significant correlations between the single dose period and steady state were found for C_{max} and AUC (r = 0.76 and 0.87, respectively) with one formulation, whereas this was not the case for the other (r = 0.27 and 0.49). The daily dose necessary to keep the plasma concentration within the therapeutic range of 55–110 μmole/liter varied from 7.9 to 22.9 mg/kg. Only mild side effects were recorded, but they were not correlated to the plasma theophylline concentration.

Keyphrases □ Absorption—kinetics and steady-state plasma concentrations of theophylline following therapeutic doses of two sustained-release preparations □ Kinetics—absorption and steady-state plasma concentrations of theophylline following therapeutic doses of two sustained-release preparations □ Theophylline—absorption kinetics and steady-state plasma concentrations following therapeutic doses of two sustained-release preparations

Theophylline produces relaxation of bronchial smooth muscles and is widely used in the treatment of reversible obstructive lung disease. The bronchodilator effect of theophylline increases with serum concentrations over a range of 28–110 μmoles/liter (5–20 μg/ml), but at levels of >110 μmoles/liter there is an increased risk of serious toxicity (1). Maximal bronchodilation with minimal toxicity occurs at levels between 55–110 μmoles/liter (10–20 μg/ml), and this is therefore normally considered the therapeutic range (2). It is very difficult to maintain serum

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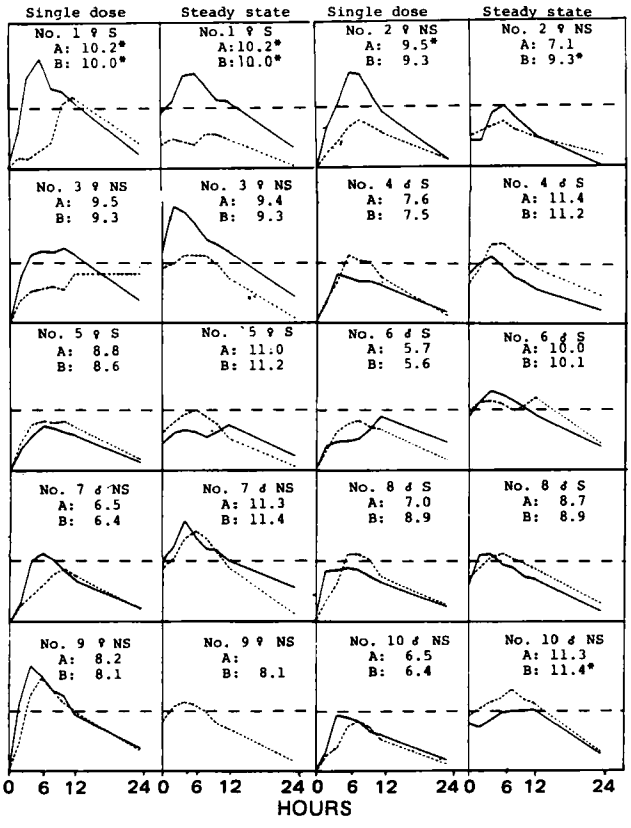

Figure 1—*Plasma concentration–time relationship for all subjects. Ordinate gives plasma concentration. The odd numbers (left in figure) received tablet B in the first period, the even numbers received tablet A. Figures in each frame are doses in milligrams per kilogram (single dose experiments) and milligram per kilogram per day (steady-state experiment). Key: (---) 55 μmoles/liter; (—) tablet A; (·····) tablet B; (S) smoker; (NS) nonsmoker; (*) occurrence of side-effects during the administration of this dose or at the next higher dose according to the dose schedule.*

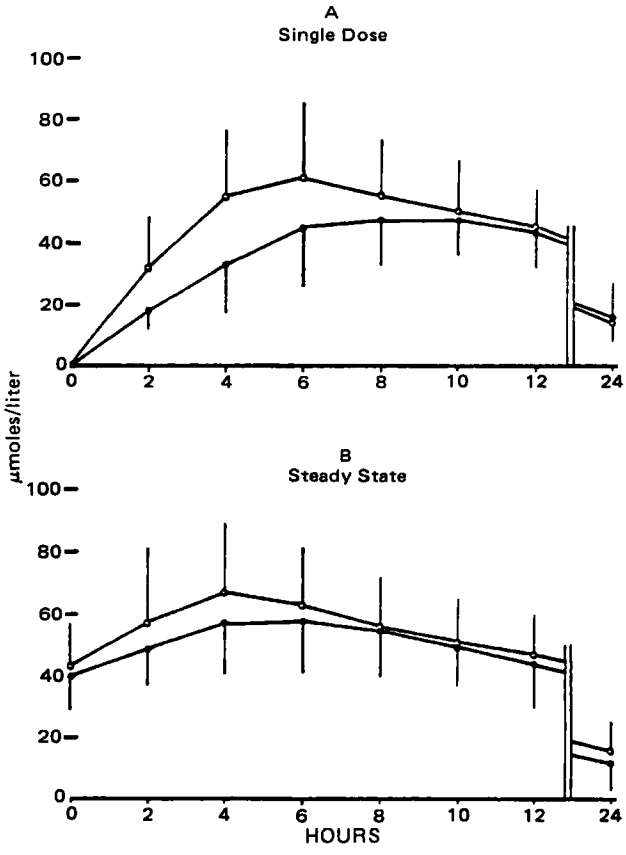

Figure 2—*(A) Plasma concentrations after administration of a single dose of tablet A (dose equivalent to 510 mg of theophylline), or tablet B (dose equivalent to 500 mg of theophylline). Mean of 10 healthy adults ±SD. Key: (○) tablet A; (●) tablet B. (B) Plasma concentrations at steady state. Tablet A (mean dose; 10.0, range: 7.1–11.4 mg/kg/day as theophylline). Tablet B (mean dose; 10.1, range: 8.1–11.4 mg/kg/day as theophylline). Mean of 10 healthy adults ±SD. Key: (○) tablet A; (●) tablet B.*

theophylline concentrations within this narrow therapeutic range during treatment with conventional tablets, due to the large interindividual variation in theophylline clearance, fast absorption, and relatively short half-life. A growing interest in sustained-release preparations has appeared during recent years and a number of different preparations are now on the market in several countries. This report deals with a comparison of two sustained-release preparations, containing theophylline–ethylenediamine and theophylline, respectively, after single dose administration, as well as repeated dosage to give levels within the therapeutic range. The theophylline dosage form was studied previously (3), and it was shown that a mean C_{max} value of 41 μmoles/liter (7.5 μg/ml) was obtained with 8 mg/kg every 12 hr. Levels of theophylline–ethylenediamine within the therapeutic range have only been investigated in single dose studies (4, 5) and the preparation has not been compared with other sustained-release preparations.

EXPERIMENTAL

Preparations—Tablet A[1] was a theophylline–ethylenediamine formulation with 350 mg of theophylline–ethylenediamine (equivalent to 255 mg of anhydrous theophylline) given as whole or half tablets. Tablet B[2] was a theophylline formulation with 200 or 300 mg of anhydrous theophylline, given as whole tablets only.

Subjects—Ten healthy volunteers (5 females and 5 males), age 26–54 years, mean 38, were included in the study. Their heights ranged from 160 to 192 cm, mean 175, and they weighed from 50 to 89 kg, mean 67. Five were smokers and five nonsmokers. All were found healthy by physical examination and laboratory testing for functions of liver, heart, kidney, and bone marrow.

Study Design and Dosage—The study was an open crossover study in which half of the subjects were randomly allocated to start on one preparation and the other half on the other preparation. The subjects received only one dose (510 mg of theophylline for tablet A and 500 mg for tablet B) for the first 24 hr. From the second day on the dose was gradually increased, starting with ~400 mg of theophylline daily and increasing in steps of 25% every 3 days (6). The final dose for each individual subject was determined by the occurrence of one of the following criteria: (*a*) The next increase in dose gave rise to side effects; (*b*) the plasma theophylline concentration 6 hr after the morning dose was within the therapeutic range (55–110 μmoles/liter); or (*c*) the dose had reached 13 mg/kg or 900 mg/day. The dosage used in the first period was used in the second period. Each preparation was given for 13 days with an 8-day wash-out period in between. The subjects were instructed not to take methylxanthine-containing beverages or food 12 hr before and on the day of blood sampling. They were also instructed to make notes on side effects during the study.

Blood Sampling—On day 1 of each period 10-ml blood samples were drawn before, and 2, 4, 6, 8, 10, 12, and 24 hr after drug administration. On the last day of each period the same sequence of blood sampling was followed after the morning dose, the maximum dose having been administered for at least 3 days. Blood samples were drawn from a cubital

[1] Tablet A: Euphyllin retard, H. Lundbeck & Co., A/S, Batch No. 2218-2.

[2] Tablet B: Theo-Dur, Draco, Batch Nos. 055889 and 056481.

Table I—Comparison of the Parameters Obtained with Two Sustained-Release Preparations

	Single Dose Period					Steady-State Period				
	Tablet A		Tablet B			Tablet A		Tablet B		
	mean	*SD*	mean	*SD*	*p*-value	mean	*SD*	mean	*SD*	*p*-value
C_{max}[a], μmoles/liter/mg	0.13	0.04	0.11	0.03	0.25	0.20	0.11	0.15	0.03	0.21
C_{min}[a], μmoles/liter/mg	—	—	—	—	—	0.13	0.06	0.11	0.02	0.30
T_{max}, hours	6.4	2.6	9.1	3.6	0.03	6.0	3.6	7.1	2.2	0.44
C_{max}–C_{min}	—	—	—	—	—	1.51	0.28	1.41	0.20	0.39
$AUC_{0\to\infty}$[a], μmoles/liter/mg hr	2.01	0.57	1.84	0.44	0.19	—	—	—	—	—
$AUC_{0\to12}$[a], μmoles/liter/mg hr	—	—	—	—	—	1.95	1.00	1.58	0.33	0.28

[a] Normalized by division by dose in milligrams of theophylline.

vein using an evacuated heparinized container[3] and using stasis times of <1 min. Within 1 hr the plasma was separated from blood cells by centrifugation and transferred to a clean vial. The theophylline concentrations were determined immediately or after storage at −20° for <24 hr. No significant decrease was found in plasma samples stored at −20° for 6 months.

Drug Estimation—Plasma theophylline was measured by an enzyme immunoassay[4] (7) adapted for use with a biochromatic analyzer[5]. Comparative analyses of patient samples analyzed by the enzyme immunoassay and HPLC methods have confirmed the lack of interference from metabolites or structurally related molecules in the enzyme immunoassay (8). The accuracy of this enzyme immunoassay is the same as the HPLC methods usually used in clinical pharmacological studies of theophylline (9). In the present study the within-day coefficient of variation was 1.4% and the between-day coefficient of variation was 3.9%.

Data Treatment—The elimination rate constant (β) was calculated from the slope of the concentration line, from 12 to 24 hr after administration, in a semilogarithmic plot as $\beta = -2.303$ slope. The area under the plasma concentration curve after the first dose ($AUC_{0\to\infty}$) was calculated by the trapezoidal rule in the time period of 0–24 hr ($AUC_{0\to24}$) and by the formula C_{24}/β in the period 24 hr to infinity ($AUC_{24\to\infty}$). In the steady-state period, the area under the curve in a dosage interval ($AUC_{0\to12}$) was calculated by the trapezoidal rule. The different parameters (concentrations dose corrected) obtained with the two preparations were compared by a paired-sample *t* test (10). The regression line illustrating the correlation of the parameters from the single dose period with those from the steady-state period with the same preparation was calculated by the least-square method [Pearson's product moment correlation (11)].

RESULTS

Plasma concentration–time curves obtained during the study are shown in Fig. 1. The plasma concentration curves show a rather large variation between the individual subjects, but do not indicate that one preparation gives more consistent plasma levels than the other.

The single (first) dose periods are compared in Fig. 2A. The curves show that the maximum plasma concentration after tablet A appeared earlier than after tablet B. This was confirmed by a statistically significant difference found by a paired *t* test (Table I). The curves also show a higher maximum plasma concentration and a larger area under the curve (AUC) after tablet A, but the statistical analysis showed no difference.

Mean plasma theophylline concentrations after repeated administration to steady state appear in Fig. 2B. The mean dose (±*SD*) on repeated administration was 10.0 (±1.5) mg/kg for tablet A, and 10.1 (±1.2) mg/kg for tablet B, giving mean peak plasma concentrations at 4 hr after administration for tablet A (67 μmoles/liter) and at 6 hr after tablet B (58 μmoles/liter). The corresponding minimum values (mean of 0 and 12 hr) were 45 μmoles/liter and 42 μmoles/liter, respectively. There was a tendency toward an earlier maximum with tablet A, but the difference was not significant (Table I). Also, values for C_{max}, C_{min} (mean of C_0 and C_{12}), and $AUC_{0\to12}$ tended to be higher for tablet A but with no significant difference. The fluctuations in the dosage interval expressed as the C_{max}–C_{min} ratio, are similar for the two preparations being a mean of 1.5 and 1.4 for tablets A and B, respectively (Table I).

The dosage, *giving* a concentration within the therapeutic range of 55–110 μmoles/liter throughout the entire period, can be calculated from the minimum concentration measured during steady state in each subject. For tablet A this dose was a mean (range) 12.8 (7.9–18.3) mg/kg/day, and for tablet B 14.1 (9.3–22.9) mg/kg/day.

A correlation analysis on the different parameters shows, that C_{max} and AUC (both normalized by division by dose) are significantly correlated in the single dose and steady-state periods ($r = 0.76$ and 0.87, respectively) during administration of tablet A, but not with tablet B ($r = 0.27$ and 0.49) (Fig. 3). Time of maximum, T_{max}, did not show correlation between single dose and repeated administration for either of the preparations.

The reports on side effects are shown in Fig. 1; it appears that the frequency of side effects was similar from the two preparations. The symptoms reported include palpitations, tremor, vomiting, nausea, headache, and insomnia, subjectively estimated as ranging from mild to severe.

DISCUSSION

The present investigation clearly demonstrates the marked sustained-release properties of the two preparations. This is in accordance with earlier investigations in which the two preparations were compared to conventional tablets (3–5, 9). The limited fluctuation seen during the steady-state dosage interval of 12 hr shows that this frequency of dosing would be reasonable during maintenance therapy with any one of these two sustained-release preparations. As expected, the dose necessary to keep the plasma theophylline concentration within the therapeutic range varied considerably between individuals (7.9–22.9 mg/kg/day).

The preparations did not differ significantly as to maximum plasma concentration, minimum plasma concentration, fluctuation in plasma concentration during the dosage interval, and area under the plasma concentration curve. This indicated that the amount of theophylline absorbed from the two preparations was the same, and that the absorption took place at almost the same rate. The significantly earlier average time of individual peak occurrence seen with tablet A in the single dose period may indicate that absorption is slightly faster with this preparation, but it does not significantly influence the steady-state plasma concentration curve. Tablet B contained theophylline only, whereas tablet A, in addition to theophylline, contained ethylenediamine to increase the solubility of theophylline. This difference does not seem to influence absorption considerably.

There is a difference, however, between the two preparations on one point. The plasma levels for tablet A after the first dose (expressed as dose normalized C_{max} or AUC) correlated significantly with those found at steady state, whereas no such correlation was found with tablet B. This indicates less intraindividual variation with tablet A possibly because of more stable release of drug from this preparation. Moreover it means that in subjects receiving tablet A it is possible to perform measurements on the first dose (C_{max} or AUC), and from these obtain a guideline for choosing the dose for further treatment. This does not, however, render a later monitoring of the drug level unnecessary. The present results do not indicate that it would be of any help to measure plasma levels after the first dose with tablet B.

In connection with the calculation of the AUC values after single dose administration, an elimination rate constant, β, has been calculated. As this value is only based on two concentrations, C_{12} and C_{24}, and one cannot be sure that absorption is complete at 12 hr after administration, β is encumbered with some uncertainty. However, the values obtained (0.06–0.18) give half-lives in the range of 3.9–11.6 hr, which are in agreement with the half-lives normally found for theophylline (1). Moreover it supports the view that the steady state can be reached with 3 days of constant dosage. A difference in half-lives between smokers and nonsmokers as demonstrated by others (12–14), could not be found, but the reason for this may be that none of the volunteers were heavy smokers. A comparison of $AUC_{0\to\infty}$ after single dose and $AUC_{0\to12}$ after dosing to steady state shows that the AUC values are not significantly different. This means that the pharmacokinetics of theophylline have not changed during treatment.

[3] Venoject.
[4] EMIT, Syva Corp., Palo Alto, CA 94304.
[5] ABA 100.

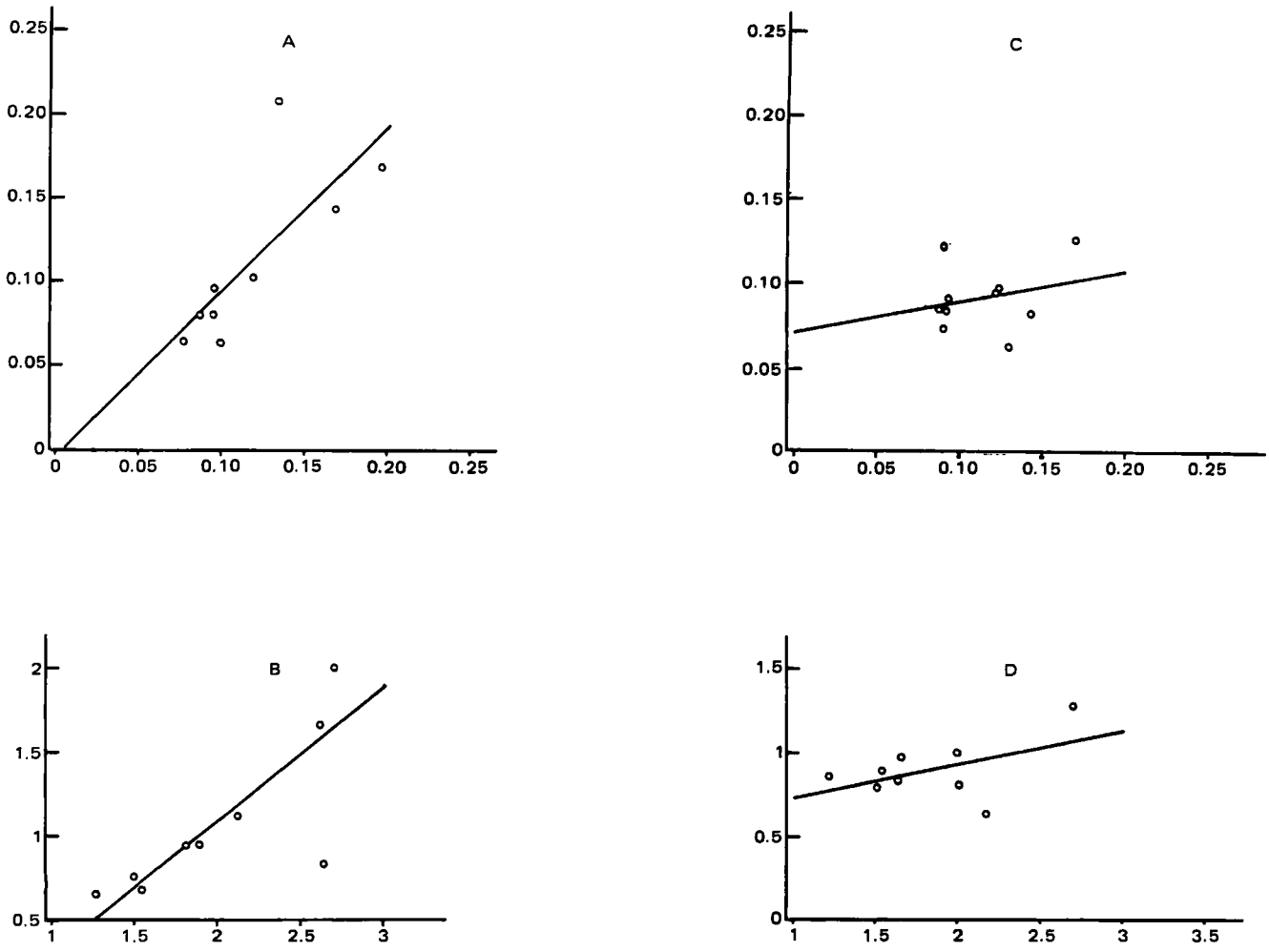

Figure 3—*Correlations between single dose (abscissa) and steady state (ordinate). Key: (A) Tablet A,* C_{max}, $y = 0.972x - 0.005$, $r = 0.76$; *(B) Tablet A,* AUC, $y = 0.799x - 0.511$, $r = 0.87$; *(C) Tablet B,* C_{max}, $y = 0.189x + 0.070$, $r = 0.27$; *(D) Tablet B,* AUC, $y = 0.199x + 0.529$, $r = 0.49$. C_{max} *values are μmoles/liter/mg of theophylline.* AUC *values are μmole hr/liter/mg of theophylline.*

The design of this investigation does not allow conclusions considering side-effects. Appearance of side-effects was not related to plasma theophylline concentrations in the range investigated. Some subjects experienced more side-effects from one preparation than from the other, whereas the opposite was experienced by others. Similarly for some, the first period seemed to be worse than the second and *vice versa.* Some subjects did not experience any adverse side-effects at all. Thus, it seems that each individual patient must be allowed to try whichever preparation is most suitable.

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