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Clinical assessment of theophylline absorption from Theolair-SR and two other sustained-release formulations relative to a conventional formulation

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Summary

In this single dose study with 8 subjects, the rate and extent of theophylline absorption from 3 sustained-release formulations (Theolair-SR tablet, Slo-phyllin Gyrocaps, and an experimental SR tablet) were compared to absorption from a conventional formulation (Theolair tablet) that has been shown to provide both prompt and complete absorption. Plasma theophylline level versus time profiles show that the rate of absorption from all 3 sustained-release formulations is slower than from the conventional tablet. In addition, the higher plasma levels at later times and the slower apparent plasma elimination rate of theophylline following the Theolair-SR tablet as compared to the conventional Theolair tablet indicate that drug absorption continues over a more prolonged period of time. Plasma AUC data indicate, with good assurance, that the extent of theophylline absorption is essentially complete from all 3 sustained-release formulations when compared to data for the conventional tablet. Statistical analyses with plasma AUC data indicate that the Theolair-SR tablet should provide both reliable and complete drug absorption. Projected plasma drug levels for multiple dosage regimens (simulated on the basis of the single dose data from this study) demonstrate that, even with a twice daily dosage regimen, the Theolair-SR tablet has acceptable sustained-release characteristics relative to the conventional Theolair tablet with 4 daily doses, and that the sustained-release properties compare favorably with those of Slo-phyllin Gyrocaps.

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Overall, the Theolair-SR tablet should be therapeutically useful for chronic treatment of patients, especially in those patients who eliminate theophylline more rapidly.

Introduction

The therapeutic activity of theophylline has been related to plasma drug concentrations in patients with chronic reversible obstructive lung disease by several investigators as described in recent reviews (Hendeles et al., 1978a; Ogilvie, 1978). Overall, these authors conclude that levels of 10 μg/ml and greater usually provide therapeutic control in most patients, and that levels between 5 and 10 μg/ml provide symptom control in some patients and therapeutic improvement in other patients. In addition, plasma levels that exceed 20 μg/ml are associated with a greater incidence of untoward reactions (Hendeles et al., 1978a; Ogilvie, 1978; Hendeles and Weinberger, 1980).

The plasma elimination kinetics of theophylline have been extensively studied in humans; plasma half-life data for theophylline have been tabulated in several review papers (Levy, 1974; Hendeles et al., 1978b; Ogilvie, 1978; Hendeles and Weinberger, 1980). These data show that the rate of drug elimination from plasma varies markedly among individual patients or healthy subjects and is relatively rapid in certain groups of individuals. For adults, the plasma half-life of theophylline has been reported to range from less than 1 h to about 13 h and the plasma half-life in smokers (mean, about 4–6 h) is shorter, on an average, than that in non-smokers (mean, about 6–9 h). In addition, the plasma half-life in children (mean, about 3–4 h) is generally shorter than that in adults.

Since theophylline is rapidly eliminated from plasma in certain patients, maintenance of therapeutic plasma levels during chronic treatment may not be achieved with conventional (immediate-release) formulations. Weinberger and Ginchansky (1976) have reported that with a 6-h dose interval in children, the differences in peak-to-trough plasma theophylline concentrations ranged from 4.0 to 15.6 μg/ml (mean, 9.1 μg/ml); these differential (peak-trough) levels were excessive (greater than 10 μg/ml) in almost half of the 22 patients studied. Thus, maintenance of therapeutic levels in the range of 10–20 μg/ml is frequently not possible in this patient population even with a 6-h dosage interval. Several authors (Weinberger and Riegelman, 1974; Ellis et al., 1976; Weinberger and Ginchansky, 1976; Weinberger et al., 1978; Riegelman and Jenne, 1980) have concluded that a reliable sustained-release formulation of theophylline that provides prolonged drug absorption would be therapeutically useful, especially in patients who eliminate theophylline at a relatively rapid rate. A sustained-release formulation of theophylline could provide more sustained plasma levels in these patients and thus better control of the disease state, particularly during the overnight period. In addition, a sustained-release formulation could provide the convenience to the patient of longer intervals between doses, and perhaps, would lead to better compliance with prescribed dosage regimens.

The objective of this study was to compare the oral absorption of theophylline from 3 different sustained-release formulations (Theolair-SR tablets, Slo-phyllin Gyrocaps, and an experimental SR tablet) to drug absorption from a reference, conventional solid dosage formulation (Theolair tablets). This conventional tablet has been shown to provide complete theophylline absorption when compared to intravenous administration (Jonkman et al., 1980) and also relative to absorption from a hydroalcoholic solution (elixir) of theophylline (Cohen et al., 1975; Holley et al., 1978); it also has been shown to provide both prompt and predictable absorption. This single dose study was conducted in healthy, adult subjects to assess both the relative rate and extent of drug absorption.

This plasma level data for the Theolair-SR tablet is from the first in a series of clinical studies with the currently marketed sustained-release formulation; emphasis in this paper is placed on the absorption characteristics of this new sustained-release formulation.

Materials and methods

Formulations

The following theophylline formulations were evaluated:

(1) Theolair-SR Slow-Release Tablet, 250 mg [1] (Formulation U-4e, Lot 77-019).
(2) Slo-phyllin Gyrocaps, 250 mg [2] (Lot 641-2977).
(3) Experimental sustained-release tablet, 250 mg [1] (Formulation U-5a, Lot 77-021).
(4) Theolair Tablet, 250 mg [1] (Reference, Conventional Formulation, Lot 79528).

Theophylline content for each formulation was determined by use of a high pressure liquid chromatographic method [3]. The mean drug content (10 individual dosage units) for each of the formulations is within approximately ±3% of label (250 mg). Since this deviation from labelled dose is relatively small, comparative plasma theophylline level data were not corrected for actual administered dose. In addition, an in vitro dissolution evaluation of the 3 sustained-release formulations was conducted by the USP (Method II) paddle stirrer procedure. To simulate in vivo conditions, aqueous acidic (pH ~ 1) dissolution media (0.1 N HCl with 0.04% polysorbate 80) was initially used; at 1.5 h, the media was neutralized with aqueous 5 N NaOH and buffered to pH 7.5 with 0.136 M phosphate. As shown in Fig. 1, the Slo-phyllin Gyrocaps formulation dissolves faster than either Riker sustained-release formulation and the experimental sustained-release tablet (U-5a) dissolves faster than the marketed Theolair-SR tablet (U-4e).

Clinical procedures

Eight, adult male subjects participated in the study (Table 1). All subjects were in good health as determined by medical history and complete physical examination

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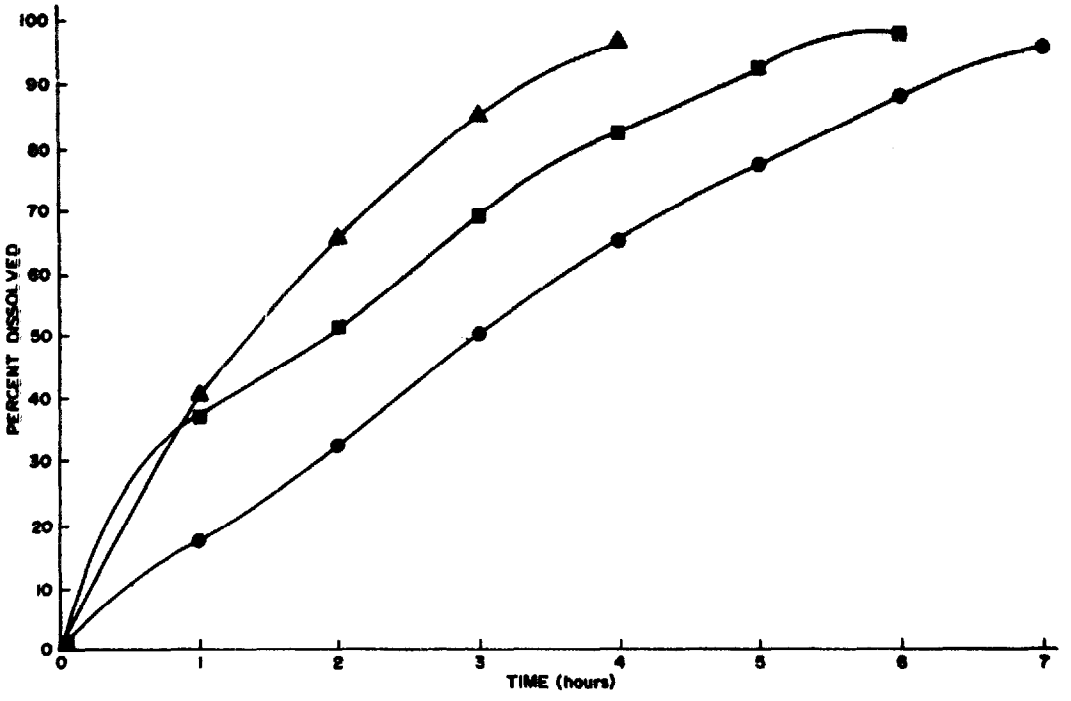

Fig. 1. Dissolution characteristics of the theophylline sustained-release formulations; USP (Method II) paddle-stirrer procedure. ▲, Slo-phyllin Gyrocaps (Lot 641-2977); ■, experimental sustained-release tablet (U-5A, Lot 77-021); ●, Theolair-SR Tablet (U-4e, Lot 77-019).

which included standard blood chemistries, hematology and urinalysis. Body weights for all subjects were within ± 10% of ideal weight (Metropolitan Life Insurance, 1959) for height and body frame.

TABLE I

DESCRIPTION OF SUBJECTS [a] AND DOSE DATA

Subject number	Age (years)	Weight (kg)	Height (cm)	Smoking history [b]	Theophylline dose (mg/kg) [c]
1	33	77.2	181	S	6.5
2	20	68.1	176	NS	7.3
3	19	63.5	168	S	7.9
4	20	79.5	188	NS	6.3
5	20	62.6	178	NS	8.0
6	18	74.9	181	S	6.7
7	30	64.0	174	S	7.8
8	19	86.2	183	NS	5.8
Mean					7.0

[a] All subjects were white males.
[b] Smoking history: S = smoker and NS = non-smoker.
[c] A single, 500 mg dose of theophylline was used for all subjects with each formulation treatment.

The open label study was conducted with one formulation per treatment period; all subjects received the same formulation on a given date. Each subject received all 4 formulation treatments with at least a 7-day wash-out period between treatments. The sequence of formulation treatments was as follows: (1) Slo-phyllin Gyrocaps; (2) Theolair-SR tablets; (3) Experimental sustained-release tablets; and (4) Conventional Theolair tablets.

All medications, including xanthine-containing preparations, salicylates and laxatives, were withheld for at least 72 h prior to and during each treatment period. In addition, all subjects abstained from alcohol and xanthine-containing foods and beverages for at least 48 h prior to each treatment day and until the last blood sample was obtained. Prior to each dosing day, all subjects fasted overnight from at least 22.00 h. The oral dose of theophylline for all formulations was a single, 500 mg dose (two dosage units of 250 mg each). On a mg/kg basis, the dose ranged from 5.8 to 8.0 mg/kg (mean 7.0 mg/kg) for the 8 subjects (Table 1). Drug was administered with 8 ounces of water; no food was ingested for at least 4 h following dosage.

Blood samples (10 ml) were obtained by direct venipuncture (heparinized Vacutainer) from each subject at specified times (Table 2) following each dose. Plasma

TABLE 2

MEAN PLASMA CONCENTRATIONS OF THEOPHYLLINE WITH STATISTICAL COMPARISONS TO THE CONVENTIONAL REFERENCE FORMULATION

Time following dosage (h)	Plasma theophylline concentration (μg/ml) [a,b]			
	Theolair tablets [c]	Theolair-SR tablets	Slo-phyllin Gyrocaps	Experimental SR tablets
0.0	0.0	0.0	0.0	0.0
0.5	9.6 (41)	1.3 (71) ***	0.4 (37) ***	3.0 (33) **
1.0	12.2 (11)	2.9 (76) ***	2.5 (56) ***	4.3 (19) ***
2.0	12.2 (12)	5.7 (82) **	5.6 (39) ***	4.8 (17) ***
4.0	10.3 (18)	7.9 (53) n.s.	8.5 (17) **	6.1 (29) ***
6.0	8.2 (21)	8.1 (29) n.s.	8.8 (11) n.s.	7.3 (31) *
8.0	6.5 (24)	6.9 (25) n.s.	7.6 (21) n.s.	6.4 (30) n.s.
12.0	4.0 (36)	4.9 (17) *	4.6 (29) n.s.	4.5 (33) n.s.
16.0	2.5 (48)	3.6 (23) ***	2.7 (38) n.s.	3.4 (33) *
24.0	1.0 (63)	2.1 (39) ***	0.9 (52) n.s.	1.8 (28) **
48.0	0.1 (125)	0.7 (87) *	0.3 (111) n.s.	0.5 (106) n.s.

[a] Mean values for the 8 subjects following a single, 500 mg dose with each formulation; the coefficient of variation is shown in parenthesis.

[b] Results of statistical analysis (independent paired t-test comparison to Theolair tablets, two-tailed test): n.s. indicates no significant difference ($P>0.05$);
* indicates significantly different at an α level of 0.05 or less;
** indicates significantly different at an α level of 0.01 or less;
*** indicates significantly different at an α level of 0.001 or less.

[c] Conventional reference formulation.

was promptly separated by centrifugation and was stored frozen (−20°C) until the time of analysis for theophylline.

Vital signs (pulse, respiration and blood pressure) and side-effects were monitored periodically during each treatment period. Only minor and infrequent effects were observed or reported; these common side-effects were consistent with those expected with a 500 mg dose of theophylline in naive subjects (Weinberger, 1979).

Analytical method

Plasma concentrations of theophylline were measured by use of a high pressure liquid chromatographic method; the procedure is similar to a method previously reported (Sitar et al., 1975) and incorporates the use of an internal standard (monohydroxypropyltheophylline). Prior to analysis of unknown samples, the method was validated for accuracy and precision. The practical lower limit for quantitation is approximately 0.5 μg/ml; the detection limit is 0.1 μg/ml.

Single, 1.0 ml aliquots of plasma were analyzed. Analytical reference samples were prepared with anhydrous theophylline and 1.0 ml of blank human plasma; these samples were routinely carried through the assay procedures in parallel with each group of plasma samples. Calibration curves (peak height response ratio for theophylline/internal standard versus plasma theophylline concentration) were linear from 0.5 to 15 μg/ml.

Pharmacokinetic analyses

The apparent plasma half-life of theophylline was determined from at least 3 and usually 4 or more analytically significant data points in the terminal (linear) phase of the log plasma concentration versus time curve; this was done by calculation of the least-squares line (linear regression). The area under the plasma concentration versus time curve (AUC) was calculated by the trapezoidal rule. The time-to-peak concentration was obtained from the time of the highest measured plasma level or by interpolation in the case of nearly identical peak levels at adjacent times.

Simulated plasma theophylline concentrations for multiple oral dosage regimens with conventional Theolair tablets, Slo-phyllin Gyrocaps and Theolair-SR tablets (U-4e) were calculated by the superposition method (Gibaldi and Perrier, 1975). Single dose, mean plasma levels from all 8 subjects were used for these pharmacokinetic simulations.

Statistical analyses

Plasma theophylline levels at each time point and various plasma pharmacokinetic parameters for each of the 3 sustained-release formulations were independently compared to corresponding data for the conventional Theolair tablet (reference formulation) using a paired *t*-test[4]. An α level of 0.05 was used for determination of statistically significant differences (two-tailed test) for all data, except the AUC parameter. Since theophylline absorption from conventional Theolair tablets

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has been shown to be complete (see Introduction), a one-tailed test (α level of 0.05) was used for AUC comparisons.

For each of the formulation treatment comparisons, the statistical power of the paired t-test was calculated[4] for the plasma AUC data; the power of the paired t-test to detect a 20% difference between formulations at an α level of 0.05 (one-tailed test) was calculated (Dixon and Massey, 1969).

Results and discussion

Plasma theophylline concentration versus time profiles

Mean plasma concentrations of theophylline at specified times following each dose are plotted versus time in Fig. 2 for all 4 formulations. These mean plasma level data for the 8 subjects with the results of the independent statistical comparison of each sustained-release formulation to conventional Theolair tablets (reference formulation) are shown in Table 2.

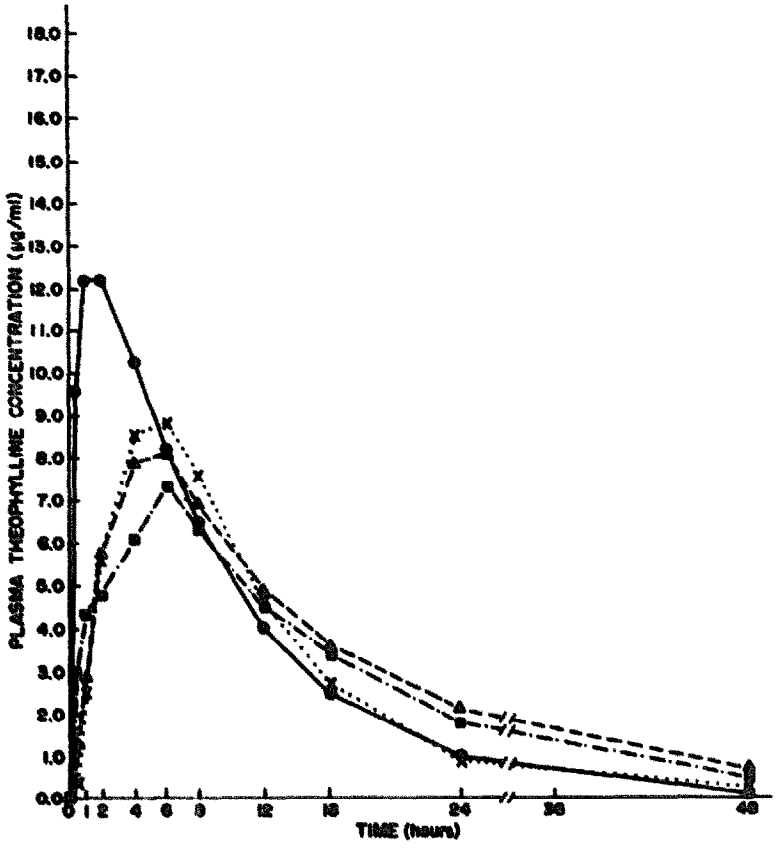

Fig. 2. Mean plasma concentrations of theophylline for the 8 subjects following a single, 500 mg dose with each formulation. ●———●, conventional Theolair Tablet (Lot 79528); ×·····×, Slo-phyllin Gyrocaps (Lot 641-2977); ▲— — —▲, Theolair-SR Tablet (U-4e, Lot 77-019); ■-·-■, experimental sustained-release tablet (U-5a, Lot 77-021).

The plasma level versus time profiles (Fig. 2) show that the rate of theophylline appearance in plasma is slower following administration of each sustained-release formulation than after the conventional formulation; this difference in rate of drug absorption is reasonably consistent in most subjects for each sustained-release formulation. Mean values for time-to-peak plasma concentration and peak plasma theophylline levels for each formulation are shown in Table 3. Times-to-peak level for each of the sustained-release formulations are considerably greater (statistically significant at the 0.001 level) than that for conventional Theolair tablets. Correspondingly, peak drug levels following dosage with each sustained-release formulation are statistically lower ($P < 0.05$) than the peak level for conventional Theolair tablets. These time-to-peak data (Table 3) and the plasma level versus time profiles (Fig. 2) indicate that the rates of drug absorption from the 3 sustained-release formulations are slower than the rate from conventional Theolair tablets and that absorption continues to occur for a more prolonged period of time after drug administration with the sustained-release formulations.

After peak plasma levels are attained, theophylline disappearance from plasma was found to be reasonably log-linear for all 4 formulations. In addition, this disappearance is reasonably log-linear (r^2 values range from 0.947 to 0.999) for all subjects with each formulation. The mean apparent plasma half-life of theophylline for each formulation is shown in Table 3. For the conventional solid dosage formulation, the half-life was found to range from 4.3 to 9.4 h (mean 5.7 h) in these 8 subjects; these values are within the range of plasma half-life values for theophylline previously reported for adults by several investigators (see Introduction). The apparent plasma half-life values for both Theolair-SR tablets and the experimental sustained-release formulation are significantly longer ($P < 0.01$) than the half-life

TABLE 3

MEAN PLASMA PHARMACOKINETIC DATA FOR THEOPHYLLINE WITH STATISTICAL COMPARISONS TO THE CONVENTIONAL REFERENCE FORMULATION

Pharmacokinetic parameter	Plasma theophylline pharmacokinetic data [a,b]			
	Theolair tablets [c]	Theolair-SR tablets	Slo-phyllin Gyrocaps	Experimental SR tablets
Time-to-peak level (h)	1.3 (50)	5.0 (30)***	5.0 (30)***	6.0 (18)***
Peak plasma level (μg/ml)	13.0 (9)	9.1 (42)*	9.3 (11)***	7.4 (29)***
Apparent plasma half-life (h)	5.7 (29)	10.7 (38)**	4.9 (18) n.s.	9.0 (17)**

[a] Mean values for the 8 subjects following a single, 500 mg dose with each formulation; the coefficient of variation is shown in parenthesis.

[b] Results of statistical analysis (independent paired *t*-test comparison to Theolair tablets, two-tailed test): n.s. indicates no significant difference ($P > 0.05$);
* indicates significantly different at an α level of 0.05 or less;
** indicates significantly different at an α level of 0.01 or less;
*** indicates significantly different at an α level of 0.001 or less.

[c] Conventional reference formulation.

with conventional Theolair tablets (Table 3); the apparent plasma half-life with Slo-phyllin Gyrocaps is not statistically different ($P > 0.05$) from that with conventional Theolair tablets. The greater half-life values (slower apparent drug elimination) for both the Theolair and the experimental sustained-release formulations are likely a result of continued theophylline absorption at later times after dosage.

Correspondingly, plasma theophylline levels at 12, 16, 24 and 48 h following the Theolair-SR tablet and at 16 and 24 h after the experimental sustained-release tablet are significantly higher ($P < 0.05$) than levels at corresponding times after conventional Theolair tablets (Table 2); plasma levels at these times after Slo-phyllin Gyrocaps are not statistically different ($P > 0.05$) from levels after the reference formulation.

The somewhat more rapid in vitro dissolution characteristics of the Slo-phyllin Gyrocaps formulation than those of either the Theolair-SR tablet or the experimental sustained-release tablet (Fig. 1) are consistent with the more prolonged plasma theophylline levels for the latter two sustained-release formulations (Fig. 2 and Table 2). Although in vitro dissolution data were used as a guide in the development of both the Theolair-SR tablet and the experimental sustained-release tablet, the difference observed in dissolution rate for these two formulations is not readily apparent in the plasma level versus time profile for the two formulations.

Overall, the plasma level versus time profile data show that the initial rate of theophylline absorption from all 3 sustained-release formulations is slower than that from conventional Theolair tablets; similar results for Slo-phyllin Gyrocaps have also been reported by other investigators (Weinberger et al., 1978). In addition, the plasma level profiles following both the Theolair-SR tablet and the experimental sustained-release tablet as compared to the conventional Theolair tablet indicate that drug absorption continues over a more prolonged period of time after dosage with these two sustained-release formulations; the data also suggest that both of these sustained-release tablets may provide more prolonged drug absorption than Slo-phyllin Gyrocaps. With a multiple dosage regimen (dose interval of greater than 6 h), the Theolair-SR tablet should provide more sustained plasma theophylline concentrations and should provide better therapeutic control of chronic reversible obstructive lung disease than a conventional dosage formulation. Projected plasma levels for multiple dosage regimens are discussed in a subsequent section (see *Simulation of plasma levels with multiple dosage*).

Relative extent of theophylline absorption

The relative extent of theophylline absorption from each of the 3 sustained-release formulations as compared to the conventional Theolair tablet (reference formulation) was determined by comparison of plasma AUC values. A comparison of plasma AUC values (0–48 h) for each of the 8 subjects with all 4 formulations is shown in Table 4. Mean AUC values (0–48 h) of 135.5, 147.0, 119.8 and 131.5 $\mu g \cdot h/ml$ are attained following administration of conventional Theolair tablets, Theolair-SR tablets, Slo-phyllin Gyrocaps, and the experimental sustained-release tablets, respectively. Independent paired treatment comparisons of AUC values for each sustained-release formulation to those for the Theolair tablet show that no

TABLE 4

PLASMA THEOPHYLLINE AUC DATA (0–48 h) FOR EACH SUBJECT WITH STATISTICAL COMPARISONS TO THE CONVENTIONAL REFERENCE FORMULATION

Subject number	Plasma AUC from 0 to 48 h (μg·h/ml) [a]			
	Theolair tablets [b]	Theolair-SR tablets	Slo-phyllin Gyrocaps	Experimental SR tablets
1	112.7	148.8	106.5	141.8
2	200.4	177.3	158.5	201.2
3	133.2	160.4	115.0	103.9
4	126.3	155.5	92.7	112.2
5	125.0	137.9	147.7	159.9
6	111.3	98.6	108.3	96.4
7	123.6	150.0	109.8	107.3
8	151.7	147.1	119.9	129.4
Mean value	135.5	147.0	119.8	131.5
Standard deviation	29.1	22.7	22.2	35.3
Coefficient of variation	21.5	15.4	18.5	26.8
Statistical analysis [c]		n.s.	*	n.s
Statistical power [d]		>0.90	>0.90	≈0.89

[a] Plasma AUC values following a single, 500 mg dose with each formulation.
[b] Conventional reference formulation.
[c] Independent paired *t*-test comparison to Theolair tablets (one-tailed test):
n.s. indicates no significant difference ($P > 0.05$);
* indicates significantly different at an α level of 0.05 or less.
[d] Power of independent paired *t*-test to detect 20% difference between formulations at an α level of 0.05 (one-tailed test).

statistically significant differences ($P > 0.05$) exist between the Theolair-SR tablet and the reference formulation or between the experimental sustained-release tablet and the reference formulation (Table 4). In addition, the treatment comparisons show that the mean AUC value for Slo-phyllin Gyrocaps is significantly lower ($P < 0.05$) than the mean for the conventional Theolair tablet; however, this difference is only about 12%. The results of statistical power calculations show that the paired *t*-test for these AUC data has sufficient power (approximately 0.89 or more, Table 4) to detect 20% differences (α level of 0.05) in absorption between each sustained-release formulation and the conventional Theolair tablet, if any differences did exist.

The relative AUC values from 0 to 48 h (ratio of each sustained-release formulation to the reference formulation) range from 0.885 to 1.320 (mean 1.102) from 0.734 to 1.182 (mean 0.896), and from 0.780 to 1.279 (mean 0.975) for Theolair-SR tablets, Slo-phyllin Gyrocaps and the experimental sustained-release tablet, respectively. The lowest ratio for any subject with the Theolair-SR tablet is 0.885; this suggests that at least 88% or more of the dose is absorbed from this formulation. The relative AUC values that are greater than 1.0 (maximum theoretical value is 1.0) probably occur as

a result of analytical error in the chromatographic method and the inherent variability in biological processes. Overall, the plasma AUC data (0–48 h) indicate, with good assurance, that the extent of drug absorption from the Theolair sustained-release tablet, as well as from Slo-phyllin Gyrocaps and the experimental sustained-release tablet, is essentially complete. These data for Slo-phyllin Gyrocaps are in agreement with similar data previously reported (Weinberger et al., 1978).

As an index of intersubject variation for each of the formulations, the coefficients of variation for plasma AUC data (0–48 h) are shown in Table 4; these values are relatively small for all 4 formulations. In addition, the intersubject variation for the Theolair-SR tablet is comparable to that for the reference formulation (Theolair tablets) and to that for Slo-phyllin Gyrocaps. These data indicate that the extent of theophylline absorption from the Theolair-SR tablet is reasonably consistent. Thus, on the basis of the plasma AUC data, this formulation should provide both reliable and complete theophylline absorption.

Simulation of plasma levels with multiple dosage

To simulate the performance of the Theolair-SR tablet with multiple dosage, plasma theophylline concentrations at or near steady-state were projected by the superposition method (Gibaldi and Perrier, 1975). Other investigators have used single dose plasma theophylline level data to simulate plasma concentrations (Bülow et al., 1975) or to estimate maximum and minimum plasma levels at steady-state (Welling et al., 1976) in asthmatic patients following multiple dosage. To calculate plasma levels for a multiple dose regimen from single dose data, Bülow et al. (1975) assumed a monoexponential increase to and decrease from the mean peak plasma levels; this is an approximation of the superposition method. Welling et al. (1976) used a one-compartment pharmacokinetic model to calculate the maximum and minimum plasma theophylline levels at steady-state; the calculated absorption and elimination rate constants obtained by non-linear regression analysis of single dose plasma level data were used. These two groups of investigators both found that calculated plasma levels at steady-state agree reasonably well with mean plasma theophylline concentrations actually measured during a multiple dosage regimen in the same group of subjects. Thus, simulation of plasma levels for multiple dosage on the basis of single dose data is a valid approach for theophylline.

The simulations based on the single dose plasma level data from this study were done to assess the performance of the Theolair-SR tablet relative to conventional Theolair tablets and to Slo-phyllin Gyrocaps. Since a range of therapeutic plasma levels has been reasonably well defined for theophylline (see Introduction), the following discussion of simulations is presented in terms of plasma drug levels. However, therapeutic response can vary among individual patients at a given plasma level; thus, therapeutic response is most relevant for optimizing dosage regimens on an individual patient basis.

Fig. 3 shows the expected plasma theophylline levels (simulated with mean plasma concentration data) following a 1000 mg/day dose with the conventional Theolair tablet (250 mg every 6 h), with Slo-phyllin Gyrocaps (500 mg every 12 h), and with the Theolair-SR tablet (500 mg every 12 h). This simulation indicates that the

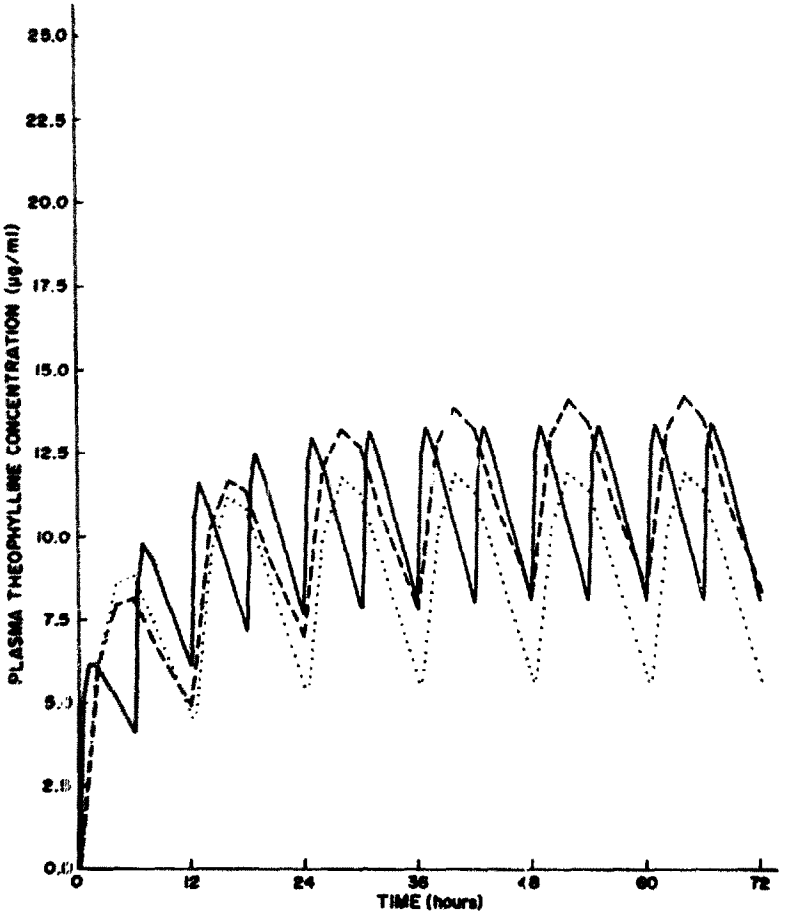

Fig. 3. Simulation of plasma theophylline concentrations following multiple dosage regimens with a 1000 mg/day dose; projected levels are based on single dose, mean plasma level data from 8 subjects with a mean plasma theophylline half-life of 5.7 h. ————, conventional Theolair Tablet (250 mg every 6 h); · · · · · ·, Slo-phyllin Gyrocaps (500 mg every 12 h); — — —, Theolair-SR Tablet (500 mg every 12 h).

Theolair-SR tablet with twice daily dosage would provide steady-state plasma levels (peak, trough and mean levels) similar to those for the conventional Theolair tablet with 4 daily doses. In addition, the simulation shows that the Theolair-SR tablet would provide a somewhat higher mean steady-state plasma level than that with Slo-phyllin Gyrocaps and that the differences in peak-to-trough plasma levels at steady-state would be similar for the two sustained-release formulations. The lower projected mean steady-state level with Slo-phyllin Gyrocaps is a direct result of the smaller mean AUC value for this formulation than that for either the Theolair-SR tablet or the conventional Theolair tablet (Table 4). Overall, this simulation demonstrates that the Theolair-SR tablet has acceptable sustained-release characteristics relative to the conventional Theolair tablet and has characteristics at least as acceptable as those of Slo-phyllin Gyrocaps.

At steady-state with a daily dose of 1000 mg (Fig. 3), projected trough plasma levels with both the Theolair-SR tablet and the conventional Theolair tablet are

similar (approximately 8 μg/ml) and are somewhat higher than trough levels with Slo-phyllin Gyrocaps (5–6 μg/ml). All of these trough levels are greater than the minimum of 5 μg/ml which has been reported to provide therapeutic control in some patients, but are less than the minimum of 10 μg/ml which has been reported to provide therapeutic control in most patients (see Introduction). Since these calculated plasma levels for multiple dosage were simulated using single dose data from subjects with an average half-life of 5–6 h (Table 3), the 1000 mg/day dose is somewhat insufficient to maintain trough levels at or above 10 μg/ml in subjects/patients who eliminate theophylline at a moderately rapid rate. However, the maintenance of trough levels greater than 10 μg/ml can be attained by adjustment of the daily dose to fit the drug elimination kinetics of individual patients.

This point is illustrated by the simulations shown in Fig. 4 which are also based on the mean plasma concentration data from this study; this figure shows the expected plasma theophylline levels following total daily doses ranging from 500 to 1500 mg (divided into two doses, with a 12-h dose interval) with the Theolair-SR tablet. These simulations indicate that this formulation[5] would provide steady-state trough plasma levels of about 4, 6, 8, 10 and 12 μg/ml with daily doses of 500, 750, 1000, 1250 and 1500 mg, respectively; thus, a larger daily dose than 1000 mg (Fig. 3) with the Theolair-SR tablet would provide steady-state trough plasma levels greater than 10 μg/ml. In addition, these simulations (Fig. 4) with a 12-h dose interval for the Theolair-SR tablet show that steady-state peak plasma levels of about 7, 11, 14, 18 and 21 μg/ml would be expected with daily doses of 500, 750, 1000, 1250 and 1500 mg, respectively. Thus, a 1250–1500 mg daily dose (625–750 mg every 12 h) with this formulation[5] should maintain steady-state plasma theophylline levels within or very near the desired range of 10–20 μg/ml for patients who eliminate the drug at a rate comparable to the subjects in this study (this also assumes a comparable volume of distribution for theophylline).

On the basis of these simulations (Figs. 3 and 4), twice daily dosage (every 12 h) with the Theolair-SR tablet should be acceptable for many patients. However, the specific daily regimen for an individual patient will ultimately depend on the drug elimination kinetics of the patient and on therapeutic response. Following multiple oral dosage (twice daily) with the Theolair-SR (Nuelin-SR) tablet, plasma (serum) theophylline levels measured in both patients and subjects have been recently reported (Jones and Sears, 1980; Russell et al., 1980; Munch et al., 1981); these data confirm that this sustained-release tablet provides an advantage over conventional-release formulations.

Overall, the simulations (Fig. 3) of expected plasma levels with multiple dosage regimens demonstrate that, even with a twice daily dosage regimen, the Theolair-SR tablet has acceptable sustained-release characteristics relative to the conventional Theolair tablet and that the sustained-release properties of the Theolair-SR tablet compare favorably with those of Slo-phyllin Gyrocaps. The Theolair-SR tablet should provide a definite advantage over conventional (immediate-release) formula-

[5] The Theolair-SR tablet (250 mg unit dose) is scored and can be split for dose adjustment.

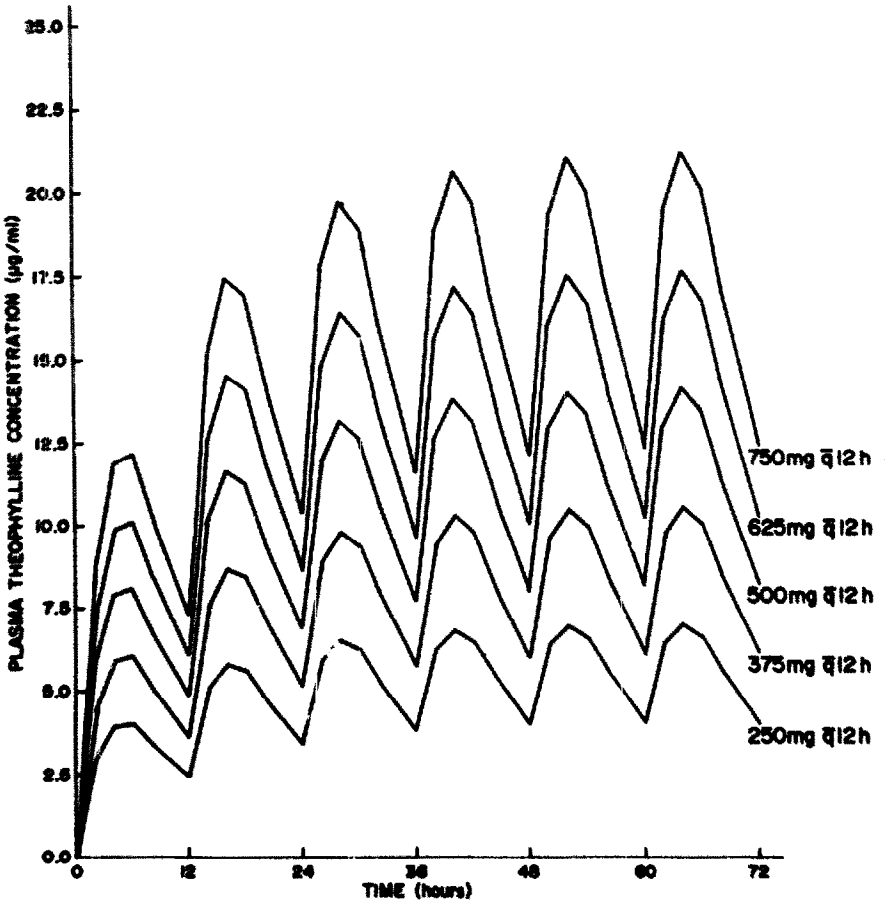

Fig. 4. Simulation of plasma theophylline concentrations following multiple dosage regimens with Theolair-SR tablets at a 12-h dose interval; projected levels are based on single dose, mean plasma level data from 8 subjects with a mean plasma theophylline half-life of 5.7 h. 750 mg every 12 h; 625 mg every 12 h; 500 mg every 12 h; 375 mg every 12 h; 250 mg every 12 h.

tions and should be therapeutically useful for chronic treatment of patients, especially in those patients who eliminate theophylline more rapidly.

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