International Journal of Pharmaceutics, 21 (1984) 3–16
Elsevier

IJP 00680

Research Papers

Comparison of inter- and intra-subject variation in oral absorption of theophylline from sustained-release products

Gary M. Pollack, Bonnie Baswell, Stanley J. Szefler and Danny D. Shen

Departments of Pharmaceutics, Pediatrics and of Pharmacology and Therapeutics, Schools of Pharmacy and Medicine, State University of New York, Buffalo, NY; Department of Medicine, Brooke Army Medical Center, San Antonio, TX; and the Department of Pediatrics, National Jewish Hospital and Research Center, Denver, CO (U.S.A.)

(Received August 16th, 1983)
(Modified version received December 2nd, 1983)
(Accepted January 18th, 1984)

Summary

A comparative study of inter- and intra-subject variation in the bioavailability of theophylline from two commercial sustained-release dosage forms (a beaded capsule and a tablet formulation) was performed in 12 healthy adult volunteers. The disposition kinetics of theophylline was characterized in each subject following a single 250 mg oral dose of a fully bioavailable liquid formulation. Duplicate single dose studies of each of the two sustained-release products were then performed on 4 separate occasions in a randomized crossover fashion. On the average, the *extent* of theophylline bioavailability from the two sustained-release dosage forms was equivalent and essentially complete as compared to that from the liquid formulation. Both sustained-release formulations exhibited reasonable consistency in the extent of bioavailability when tested on two different trial days in a given subject (the mean percentage difference in extent of absorption was $11.5 \pm 8.3\%$ for the beaded capsule and $11.8 \pm 12.3\%$ for the tablet). The *rate* of theophylline absorption from the beaded capsule formulation was more rapid than from the tablet formulation as indicated by an earlier time to reach peak serum concentration (6.0 ± 1.9 vs 8.9 ± 2.5 h). Individual time course of cumulative absorption from the sustained-release formulations was determined using the Wagner-Nelson procedure. The overall variability in the cumulative absorption profile was greater for the tablet as compared to the capsule formulation. More significant was the fact that within each

Correspondence: D.D. Shen, School of Pharmacy, State University of New York, H549 Cooke-Hochstetter Complex, Amherst, NY 14260, U.S.A.

subject the absorption profiles were less reproducible between trials with the tablet as compared to the capsule. Dose-to-dose variation in the release/absorption kinetics of theophylline from these sustained-release products may lead to unpredictable fluctuations in steady-state serum theophylline concentration–time profiles during chronic drug administration.

Introduction

The optimal serum concentration range of theophylline for the prophylactic treatment of asthma is considered to be between 10 and 20 μg/ml (Mitenko and Ogilvie, 1973; Pollock et al., 1977). In order to maintain steady-state serum theophylline concentration within this narrow range, it is necessary to dose at relatively short intervals (on the order of one elimination half-life) with rapidly absorbed theophylline dosage forms. This regimen may be impractical in rapid metabolizers of theophylline (e.g. young children), whose theophylline elimination half-lives are less than 4 h (Ellis, 1978). Alternatively, a sustained-release preparation may be used to decrease the fluctuations in theophylline serum concentration and extend the dosage interval.

Sustained-release products differ from conventional oral dosage forms in that the rate of release is equally important as the extent of bioavailability in judging the acceptability of a given product. Ideally, the sustained-release formulation should release the drug at an apparently constant rate over the entire dosing interval (i.e. so-called zero-order release). Also, dose-to-dose variability in both the rate and extent of release should be small, since such variation in release rate may lead to unpredictable fluctuations in steady-state serum concentrations.

The present study was designed to assess the inter- and intra-subject variability in the bioavailability characteristics of theophylline from two representative types of commercial sustained-release products. A recently marketed controlled-release capsule was compared to a widely used sustained-release tablet.

Materials and Methods

Subjects

Twelve healthy volunteers (6 male, 6 female) between 24 and 33 years of age and weighing between 55.4 and 82.0 kg participated in the study. All subjects were non-smokers. Written informed consent, medical history, and a physical examination including laboratory tests (hematology: hematocrit, hemoglobin, WBC, RBC, differential count; blood chemistry: alkaline phosphatase, SGOT, SGPT, LDH, BUN, total protein, serum albumin, glucose, total bilirubin, cholesterol, phosphorous, and calcium) were obtained prior to the study. Results for all volunteers were within the normal range.

Drug products

Two sustained-release theophylline products were tested: Product I [1], containing 250 mg theophylline, and Product II [2], containing 300 mg theophylline. A theophylline liquid formulation [3] (90 mg per 5 ml and 250 mg total dose), which previously was shown to be completely bioavailable (Lesko et al., 1979), was chosen as the reference dosage form for the determination of the relative bioavailability of the two sustained-release products. The serum concentration–time data of the liquid preparation also provided the distribution and elimination parameters of theophylline for each subject.

Drug administration

Each volunteer received single doses of theophylline on 5 separate occasions. All of the subjects received the liquid formulation on the first trial day. During the remainder of the study, each subject received Product I on two separate trial days and Product II on another two trial days in a randomized crossover fashion. Each of the 5 trial days was separated by a washout period of one week. The participants were instructed to avoid other medications during the study, and to abstain from all xanthine-containing foods and beverages for 48 h before and 30 h after each theophylline administration. Subjects were asked to fast from 8 h before to 4 h after each administration of theophylline, at which time a standard meal, consisting of a cheeseburger, salad, fruit and clear beverage, was provided. The theophylline preparations were ingested with 240 ml of water.

Blood sampling

Following administration of the liquid formulation, blood samples were drawn from the antecubital vein at 0, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10, 12 and 16 h through an indwelling catheter. In the case of sustained-release dosage forms, blood samples were drawn at 0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10, 12, 16, 24 and 30 h. The 24 and 30 h samples were drawn by venipuncture. During each trial, the theophylline test dose was given at the same time of day (i.e. 08.00 h) to avoid possible differences due to circadian variations in theophylline absorption and/or disposition (Scott et al., 1981).

Analysis of theophylline

Serum theophylline concentrations were determined by high-performance liquid chromatography. Serum samples (100–250 μl) were acidified with 30 μl of 1 N HCl and shaken (10 min) with 1 ml 95% chloroform/5% isopropanol (v/v) containing 0.5 μg/ml β-hydroxypropyl theophylline as the internal standard. A portion (0.8 ml) of the organic layer was transferred, dried under nitrogen at 30 °C, and reconstituted

---

[1] Somophyllin-CRT, sustained-release beaded capsules, Fisons, Bedford, MA; lot no. 22408, Expiration date 12-82.

[2] Theo-Dur, sustained-release tablet, Key Pharmaceuticals, Miami, FL; lot no. 080131, Expiration date 8-82.

[3] Somophyllin liquid, Fisons, Bedford, MA; lot no. 15708, Expiration date 9-82.

with 300 μl of mobile phase, of which 50 μl was injected on column. Chromatographic separation was achieved on a Whatman Partisil-5 ODS (25 cm × 4.6 mm) column, with a 15% acetonitrile/85% 0.2 M sodium acetate buffer (pH 4.0) mobile phase at a flow rate of 1.5 ml/min. The eluate was simultaneously monitored at 254 and 280 nm using a dual channel UV detector. The sensitivity limit (i.e. at a signal-to-noise ratio > 4) of this assay was between 0.25 and 0.5 μg/ml. The within-assay coefficient of variation for a 1 μg/ml quality control serum was < 2.8%. A sample of the quality control serum was processed alongside the study samples during each assay run. The between assay coefficient of variation was 4.9% over a 4 month period. All of the samples from each volunteer were assayed at the same time to minimize inter-assay error.

Calculation of absorption parameters

The serum theophylline concentration–time data following administration of the liquid formulation were analyzed according to a linear one-compartment open model with a first-order absorption input (Gibaldi and Perrier, 1981). The observed serum concentration–time data were fitted with the following equation using a non-linear least-squares regression computer program (Metzler et al., 1974):

$$C = \frac{FD}{V} \cdot \frac{k_a}{k_a - K} \cdot \left\{ e^{-K(t - t_0)} - e^{-k_a(t - t_0)} \right\} \qquad (1)$$

where F is the fraction of the administered dose D reaching the systemic circulation, V is the apparent volume of distribution, t_0 is the absorption lag time, k_a and K are the apparent first-order absorption and elimination rate constants, respectively, and t is the time after administration of the drug. Assuming the bioavailability of theophylline from the liquid preparation to be complete (i.e. setting F equal to 1.0), estimates for both the apparent volume of distribution and serum clearance of theophylline can be obtained from the oral data (Gibaldi and Perrier, 1981).

The area under the serum concentration–time curve (AUC) over the 30 h of blood sampling was estimated using the cubic-spline numerical integration method (Yeh and Kwan, 1978). The remaining AUC beyond the final serum concentration measurement (C*) was extrapolated by C*/K, where K is the elimination rate constant determined following administration of the liquid formulation. An accurate assessment of the elimination rate constant of theophylline was not feasible after the administration of sustained-release dosage forms due to the fact that in some subjects continual absorption was still evident 24–30 h after drug administration. The extrapolated AUC constituted only 10–15% of the total AUC.

To elucidate the absorption kinetics of the two sustained-release preparations, the cumulative fraction of drug absorbed ($F_{a,t}$) at each sampling time was calculated by the Wagner-Nelson equation (Wagner and Nelson, 1963):

$$F_{a,t} = \frac{X_{a,t}}{X_{a,\infty}} = \frac{C_t + K\int_0^t C\,dt}{K\int_0^\infty C\,dt} \qquad (2)$$

where $X_{a,t}$ and $X_{a,\infty}$ are the cumulative amount of drug absorbed from time zero to times t and infinity, respectively. The term C_t represents the serum concentration of theophylline at time t. Again, the elimination rate constant estimated from the theophylline liquid data was utilized, with the assumption that significant change in the elimination kinetics of theophylline did not occur over time.

The in vivo release/absorption characteristics of the solid dosage forms were also evaluated by statistical moments analysis (Riegelman and Collier, 1980). For an orally administered drug solution, the mean residence time (MRT) of the drug in the body is defined as:

$$MRT_{soln} = MAT_{soln} + MRT_{t\infty} \tag{3}$$

where MAT_{soln} and $MRT_{t\infty}$ represent the mean absorption and mean elimination times, respectively. For a solid dosage form, a third component, the mean dissolution time (MDT) must be added. Assuming that the absorption and elimination of the drug are independent of the dosage form administered, it follows that:

$$MDT_{prod} = MRT_{prod} - MRT_{soln} \tag{4}$$

The mean residence times for each of the formulations were calculated as the first moment of the serum concentration–time curve divided by the AUC (Benet and Galeazzi, 1979).

Statistical comparisons

The descriptive pharmacokinetic parameters (i.e. peak concentration, time to peak, AUC, mean dissolution time, and relative bioavailability estimates) for the liquid and solid dosage forms were compared using a one-way Analysis of Variance. Data on the sustained-release dosage forms from duplicate trial days were averaged for the purpose of comparison between different preparations. Significant differences between treatment pairs were identified by the method of linear contrast.

The inter- and intra-subject variation in the cumulative time course of theophylline absorption (i.e. data generated from the Wagner-Nelson analysis) were evaluated for each dosage form as follows. At each selected time point (i.e. 2, 4, 6, 8 and 12 h), the total and intra-subject (or between trial days) sum of squares (SS) of the cumulative fraction absorbed were calculated according to the following equations:

$$SS_{total} = \sum \{\bar{F}_{a,t} - F_{a,t}(i,j)\}^2 \tag{5}$$

$$SS_{intra\text{-}subject} = \sum \{F_{a,t}(i,1) - F_{a,t}(i,2)\}^2 \tag{6}$$

where $\bar{F}_{a,t}$ is the grand mean in cumulative fraction absorbed and $F_{a,t}(i,j)$ is the cumulative fraction absorbed for the ith subject on the jth trial day. The difference between total and within subject SS should largely reflect the SS of deviations

between subjects [5]. A mean square (MS) or variance estimate was calculated by dividing the SS by the degrees of freedom. To facilitate a comparison of variance across time and drug products, a relative measure of dispersion (i.e. coefficient of variation or CV) based on the grand mean was calculated by Eqn. 7.

$$\%CV = \frac{\sqrt{MS}}{\overline{F}_{a,t}} \times 100 \tag{7}$$

Results

The mean estimates of theophylline disposition parameters, derived from the serum concentration–time data following oral administration of the liquid formulation, are presented in Table 1. As expected, the absorption of theophylline from the liquid preparation was very rapid. Individual estimates of the elimination rate constant (K), apparent volume of distribution (V) and serum clearance (Cl) are consistent with previously reported data obtained after *intravenous* administration of theophylline in healthy adult subjects (Hendeles et al., 1980).

The mean serum theophylline concentration–time profiles for the two sustained-

[5] The residual SS, i.e. $SS_{total} - SS_{intra\text{-}subject}$ is actually a pooled SS due to subjects and other sources of variation, e.g. analytical and sampling errors. It is assumed that contribution from these other sources of variation is relatively small and constant.

TABLE 1

PHARMACOKINETIC PARAMETERS DERIVED FROM SERUM DRUG CONCENTRATION–TIME DATA IN 12 NORMAL VOLUNTEERS AFTER A SINGLE 250 mg ORAL DOSE OF THEOPHYLLINE LIQUID FORMULATION

Parameters	Mean ± S.D. [a]
t_0(min)	3.05 ± 2.05
k_a(h^{-1})	16.7 ± 30.1
$t_{1/2abs}$(min)	2.49
K(h^{-1})	0.102 ± 0.023
$t_{1/2el}$(h)	6.79
V(liter/kg)	0.425 ± 0.042 [b]
Cl(ml/h/kg)	43.1 ± 9.0 [b]

[a] Estimated using a non-linear least-squares regression computer program. The correlation coefficient of individual fits ranged from 0.981 to 0.998.

[b] Assuming that the bioavailability of theophylline from the oral liquid preparation is essentially complete.

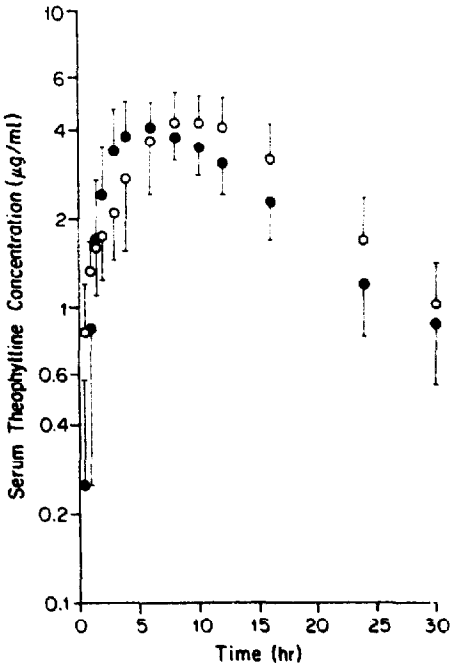

Fig. 1. Time course of mean serum theophylline concentrations following oral administration of sustained-release products I (●) and II (○). Each capsule of Product I contained 250 mg of theophylline, whereas each tablet of Product II contained 300 mg of theophylline. Bars represent mean ± S.D. of 24 determinations.

release products are compared in Fig. 1. The mean concentration at each time point was calculated by pooling data from the two trial days for all 12 volunteers (i.e. $n = 2 \times 12$ or 24). The rate of absorption of theophylline from Product II was noticeably slower than from Product I. However, the overall AUC appears to be comparable between the two preparations. The mean estimates of the absorption parameters for the liquid and the two solid dosage forms are presented in Table 2. Both the time to peak serum concentration and the MDT were significantly longer for Product II as compared to Product I. The trend towards a lower peak serum theophylline concentration for Product II (when normalized per 100 mg dose) is also consistent with a slower absorption. The mean overall AUC (normalized per 100 mg dose) did not differ significantly between the 3 preparations. Hence, the two sustained-release products exhibited comparable extent of bioavailability.

When individual data sets were examined, the variation in the time course of theophylline concentration between the two trial days was greater with Product II than with Product I. Fig. 2 shows a representative example of the day-to-day reproducibility in the serum theophylline concentration time course of the two products in one subject. Much of the between day variability appears to be associated with the rate rather than the extent of drug absorption. Secondary rises in serum concentration such as those observed in Fig. 2 were also observed in the majority of subjects after administration of Product II. The results of duplicate bioavailability estimates for each of the sustained-release products are shown in Fig.

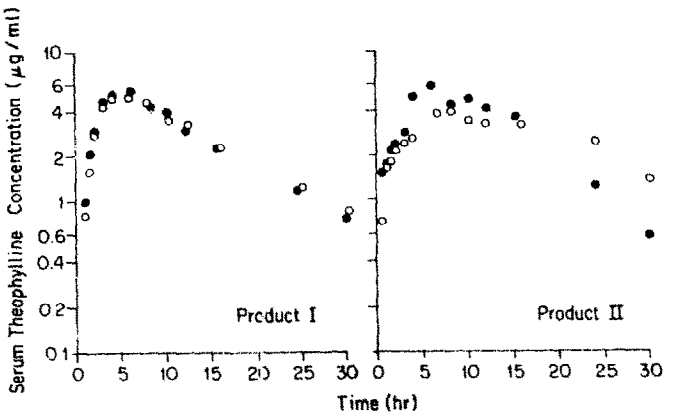

Fig. 2. Comparison of between-trial variation in the time course of serum theophylline concentrations following administration of the two sustained-release products. Data from Subject no. 1.

3. While the range of bioavailability was greater for Product II (0.53–1.16) than for Product I (0.72–1.17), a comparison of between day variances by *F*-test did not show a statistically significant difference. The average percentage difference in oral bioavailability between trials was 11.5 ± 8.3 for Product I and 11.8 ± 12.3 for Product II. The slightly lower mean bioavailability estimate for Product II was largely due to an unusually low bioavailability of this product in one subject (no. 3).

Individual cumulative fraction absorbed versus time plots, derived from Wagner-Nelson analysis of serum theophylline concentration–time data for the two sus-

TABLE 2

ABSORPTION CHARACTERISTICS OF THE LIQUID AND SUSTAINED-RELEASE THEOPHYLLINE PREPARATIONS

Parameter	Liquid	Product I [a]	Product II [a]
Peak serum concentration (μg/ml) [b,c]	3.40 ± 0.62 [d]	1.71 ± 0.32	1.58 ± 0.44
		$P < 0.001$	NS
		$P < 0.001$	
Time to peak (h) [c]	0.72 ± 0.33	5.98 ± 1.19	8.91 ± 2.48
		$P < 0.001$	$P < 0.001$
		$P < 0.001$	
AUC from time 0 → ∞ (μg·h/ml) [b]	34.6 ± 7.5	31.2 ± 7.1	30.2 ± 7.8
Mean dissolution time (h) [c]		5.15 ± 0.24	6.06 ± 0.37
		$P < 0.05$	
Relative bioavailability [e]		0.907 ± 0.106	0.876 ± 0.139
		NS	

[a] Pooled data from the 2 study days (i.e. $n = 2 \times 12$ or 24).

[b] Normalized per 100 mg administered dose.

[c] Statistically significant differences among the 3 preparations as indicated by one way analysis of variance.

[d] Mean ± S.D.

[e] Statistically significant differences between the sustained-release products as indicated by paired *t*-test.

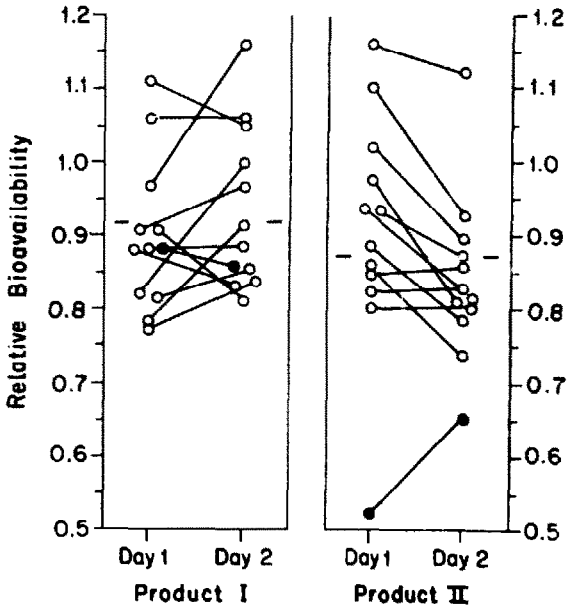

Fig. 3. Between-trial variability in the extent of bioavailability of the two sustained-release products. Bars represent mean of 12 determinations. Solid circle represents Subject no. 3 (see text).

tained-release products, are presented in Figs. 4 and 5. An initial time lag in absorption, ranging from 0 to 1.5 h, was apparent for Product I; followed by a rapid absorption phase over the first 6–8 h with progressively slower absorption thereafter. Approximately 90% of the bioavailable dose was absorbed by 12 h after drug

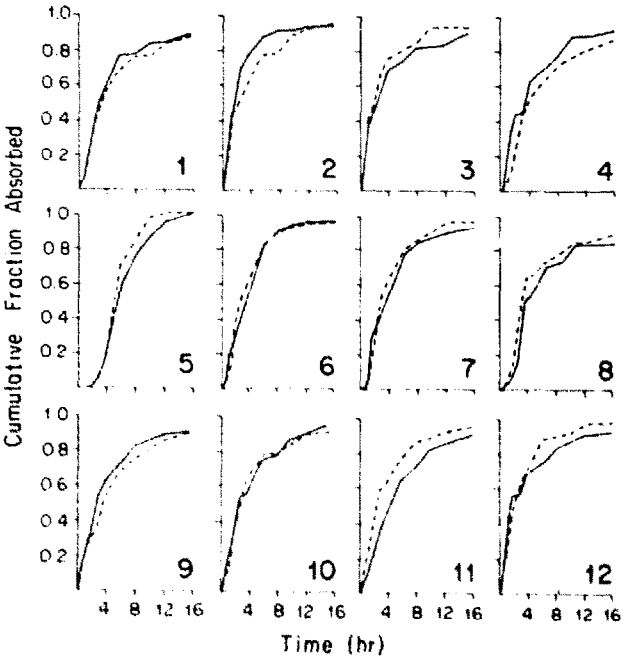

Fig. 4. Individual cumulative fraction absorbed versus time plots for Product I. The solid and dotted lines represent data from trials 1 and 2, respectively.

TABLE 3

SUMMARY STATISTICS ON THE VARIATION IN CUMULATIVE ABSORPTION OF THEOPHYLLINE AT SELECTED TIMES AFTER ADMINISTRATION OF THE TWO SUSTAINED-RELEASE PRODUCTS

Product	Parameters	Time after drug administration (h)				
		2	4	6	8	12
I	$\overline{F_{a,t}}$ [a]	0.317	0.587	0.745	0.811	0.899
	%CV:					
	Intra-subject	7.44	3.37	7.20	2.36	4.49
	Inter-subject	45.7	24.3	9.56	7.35	5.75
	Total	44.8	23.8	9.46	7.20	5.70
II	$\overline{F_{a,t}}$ [a]	0.221	0.384	0.560	0.708	0.874
	%CV:					
	Intra-subject	13.2	34.4	20.7	5.54	4.97
	Inter-subject	5.76	13.4	15.6	15.5	10.8
	Total	25.7	34.9	27.7	21.4	12.1

[a] Grand mean cumulative fraction absorbed.

administration. In the majority of subjects, excellent day-to-day reproducibility in cumulative absorption–time profiles were observed with Product I. A notable difference in the time course of cumulative absorption (i.e. > 10–15%) between the two trial days was apparent in only 4 of the 12 subjects (viz. nos. 2, 4, 11 and 12).

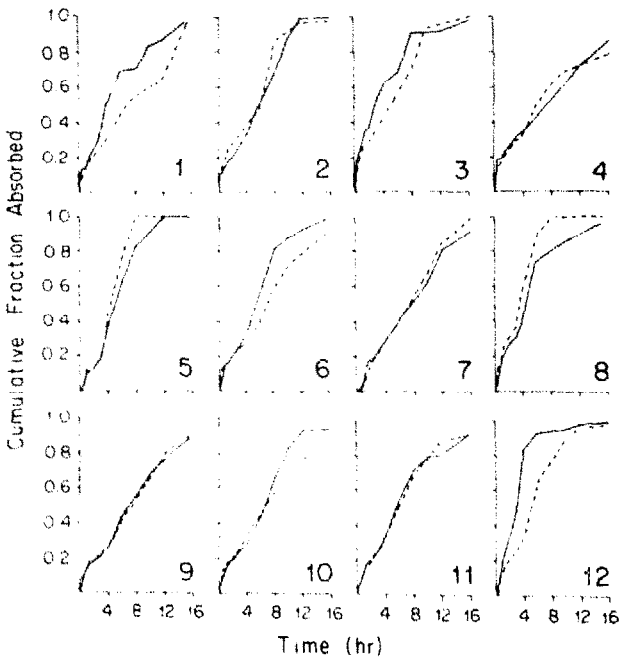

Fig. 5. Individual cumulative fraction absorbed versus time plots for Product II. The solid and dotted lines represent data from trials 1 and 2, respectively.

The individual cumulative absorption-time profiles for Product II all show an initial rapid release of theophylline such that approximately 10% of the available dose was absorbed over the first 30 min. This "burst" of drug was followed by a reasonably constant rate of release over the next 10–12 h. Deviation from zero-order kinetics became apparent after 12 h. Overall, the absorption of theophylline was more sustained from Product II than Product I, with approximately 90% of the available dose being absorbed by 15 h. However, day-to-day variation in the absorption kinetics of theophylline was much more evident with Product II than with Product I. The cumulative absorption profiles in over half the subjects showed significant fluctuation between the two trial days.

The inter- and intra-subject variations in cumulative absorption–time data for each sustained-release preparation were subjected to statistical analysis. The results expressed in terms of coefficients of variation are summarized in Table 3. The intra-subject CV for Product I was much smaller than the inter-subject CV at all times. This was not the case with Product II. In fact at 2 and 4 h, intra-subject CV well exceeded inter-subject CV. The situation was reversed at later times.

When data from the two products were compared, except at 2 h, the overall CV for Product II was consistently higher than Product I. A similar pattern was observed with the inter-subject component of the overall variance. The greater inter-subject variation in absorption rate during the initial 2 h period for Product I probably reflects the variable time lag in absorption. The most striking comparison between products is with the intra-subject CV. At all of the time points, the intra-subject CV in cumulative absorption was much smaller with Product I as compared to Product II. The largest difference in intra-subject variability between the two products was observed at 4 h (3.37% vs 34.4%).

Discussion

The present study indicates that theophylline bioavailability from the two commercial sustained-release products was essentially complete, which is in agreement with results of previously reported studies (Weinberger et al., 1978; Lesko et al., 1981). However, the two preparations differed substantially in their rates of bioavailability. Absorption from Product II occurred slowly, apparently at a constant rate for 10–12 h following an initial burst. On the other hand, with Product I a lag in absorption was observed followed by a relatively rapid absorption for 4–6 h and a slower absorption through the remainder of the profile. The overall rate of theophylline absorption from Product II was slower than from Product I, with 90% absorption occurring at 15 h for Product II versus 12 h for Product I. The time to peak and mean dissolution times were also longer for Product II than Product I.

The variation in theophylline release/absorption kinetics was greater for Product II than Product I, with respect to both between-subjects and between-trials within the same subject. Large inter-subject variability in the oral bioavailability of other drugs has previously been reported (Huffman et al., 1975), and is generally attributed to individual differences in gastrointestinal physiology, e.g. gastric emptying

rate and intestinal transit times. On the other hand, there are few reports of intra-subject variation in the gastrointestinal absorption of drugs. Intra-subject variation in the rate of absorption of the theophylline sustained-released products may lead to seemingly unpredictable day-to-day fluctuations in the steady-state serum theophylline concentration–time profiles.

Variation in steady-state serum concentrations of a drug released from a conventional dosage form are usually attributed to intra-subject variations in the disposition of the drug. However, with a sustained-release dosage form the release rate becomes an important factor in the control of steady-state serum drug concentrations, so that dose-to-dose variation in both absorption and elimination contribute to the overall fluctuations in serum concentration. Moreover, in the case of truly sustained-released drug products, doses are always administered at times when drug absorption has not reached completion. The carryover of residual drug from one dosage interval to the next must be taken into consideration. The amount of drug remaining to be absorbed at the end of a dosage interval is obviously dependent on the rate of absorption during the dosage interval. Thus, when considering the effects of variable absorption on serum drug concentrations during any given dosage interval, the absorption rate during the interval and in previous intervals should be taken into account.

Given this complicated situation, it is difficult to predict the exact impact of a given degree of variability in drug absorption after a single dose on steady-state serum drug concentration during repetitive drug administration. However, the expected fluctuations in serum concentration of theophylline resulting from this variability may be estimated through the use of pharmacokinetic simulations similar to those reported by Weinberger et al. (1981). The release rate of theophylline from Product I was found to be relatively rapid, and simulations employing the mean absorption parameters from Product I indicated that twice daily dosing of this product would lead to unacceptable fluctuations in the serum concentration of theophylline for subjects with a theophylline elimination half-life of 4 h or less. Thus, computer simulations of the impact of variable absorption on serum theophylline concentrations during twice daily dosing were performed with the data obtained from Product II only. Using the *mean* absorption parameters for Product II obtained in the present study, the predicted fluctuations in the serum concentration of theophylline during a dosage interval for a hypothetical subject with an elimination half-life of 2 h were assessed. In the simulation, theophylline dosage was selected to maintain a mean steady-state serum theophylline concentration of 15 μg/ml, and the degree of fluctuation was found to be acceptable (9.5–17.5 μg/ml). These results seem to suggest that administration of Product II every 12 h to a patient with rapid theophylline clearance is acceptable. However, when intra-subject variability in absorption was included in the simulation, the predicted fluctuation in theophylline serum concentration during a dosage interval was at times unacceptably large, with trough concentrations below 9 μg/ml and peak concentrations greater than 20 μg/ml during some dosage intervals.

Certain limitations in the interpretation of the results from this study should be pointed out. Drug administration was conducted under ideal fasting conditions,

which may lead to an underestimation of the variability associated with drug absorption in an actual clinical situation. For example, one recent report showed that food drastically decreases the absorption rate of theophylline from a sustained-release product (Pederson, 1981). For practical reasons, each subject only received each product twice allowing only an approximate estimate of intra-subject variability in absorption. In addition, part of the variability in the serum concentration–time data could be due to changes in the disposition kinetics of theophylline. In retrospect, replicate studies with either an intravenous or fully bioavailable oral theophylline preparation in the same panel of subjects could have provided the necessary information. Intra-subject variation in the elimination kinetics of theophylline has been investigated in a few published studies (Walson et al., 1977; Loren et al., 1977; Leung et al., 1977; Ginchansky and Weinberger, 1977; Upton et al., 1982). It appears that significant day-to-day variation in serum theophylline half-life can occur in normal volunteer studies, although the magnitude of this variation is usually small (i.e. CV < 10%). Therefore, an absolute and specific determination of the intra-subject variation in the absorption of theophylline is not possible with the present set of data. Nonetheless, the results can still provide valid conclusions concerning product performance on a comparative basis, i.e. Product II is characterized by a greater variability in drug release/absorption rate as compared to Product I. Moreover, they point to the importance of assuring dose-to-dose consistency in the release characteristics of drug from sustained-release dosage forms in the assessment of drug product bioequivalency.

As a final note, it is worthwhile to consider the possible cause(s) of variability in the release and/or absorption characteristics of oral sustained-release dosage forms. In general, they can be attributed either to physicochemical problems in the formulation and/or manufacturing of the dosage form or to the variations in the gastrointestinal physiology. While the former source of variation can be overcome by improvements and innovations in dosage form design, the inherent problem of biological variation may pose an insurmountable obstacle to the development of extended oral sustained-release products. It is generally accepted that drug absorption from the gastrointestinal tract is site-specific and often limited by finite transit time. It is quite conceivable that as the dosage form is propelled by peristaltic movement to the distal portion of the intestinal tract, absorption is slowed and becomes erratic. Hence, the greater degree of variation in the release characteristics of theophylline from Product II may simply be a consequence of the sustained (but desirable) pattern of release.

Acknowledgements

Supported in part by a grant from the Fisons Corporation, Bedford, MA. The authors acknowledge Kathleen A. Flesher, R.N. and Marian Pazik, B.S. for their technical assistance.

References

Benet, L.Z. and Galeazzi, R.L., Noncompartmental determination of the steady-state volume of distribution. J. Pharm. Sci., 68 (1979) 1071–1074.

Ellis, E.F., Allergy: Principles and Practice, C.V. Mosby, St. Louis, 1978, p. 435.

Gibaldi, M. and Perrier, D., Pharmacokinetics, Marcel Dekker, New York, 1981.

Ginchansky and Weinberger, M., Relationship of theophylline clearance to oral dosage in children with chronic asthma. J. Pediatr., 91 (1977) 655–660.

Hendeles, L., Weinberger, M.M. and Johnson, G., Applied Pharmacokinetics—Principles of Therapeutic Drug Monitoring, Applied Therapeutics, San Francisco, 1980, p. 95.

Huffman, D.H., Manion, C.V. and Azarnoff, D.L., Intersubject variation in absorption of digoxin in normal volunteers. J. Pharm. Sci., 64 (1975) 433–437.

Lesko, L.J., Canada, A.T., Eastwood, G., Walker, D. and Brousseau, D.R., Pharmacokinetics and relative bioavailability of oral theophylline capsules. J. Pharm. Sci., 68 (1979) 1392–1394.

Lesko, L.J., Canada, A.T., Eastwood, G.L. and Clemente, D.R., The relative bioavailability of a controlled-release theophylline formulation after multiple doses. Immunol. Aller. Pract., 3 (1981) 15–22.

Leung, P., Kalisker, A. and Bell, T.V., Variation in theophylline clearance rate with time in chronic childhood asthma. J. Allergy Clin. Immunol., 58 (1977) 440–444.

Loren, M., Millich, D.R., Chai, H. and Barwise, G., Aminophylline bioavailability and the across-time stability of plasma theophylline levels. J. Pediatr., 90 (1977) 473–476.

Metzler, C.M., Elfring, G.L. and McEwen, A.J., A package of computer programs for pharmacokinetic modeling. Biometrics, 30 (1974) 562–568.

Mitenko, P.A. and Ogilvie, R.I., Rational intravenous doses of theophylline. N. Engl. J. Med., 289 (1973) 600–603.

Pederson, S., Delay in the absorption rate of theophylline from a sustained release theophylline preparation caused by food. Br. J. Clin. Pharmacol., 12 (1981) 904–905.

Pollock, J., Kiechel, F., Cooper, D. and Weinberger, M., Relationship of serum theophylline concentration to inhibiton of exercise-induced bronchospasm and comparison with cromolyn. Pediatrics, 60 (1977) 840–844.

Riegelman, S. and Collier, P., The application of statistical moment theory to the evaluation of in vivo dissolution time and absorption time. J. Pharmacokin. Biopharm., 8 (1980) 509–534.

Scott, P.H., Tabachnik, E., MacLeod, S., Correia, J., Newth, C. and Levison, H., Sustained-release theophylline for childhood asthma. Evidence for circadian variation of theophylline pharmacokinetics. J. Pediatr., 99 (1981) 476–479.

Upton, R.A., Thiercelin, J.F., Guentert, T.W., Wallace, S.M., Powell, J.R., Sansom, L. and Riegelman, S., Intra-individual variability in theophylline kinetics. J. Pharmacokin. Biopharm., 10 (1982) 123–134.

Wagner, J.G. and Nelson, E., Percent absorbed time plots derived from blood level and/or urinary excretion data. J. Pharm. Sci., 52 (1963) 610–611.

Walson, P.D., Strunk, R.C. and Taussig, L.M., Intrapatient variability in theophylline kinetics. J. Pediatr., 90 (1977) 321–324.

Weinberger, M.M., Hendeles, L. and Bighley, L., The relation of product formulation to absorption of oral theophylline. N. Engl. J. Med., 299 (1978) 852–857.

Weinberger, M.M., Hendeles, L. and Wong, L., Relationship of formulation and dosing interval to fluctuation of serum theophylline concentration in children with chronic asthma. J. Pediatr., 99 (1981) 145–153.

Yeh, K.C. and Kwan, K.C., A comparison of numerical integrating algorithms by trapezoidal, Lagrange and spline approximation. J. Pharmacokin. Biopharm., 6 (1978) 79–98.