(11) S. A. Kaplan, R. E. Weinfeld, and C. W. Abruzzo, *Adv. Automated Anal.*, **2**, 405 (1971).
(12) A. Bye and A. F. J. Fox, *Clin. Chem.*, **20**, 288 (1974).
(13) S. A. Kaplan, R. E. Weinfeld, C. W. Abruzzo, and M. Lewis, *J. Pharm. Sci.*, **61**, 773 (1972).
(14) S. A. Kaplan, R. E. Weinfeld, C. W. Abruzzo, K. McFaden, M. L. Jack, and L. Weissman, *J. Infect. Dis., Suppl.*, **128**, S547 (1973).
(15) J. Rieder, *Chemotherapy*, **17**, 1 (1972).
(16) *Ibid.*, **22**, 84 (1976).
(17) C. W. Sigel, M. E. Grace, C. A. Nichol, and G. H. Hitchings, *J. Pharm. Sci.*, **63**, 1202 (1974).
(18) D. E. Schwartz, B. A. Koechlin, and R. E. Weinfeld, *Chemotherapy, Suppl.*, **14**, 22 (1969).
(19) S. A. Kaplan, R. E. Weinfeld, and T. L. Lee, *J. Pharm. Sci.*, **62**, 1865 (1973).
(20) J. Rieder, *J. Infect. Dis., Suppl.*, **128**, S567 (1973).

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Pharmacokinetics and Relative Bioavailability of Oral Theophylline Capsules

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Abstract □ The oral bioavailability of liquid-filled theophylline capsules relative to a nonalcoholic aminophylline solution was determined in normal volunteers. In addition, theophylline absorption and elimination kinetics were reexamined. There were no statistically significant differences between the bioavailability of capsules and liquid as measured by the area under the curve (AUC) from time $0 \rightarrow \infty$ ($p > 0.05$). The bioavailability parameters of C_{max}, t_{max}, and AUC were determined from actual serum theophylline concentration–time data and from a nonlinear least-squares fit of the serum concentration–time data. Theophylline absorption from the capsules was noticeably faster than from the liquid in most subjects, although the differences in absorption rates were not significantly different ($p > 0.05$). The determined apparent volume of distribution, elimination half-life, and plasma clearance of theophylline were similar to values reported by other investigators. Marked inter- and intraindividual variations in the elimination half-life were noted.

Keyphrases □ Theophylline—oral dosage forms, pharmacokinetics, bioavailability, capsule compared to liquid □ Muscle relaxants (smooth muscle)—theophylline, oral dosage forms, pharmacokinetics, bioavailability, capsule compared to liquid □ Bioavailability—theophylline, various oral dosage forms

The clinical importance of satisfactory oral theophylline bioavailability is well recognized in the scientific and medical communities. Bioavailability problems, particularly with tablets and capsules, are thought to be related primarily to the dosage form formulation and not to physiological factors that influence absorption (1).

Although reported bioavailability studies of various theophylline oral dosage forms have demonstrated satisfactory bioavailability, all commercial oral theophylline dosage forms may not have equally satisfactory bioavailability (2, 3). It is important to evaluate the bioavailability of each theophylline formulation to confirm that formulation factors do not affect *in vivo* absorption.

One major goal of this investigation was to evaluate the relative bioavailability of liquid-filled oral theophylline capsules[1] in a random, crossover study. The rationale was to determine if any formulation factors associated with liquid-filled capsules might affect theophylline bioavailability when compared to the bioavailability from a nonalcoholic, rapidly absorbed aminophylline oral liquid[2]. Another major goal was to examine the absorption and elimination kinetics of theophylline when administered as a liquid-filled capsule or as a liquid.

EXPERIMENTAL

Subjects—Seven male and seven female subjects, 21–40 years old, were selected with the approval of the Institutional Human Subjects Review Committee. Valid written informed consent was obtained from each subject prior to entrance into the study. The body weight (mean ± *SD*, 67 ± 12 kg) of the volunteers was within 10% of normal limits for their height and build (4).

All subjects were determined to be in good physical health, with no history of alcoholism or cardiovascular disease. They were judged to be medically sound based on a medical history, physical examination, vital signs, ECG, and the usual battery of blood and urine clinical chemistry tests. All subjects were nonsmokers and had not smoked regularly at any time within the last 3 years.

All subjects were instructed to refrain from any medication for at least 7 days prior to the study and to abstain from alcohol and xanthine-containing foods or beverages for 24 hr prior to dosing. All volunteers were fasted, with the exception of water, for 12 hr prior to dosing, and the fasting was continued for 4 hr after dosing. A modest meal, low in carbohydrates and fat, was served at 4 hr, and a light dinner, likewise low in fat and carbohydrates, was served at 8 hr after dosing.

Drug Administration and Blood Sampling—On each study day, an oral dose equivalent to 300 mg of anhydrous theophylline was randomly administered either as liquid-filled capsules or as a nonalcoholic aminophylline solution. Previous analysis for potency showed the capsules to contain 98% of the label claim. The study days were separated by a washout period of 7 days, after which the subjects took the alternate formulation. On each study day, the subjects were administered the medication with 240 ml of water at approximately 8:00 am.

Predose blood samples (1 ml) were obtained immediately before dosing *via* an indwelling catheter in the forearm vein. After dosing with the capsules, blood samples were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hr. After dosing with the liquid, blood samples

[1] Somophyllin capsules, lots 02977 and 07677, Fisons Corp., Bedford, Mass.

[2] Somophyllin oral liquid, lot 02287, Fisons Corp., Bedford, Mass.

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were collected at 5, 10, 15, 20, 25, 30, 40, and 50 min and at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hr. Some of the later blood samples were drawn by venipuncture after removal of the indwelling catheter. Serums were separated from coagulated blood samples and frozen at −20° until assayed for theophylline. During each study period, blood pressure and pulse and respiratory rates were recorded at regular intervals. Any side effects were noted.

Theophylline Assay—Serum theophylline determinations were made by high-pressure liquid chromatography (HPLC) as follows. Serum, 200 μl, was treated with an equal volume of acetonitrile containing the internal standard, β-hydroxyethyltheophylline, to precipitate serum proteins. After centrifugation, a 20-μl sample of the supernate was injected immediately on a microparticulate reversed-phase column[3]. The column was used with a septumless injector[4], a solvent delivery system consisting of a dual-piston pump[5], and a fixed-wavelength UV absorbance detector[6] equipped with a 280-nm filter. The eluting solvent was 7% acetonitrile in a 0.01 *M* acetate buffer adjusted to pH 4. The flow rate through the column was 2 ml/min. The sensitivity for 0.005 aufs was 0.5 μg/ml of serum.

The coefficient of variation for intra- and interday analyses of duplicate serum theophylline controls was negligible (<2%). This method is specific for theophylline. Theophylline recovery was virtually 100% from spiked serum samples, and a plot of peak height ratio (theophylline/internal standard) as a function of theophylline concentration was linear up to 40 μg/ml. During the study, the analyst was unaware of the treatment regimen.

Pharmacokinetic Analysis—Serum theophylline concentrations (mean ± *SE*) were tabulated at each sampling time and plotted as a function of time on Cartesian coordinates. Individual serum data for each subject after each dose were fitted graphically to obtain initial estimates and by nonlinear least-squares regression analysis to a one-compartment pharmacokinetic model defined by:

$$C = \frac{FD}{V_d}\left(\frac{K_a}{K_a - K_E}\right)(e^{-K_E t} - e^{-K_a t}) \qquad \text{(Eq. 1)}$$

where C is the theophylline concentration at any time, t, after dosing; F is the fraction of dose, D, absorbed; V_d is the apparent volume of distribution; and K_a and K_E are the apparent first-order rate constants of absorption and elimination, respectively. In some cases, a lag time, t_0, had to be introduced into Eq. 1 to obtain an optimal fit.

Nonlinear regression analysis was performed on a digital computer[7] using the NONLIN program (5). From computer analysis, values for K_a, absorption half-life ($t_{1/2\text{-abs}}$), K_E, and elimination half-life ($t_{1/2\text{-elim}}$) were obtained. Additional pharmacokinetic parameters were calculated as:

$$Cl = \frac{FD}{AUC_{0\to\infty}BW} \qquad \text{(Eq. 2)}$$

where Cl is plasma clearance, $AUC_{0\to\infty}$ is the area under the actual serum theophylline concentration–time curve from zero to infinity, BW is the individual body weight in kilograms, and F is assumed to be 1, and:

$$V_d = \frac{Cl}{K_E} \qquad \text{(Eq. 3)}$$

where V_d and K_E are as defined for Eq. 1.

The area under the individual serum concentration–time curve from zero to infinity was determined by the trapezoidal rule. When the last data point was >0.5 μg/ml, the area from the last data point to infinity was calculated as the quotient of the last data point and the overall elimination rate constant, K_E. The $AUC_{0\to\infty}$ also was calculated from computer-fit parameters as described in:

$$AUC_{0\to\infty} = \frac{FD}{V_d}\left(\frac{K_a}{K_a - K_E}\right)\left(\frac{1}{K_E} - \frac{1}{K_a}\right) \qquad \text{(Eq. 4)}$$

where $(FD/V_d)[K_a/(K_a - K_E)]$ was the intercept of the best computer fit of the individual data.

The other bioavailability parameters, time of maximum serum theophylline concentration (t_{max}) and maximum serum theophylline concentration (C_{max}), were obtained directly from the actual serum assay values and from the nonlinear least-squares fit.

The relative bioavailability, F_{rel}, of the liquid-filled theophylline capsules was calculated using the $AUC_{0\to\infty}$ values corrected for intraindividual variation in the elimination rate:

$$F_{rel} = \frac{(AUC_{0\to\infty}, \text{capsule})(K_E, \text{capsule})}{(AUC_{0\to\infty}, \text{liquid})(K_E, \text{liquid})} \qquad \text{(Eq. 5)}$$

Statistical Analysis—A two-way analysis of variance for a randomized complete block experimental design was performed on the bioavailability parameters calculated from the actual assay values ($AUC_{0\to\infty}$, t_{max}, and C_{max}) obtained for each dosage form to determine the significance of differences between the capsules and liquid. A paired t-test of the other pharmacokinetic parameters determined if there were any significant differences in the mean values after administration of a capsule or liquid.

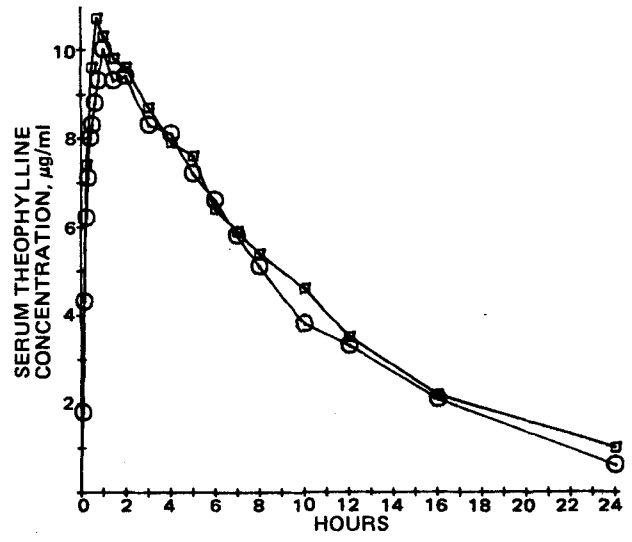

Figure 1—*Mean serum theophylline levels in 14 subjects after a 300-mg oral theophylline dose. Key: □, capsules; and ○, liquid.*

RESULTS AND DISCUSSION

The mean (±*SE*) serum theophylline levels in 14 subjects as a function of time after administration of 300 mg of theophylline either as a liquid-filled oral capsule or as an oral liquid are illustrated in Fig. 1. As expected, individual serum theophylline concentrations at each sampling time varied, but the curves of mean serum theophylline levels in Fig. 1 show that the two dosage forms produced serum levels over time that were essentially the same. Semilogarithmic plots of mean serum theophylline concentrations *versus* time revealed a monoexponential decrease in observed serum levels after the peak with no significant distribution phase, indicating that a one-compartment open model is appropriate for evaluating the pharmacokinetics of these data. The correlation coefficients observed for individual serum level data fitted to the one-compartment open model were ≥0.95 in all cases.

The bioavailability parameters, *i.e.*, the area under the serum level–time curve ($AUC_{0\to\infty}$), the maximum serum level (C_{max}), and the time to maximum serum level (t_{max}), are listed in Table I. The parameters were obtained from both the experimentally observed serum theophylline levels and the computer-generated, one-compartment fits of the individual data. The AUC values for both the capsules and the liquid, when corrected for intraindividual variation in elimination, were not significantly different ($p > 0.05$). The mean (±*SE*) relative bioavailability (F_{rel}) of the oral theophylline capsules was 1.01 ± 0.06 (Table I) with a range of 0.70–1.56. With paired individual data, the F_{rel} was larger for the capsules in six of the 14 subjects. The difference in bioavailability between the formulations was not significant ($p > 0.05$). A previous study showed that the absolute bioavailability of the oral aminophylline liquid used as a reference dosage form in this study was 100%[8]. Thus, the absolute bioavailability of the oral theophylline capsules probably approximates 100%.

The oral liquid was absorbed rapidly, as noted from the mean (±*SE*) t_{max} value of 1.24 ± 0.3 hr (range of 0.25–4.0 hr). The oral capsules appeared to have rapid and complete dissolution *in vivo*, as indicated from the mean (±*SE*) t_{max} value of 0.98 ± 0.3 hr (range of 0.25–5.0 hr). Al-

[3] μBondapak C_{18}, Waters Associates, Milford, Mass.
[4] Model U6K, Waters Associates, Milford, Mass.
[5] Model 6000A, Waters Associates, Milford, Mass.
[6] Model 440, Waters Associates, Milford, Mass.
[7] Prime Computer Co., Framingham, Mass.

[8] Data on file, Fisons Corp., Bedford, Mass.

Table I—Bioavailability Parameter Values (Mean ± *SE*) for Theophylline after Oral Administration of a 300-mg Dose to 14 Subjects

Parameter	Formulation		Statistical Significance
	Liquid	Capsule	
AUC^a, μg hr/ml			
Observed[b]	98.0 ± 6.4	104 ± 8.3	NS ($p > 0.05$)
Calculated[c]	95.0 ± 6.4	118 ± 11.0	
C_{max}, μg/ml			
Observed	11.5 ± 0.7	15.1 ± 1.2	Significant
Calculated	10.3 ± 0.6	11.5 ± 0.7	($p < 0.05$)
t_{max}, hr			
Observed	1.24 ± 0.3	0.98 ± 0.30	NS ($p > 0.05$)
Calculated	1.20 ± 0.2	0.92 ± 0.20	
F_{rel}[d]			
Observed	—	1.01 ± 0.06	NS ($p > 0.05$)
Calculated	—	1.09 ± 0.04	

[a] From zero to infinity. [b] Based on actual assay values in serum. [c] Based on computer fit of data to one-compartment model. [d] Corrected for intraindividual variation in elimination.

though the t_{max} observed after capsule administration occurred earlier in time, the differences were not significant ($p > 0.05$). Intersubject variability in theophylline absorption was estimated using the coefficients of variation (standard deviation × 100/mean) of the bioavailability parameters of both dosage forms, and the t_{max} values showed the greatest variation.

The mean t_{max} observed in this study for the oral liquid was similar to the mean t_{max} reported (1) for a hydroalcoholic theophylline solution (1.4 hr, $SE = 0.03$) administered to 10 patients and similar to the mean t_{max} reported (3) for a similar solution administered to 12 subjects (1.208, $SD = 0.620$). The ranges and variability of t_{max} in the earlier studies were essentially the same as those observed in the present investigation. By contrast, the mean t_{max} observed in the oral capsule study (0.98 ± 0.3 hr) was earlier than the mean t_{max} reported (1, 3) for oral, compressed tablets (2.0 ± 0.9 and 1.458 ± 0.542, respectively), although greater intrapatient variability was observed in this study. The rapid absorption from the oral capsules may be related to the absence of the disintegration step characteristic of oral tablets or to the suspending medium within the oral capsule. Indeed, Lindenbaum (6) reported that digoxin bioavailability from a liquid concentrate contained in a soft gelatin capsule was better than the bioavailability of a nonalcoholic digoxin solution or tablet, although this result has not been found consistently (7).

The measured mean C_{max} after capsule administration was 15.1 ± 1.2 μg/ml. This C_{max} was significantly different ($p < 0.05$) from the measured mean C_{max} of 11.5 ± 0.7 μg/ml for the oral liquid. The higher C_{max} of the capsules is consistent with the shorter t_{max} and faster K_a (Table II) observed for this formulation.

The values for theophylline absorption, distribution, and elimination calculated for the capsules and liquid are listed in Table II. The mean (±*SE*) K_a for the capsule (13.98 ± 3.1) was significantly different ($p < 0.05$) from the mean (±*SE*) K_a (5.22 ± 1.18) for the liquid, although the corresponding mean $t_{abs\text{-}1/2}$ (±*SE*) values for the capsules (0.18 ± 0.06) and liquid (0.27 ± 0.07) were not significantly different ($p > 0.05$). The absorption lag times (t_0) were averaged for the capsule and liquid formulations. The difference between the mean lag times was significant ($p < 0.05$), with the capsule t_0 equal to 0.143 ± 0.038 (±*SE*) and the liquid equal to 0.047 ± 0.017. The faster K_a after the capsule accounted for the higher C_{max} and shorter t_{max} observed for the formulation.

Theophylline elimination kinetics after capsule and liquid administration were essentially the same. The K_E for the capsule was 0.11 ± 0.01 (±*SE*), and the corresponding $t_{1/2}$ was 6.98 ± 0.61 (±*SE*). The K_E and the $t_{1/2}$ for the liquid were 0.12 ± 0.01 (±*SE*) and 6.19 ± 0.31, respectively, and there were no significant differences ($p > 0.05$) between the formulations in either K_E or $t_{1/2}$. These elimination parameters are in agreement with those reported for theophylline by other investigators (8). Some researchers have reported significant intrapatient variability in K_E and $t_{1/2}$ after single doses, with both short and long time intervals separating the individual doses. In this study, intrapatient variability in K_E and $t_{1/2}$ also was noted. For example, nine subjects exhibited an increase in $t_{1/2}$ and five subjects had a decrease in $t_{1/2}$ from one study period to the next. The mean percentage difference in $t_{1/2}$ was 26% (range of −30–+54%).

By contrast, there was very little intrapatient variability in V_d. After the capsule, the mean V_d was 0.38 ± 0.01 (±*SE*); after the liquid, the mean V_d was 0.42 ± 0.02 (±*SE*). These values are within the range of

Table II—Pharmacokinetic Parameters (Mean ± *SE*) for Theophylline after Oral Administration of a 300-mg Dose to 14 Subjects

Parameter	Formulation		Statistical Significance
	Liquid	Capsule	
K_a, hr^{-1}	5.22 ± 1.18	13.98 ± 3.10	Significant ($p < 0.05$)
$t_{1/2\text{-}abs}$, hr	0.27 ± 0.07	0.18 ± 0.16	NS ($p > 0.05$)
t_0, hr[a]	0.047 ± 0.017	0.143 ± 0.038	Significant ($p < 0.05$)
K_E, hr^{-1}	0.12 ± 0.01	0.11 ± 0.01	NS ($p > 0.05$)
$t_{1/2\text{-}elim}$, hr	6.19 ± 0.31	6.98 ± 0.61	NS ($p > 0.05$)
V_d, liters/kg	0.42 ± 0.02	0.38 ± 0.01	NS ($p > 0.05$)
Cl_B, ml/min/kg	0.84 ± 0.06	0.70 ± 0.07	NS ($p > 0.05$)

[a] Where t_0 is equal to absorption lag time.

mean values expected for the subject population in this study (9). The difference in V_d between formulations was not significant ($p > 0.05$).

Theophylline clearance was not significantly different after the capsule or liquid ($p > 0.05$). However, the mean clearance after the liquid was 0.84 ± 0.06 ml/min/kg (±*SE*), slightly faster than, but not significantly different from, the mean clearance of 0.70 ± 0.07 ml/min/kg (±*SE*) found for the capsule. The difference between the mean clearance values was not unexpected and was primarily related to the intrapatient variability in K_E and/or $t_{1/2}$ and not in V_d. The mean clearance values were similar to and within the range of values reported elsewhere (10, 11).

No significant side effects were reported during the study. Palpitations and mild headaches occurred in two subjects and coincided with peak serum theophylline concentrations. Vital signs were not altered during the study.

SUMMARY

Liquid-filled, soft gelatin theophylline capsules are unique among the large number of theophylline dosage forms. Solid oral theophylline dosage forms are thought to have many practical advantages over theophylline solutions. For example, the capsules evaluated in this study effectively masked the bitter theophylline taste. In addition, liquid-filled capsules may improve GI tract tolerance of the sometimes irritating theophylline.

The capsules evaluated appear to be a solid dosage form with rapid dissolution *in vivo*. They produce serum theophylline concentrations comparable to an oral theophylline liquid, and the relative bioavailability is the same as the oral liquid. Thus, in practice, these capsules would act as a reliable dosage form for oral theophylline administration.

REFERENCES

(1) L. Hendeles, M. Weinberger, and L. Bighley, *Am. J. Hosp. Pharm.*, **34**, 525 (1977).

(2) P. A. Mitenko and R. I. Ogilvie, *Clin. Pharmacol. Ther.*, **16**, 720 (1974).

(3) R. A. Holley, C. A. Mildon, and I. W. French, *Curr. Ther. Res.*, **23**, 330 (1978).

(4) "Desirable Weights of Adults," Statistical Bull. 40, Metropolitan Life Insurance, New York, N.Y., 1959.

(5) C. M. Metzler, Technical Report 7292-69-7293-005, Upjohn Co., Kalamazoo, Mich., 1969.

(6) J. Lindenbaum, *Curr. Ther. Res.*, **21**, 278 (1977).

(7) L. Padeletti and A. Brat, *Int. J. Clin. Pharmacol.*, **16**, 320 (1978).

(8) P. D. Walson, R. C. Strong, and L. M. Taussig, *J. Pediatr.*, **91**, 321 (1977).

(9) J. W. Kern and A. G. Lipman, *Drug Intell. Clin. Pharm.*, **11**, 152 (1977).

(10) P. A. Mitenko and R. I. Ogilvie, *Clin. Pharmacol. Ther.*, **14**, 509 (1972).

(11) M. W. Weinberger, R. A. Matthay, E. J. Ginchansky, C. A. Chidsey, and T. L. Petty, *J. Am. Med. Assoc.*, **235**, 2110 (1976).

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